ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial contains 100 mg of daratumumab (20 mg daratumumab per mL).
Each 20 mL vial contains 400 mg of daratumumab (20 mg daratumumab per mL).

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

Excipient with known effect

Each 5 mL vial of solution for infusion contains 273.3 mg of sorbitol (E420).
Each 20 mL vial of solution for infusion contains 1093 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
The solution is colourless to yellow, with a pH of 5.5 and osmolality of 310 to 370 mOsm/kg.

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 should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

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

Posology

Dosing schedule in combination with lenalidomide and dexamethasone (4-week cycle regimen) and for monotherapy
The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide and dexamethasone (Rd) (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.

Dexamethasone should be administered at 40 mg/week (or a reduced dose of 20 mg/week for patients > 75 years).

For dose and schedule of medicinal products administered with DARZALEX, 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 DARZALEX 16 mg/kg body weight administered as an intravenous infusion 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, 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 DARZALEX 16 mg/kg body weight administered as an intravenous infusion 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.

Dexamethasone should be 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 should be administered on days 1, 2, 8, 9, 15, 16 in cycles 5 and 6.

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

Dosing schedule in combination with bortezomib and dexamethasone (3-week cycle regimen)
The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in table 4.

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

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

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

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

Dexamethasone should be administered at 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 of the first 8 bortezomib treatment cycles or a reduced dose of 20 mg/week for patients > 75 years, underweight (BMI < 18.5), poorly controlled diabetes mellitus or prior intolerance to steroid therapy.

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

Infusion rates
Following dilution the DARZALEX infusion should be intravenously administered at the initial infusion rate presented in table 5 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.
To facilitate administration, the first prescribed 16 mg/kg dose at week 1 may be split over two consecutive days i.e. 8 mg/kg on day 1 and day 2 respectively, see table 5 below.

Table 5: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution volume	**Initial rate (first hour)**	**Rate increment[a]**	**Maximum rate**
Week 1 Infusion				
Option 1 (Single dose infusion)				
Week 1 day 1 (16 mg/kg)	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Option 2 (Split dose infusion)				
Week 1 day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg) infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (week 3 onwards, 16 mg/kg) infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

[b] A dilution volume of 500 mL for the 16 mg/kg dose should be used only if there were no IRRs the previous week. Otherwise, use a dilution volume of 1000 mL.

[c] A modified initial rate (100 mL/hour) for subsequent infusions (i.e. week 3 onwards) should only be used only if there were no IRRs during the previous infusion. Otherwise, continue to use instructions indicated in the table for the week 2 infusion rate.

Management of infusion-related reactions
Pre-infusion medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) prior to treatment with DARZALEX.

For IRRs of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms.

Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below (see section 4.4).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (table 5).
- Grade 3 (severe): Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate (table 5). The procedure above should be repeated in the event of recurrence of grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a grade 3 or greater infusion reaction.
- Grade 4 (life-threatening): Permanently discontinue DARZALEX treatment.

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.

Recommended concomitant medicinal products

Pre-infusion medicinal product
Pre-infusion medicinal products should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of DARZALEX as follows:

- Corticosteroid (long-acting or intermediate-acting)
  - Monotherapy:
    Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).
  - Combination therapy:
    Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX infusion. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-infusion medicinal product on DARZALEX infusion days (see section 5.1).
    Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX infusion days when patients have received dexamethasone as a pre-infusion medicinal product.
- Antipyretics (oral paracetamol 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

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

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-infusion medicinal products including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion 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 dose 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. Based on population PK analyses, no dose 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.

Method of administration

DARZALEX is for intravenous use. It is administered as an intravenous infusion following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. For instructions on dilution of the medicinal product before administration, see section 6.6.

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 name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

DARZALEX can cause serious IRRs, including anaphylactic reactions (see section 4.8). These reactions can be life-threatening and fatal outcomes have been reported.

All patients should be monitored throughout the infusion for IRRs. For patients that experience any grade IRRs, continue monitoring post-infusion until symptoms resolve.

In clinical studies, IRRs were reported in approximately half of all patients treated with DARZALEX.

The majority of IRRs occurred at the first infusion and were grade 1-2 (see section 4.8). Four percent of all patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema, pulmonary oedema and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma). Symptoms predominantly included nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension and blurred vision (see section 4.8).

Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with DARZALEX. DARZALEX infusion should be interrupted for IRRs of any severity and medical management/supportive treatment for IRRs should be instituted as needed. For patients with grade 1, 2, or 3 IRRs, the infusion rate should be reduced when re-starting the infusion. If an anaphylactic reaction or life-threatening (grade 4) infusion reaction occurs, appropriate emergency resuscitation 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 infusions. Additionally the use of post-infusion medicinal products (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX (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 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. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions or growth factors.

Infections

DARZALEX can cause serious, life-threatening, or fatal infections (see section 4.8).

Patients should be closely monitored for signs and symptoms of infection prior to and during treatment with DARZALEX and treated appropriately. Prophylactic antimicrobials according to treatment guidelines should be considered prior to, during or post-treatment (see section 4.2).

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be 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.

Excipients

This medicinal product contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

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 of daratumumab in combination with lenalidomide, pomalidomide, thalidomide, bortezomib and dexamethasone indicated no clinically-relevant drug-drug interaction between daratumumab and these small molecule medicinal products.

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 or limited amount of data from the use of daratumumab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). DARZALEX is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether daratumumab is excreted in human milk.
A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from 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) were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, dyspnoea, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, asthenia, peripheral neuropathy, upper respiratory tract infection, musculoskeletal pain and COVID-19. Serious adverse reactions were sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

Tabulated list of adverse reactions

Table 6 summarises the adverse reactions that occurred in patients receiving DARZALEX. The data reflects exposure to DARZALEX (16 mg/kg) in 2066 patients with multiple myeloma including 1910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. Post-marketing adverse reactions are also included.

In study MMY3006, the number of CD34+ cell yield was numerically lower in the D-VTd arm compared with the VTd arm (Median: D-VTd: 6.3 x 10^6/kg; VTd 8.9 x 10^6/kg) and among those who completed mobilisation, more patients in the D-VTd group received plerixafor compared to those in the VTd arm (D-VTd: 21.7%; VTd: 7.9%). The rates of engraftment and haematopoietic reconstitution was similar among the transplanted subjects in the D-VTd and VTd arms (D-VTd: 99.8%; VTd: 99.6%; as measured by the recovery of neutrophils > 0.5 x 10^9/L, leukocytes > 1.0 x 10^9/L, and platelets > 50 x 10^9/L without transfusion).

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000). Within each frequency grouping adverse reactions are presented in the order of decreasing seriousness.

Table 6: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System organ class	Adverse reaction	Frequency	Incidence (%)	
			Any grade	Grade 3-4
Infections and infestations	Upper respiratory tract infection[a]	Very common	46	4
	COVID-19[a,d]		23	6
	Pneumonia[a]		19	11
	Bronchitis[a]		17	2
	Urinary tract infection	Common	8	1
	Sepsis[a]		4	4
	Cytomegalovirus infection[a]		1	< 1*
	Hepatitis B Virus reactivation[b]	Uncommon	-	-
Blood and lymphatic system disorders	Neutropenia[a]	Very common	44	39
	Thrombocytopenia[a]		31	19
	Anaemia[a]		27	12
	Lymphopenia[a]		14	11
	Leukopenia[a]		12	6
Immune system disorders	Hypogammaglobulinaemia[a]	Common	3	< 1*
	Anaphylactic reaction[b]	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very common	12	1
	Hypokalaemia[a]		10	3
	Hyperglycaemia	Common	7	3
	Hypocalcaemia		6	1
	Dehydration		3	1*
Psychiatric disorders	Insomnia	Very common	16	1*

Nervous system disorders	Peripheral neuropathy[a]	Very common	35	4
	Headache		12	< 1*
	Paraesthesia		11	< 1
	Dizziness		10	< 1*
	Syncope	Common	2	2*
Cardiac disorders	Atrial fibrillation	Common	4	1
Vascular disorders	Hypertension[a]	Very common	10	5
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	25	< 1*
	Dyspnoea[a]		21	3
	Pulmonary oedema[a]	Common	1	< 1
Gastrointestinal disorders	Constipation	Very common	33	1
	Diarrhoea		32	4
	Nausea		26	2*
	Vomiting		16	1*
	Abdominal pain[a]		14	1
	Pancreatitis[a]	Common	1	1
Skin and subcutaneous tissue disorders	Rash	Very common	13	1*
	Pruritus	Common	7	< 1*
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[a,e]	Very common	37	4
	Arthralgia		14	1
	Muscle spasms		14	< 1*
General disorders and administration site conditions	Oedema peripheral[a]	Very common	27	1
	Fatigue		26	4
	Pyrexia		23	2
	Asthenia		21	2
	Chills	Common	9	< 1*
Injury, poisoning and procedural complications	Infusion-related reaction[c]	Very common	40	4

* No grade 4.

[a] Indicates grouping of terms.

[b] Post-marketing adverse reaction.

[c] Infusion-related reaction includes terms determined by investigators to be related to infusion, see below.

[d] Incidence is based on a subset of patients who received at least one dose of study treatment on or after 01 February 2020 (the start of the COVID-19 pandemic) from studies MMY3003, MMY3006, MMY3008 and MMY3013, and all daratumumab treated patients from studies MMY3014, MMY3019, and SMM3001 (N=1177).

[e] Musculoskeletal pain includes back pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.

Description of selected adverse reactions

Infusion-related reactions (IRRs)
In clinical studies (monotherapy and combination treatments; N=2066) the incidence of any grade IRRs was 37% with the first (16 mg/kg, week 1) infusion of DARZALEX, 2% with the week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a grade 3/4 IRR with the week 2 or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours). The incidence of infusion modifications due to reactions was 36%. Median durations of 16 mg/kg infusions for the 1st week, 2nd week and subsequent infusions were approximately 7, 4 and 3 hours respectively.
Severe IRRs included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma), hypoxia, and hypertension. Other adverse IRRs included nasal congestion, cough, chills, throat irritation, blurred vision, vomiting and nausea (see section 4.4).

When DARZALEX dosing was interrupted in the setting of ASCT (study MMY3006) for a median of 3.75 (range: 2.4; 6.9) months, upon re-initiation of DARZALEX the incidence of IRRs was 11% at first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption due to ASCT. IRRs occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (grade 3/4: < 1%) with those reported in previous studies at week 2 or subsequent infusions.

In study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at week 1 split over two days i.e. 8 mg/kg on day 1 and day 2 respectively. The incidence of any grade IRRs was 42%, with 36% of patients experiencing IRRs on day 1 of week 1, 4% on day 2 of week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for week 1-day 1, 4.2 h for week 1-day 2, and 3.4 hours for the subsequent infusions.

Infections
In patients receiving DARZALEX combination therapy, grade 3 or 4 infections were reported as follows:
Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 28%, 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 DARZALEX 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 2459 patients who received DARZALEX at the recommended dose, 38% were 65 to 75 years of age, and 15% 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=1213), 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=710), 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. Doses up to 24 mg/kg have been administered intravenously in a clinical study.

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 reactions and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FC01.

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 intravenous daratumumab in clinical studies, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

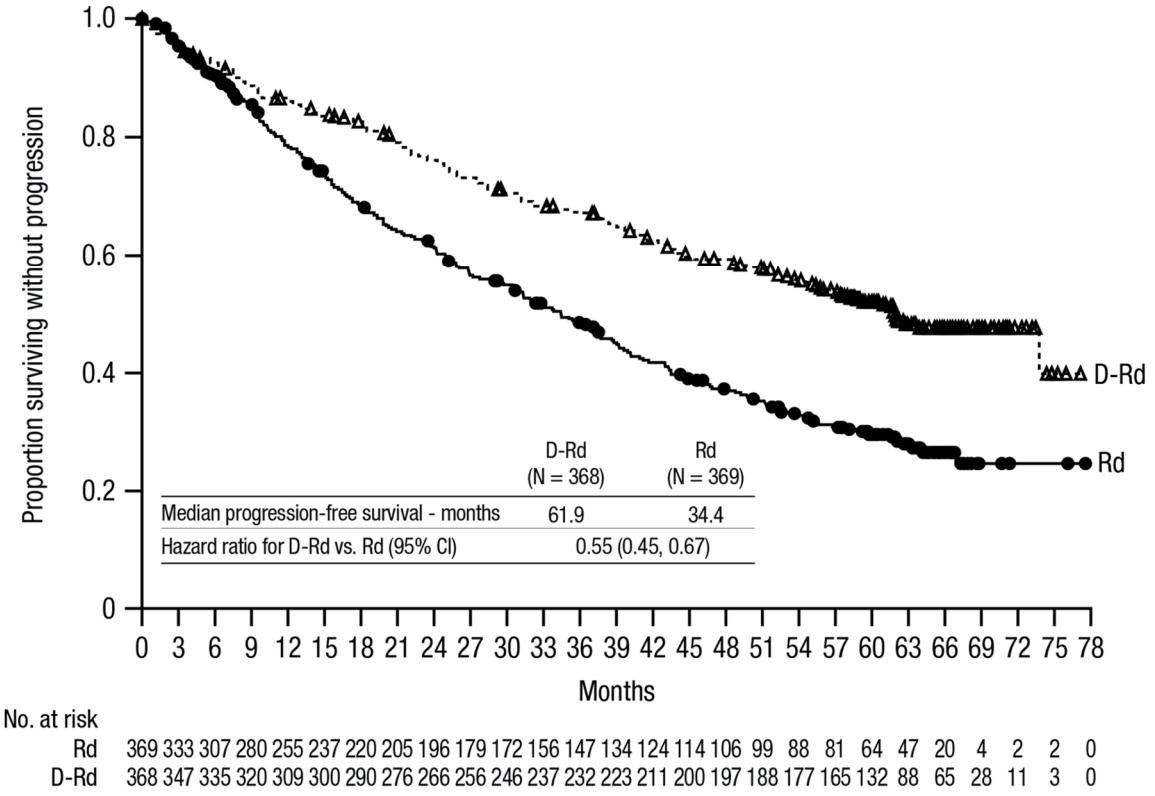
Clinical efficacy and safety

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 DARZALEX 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 DARZALEX 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 and overall survival (OS).

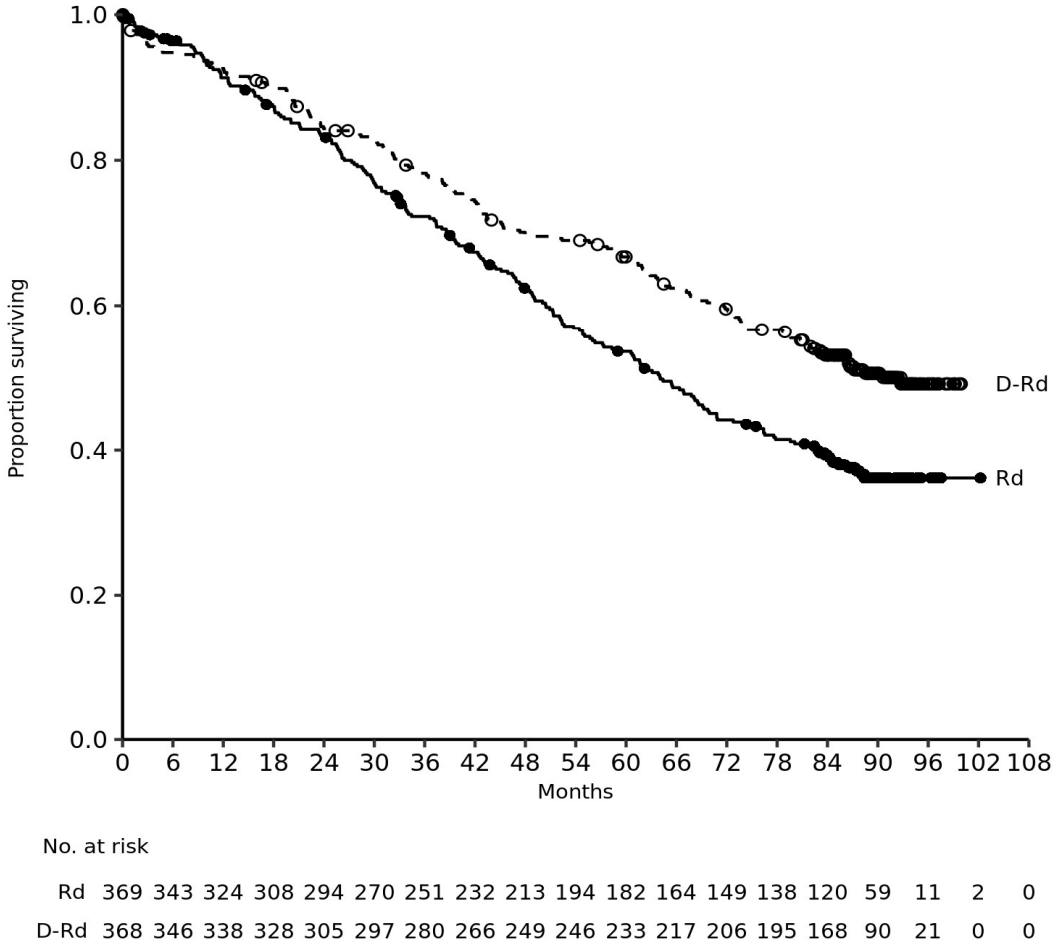
With a median follow-up of 28 months, the primary analysis of PFS in study MMY3008 showed an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; $p < 0.0001$), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis after a median follow-up of 64 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 61.9 months in the DRd arm and 34.4 months in the Rd arm (HR=0.55; 95% CI: 0.45, 0.67).

Figure 1: Kaplan-Meier curve of PFS in study MMY3008



With a median follow-up of 56 months, DRd has shown an OS advantage over the Rd arm (HR=0.68; 95% CI: 0.53, 0.86; p=0.0013). Results of an updated OS analysis after a median of 89 months continued to show an improvement in OS for patients in the DRd arm compared to the Rd arm. Median OS was 90.3 months in the DRd arm and was 64.1 months in the Rd arm (HR=0.67; 95% CI: 0.55, 0.82).

Figure 2: Kaplan-Meier curve of OS in study MMY3008



Additional efficacy results from study MMY3008 are presented in table 7 below.

Table 7: 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.

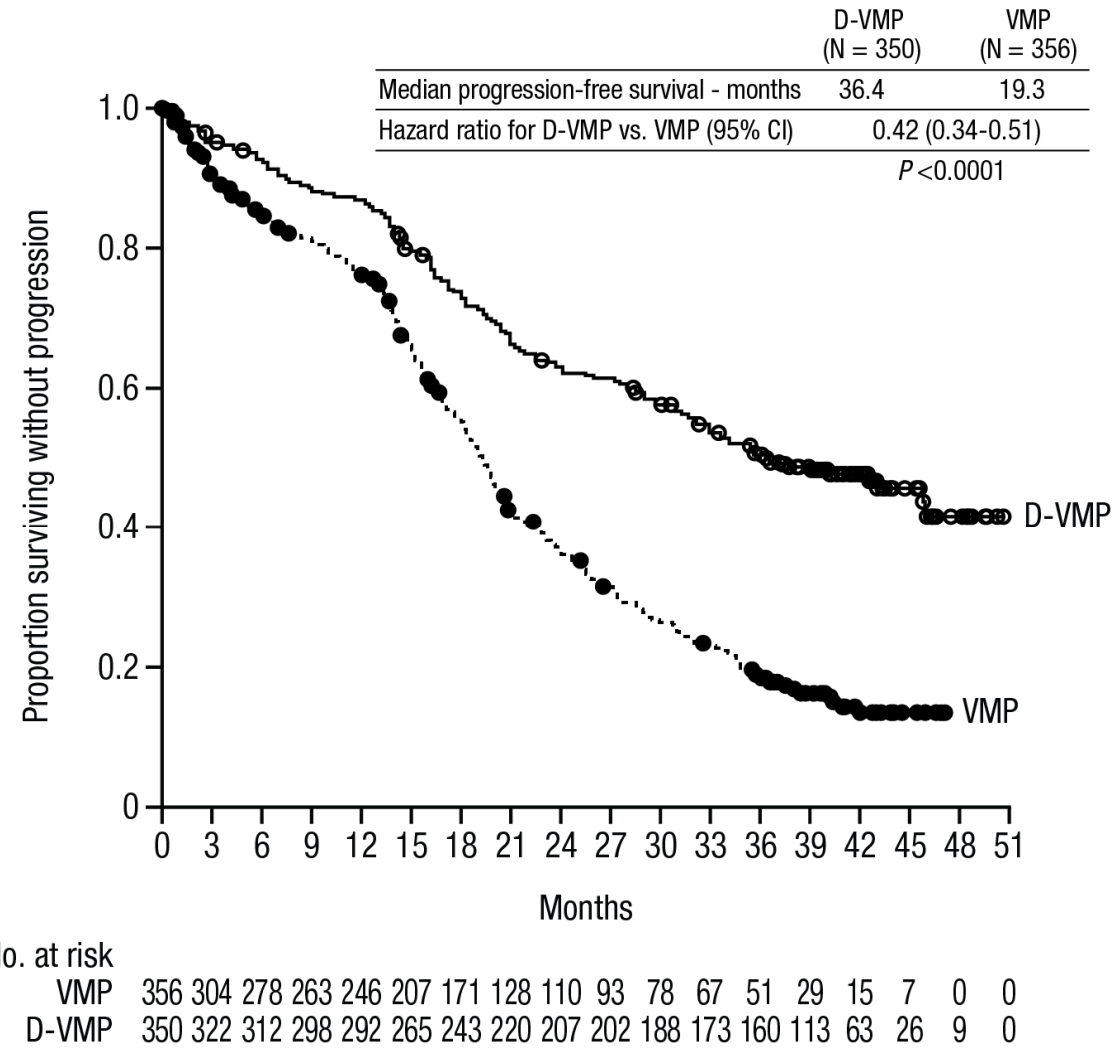
Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant

Study MMY3007, an open-label, randomised, active-controlled phase III study, compared treatment with DARZALEX 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). DARZALEX 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).

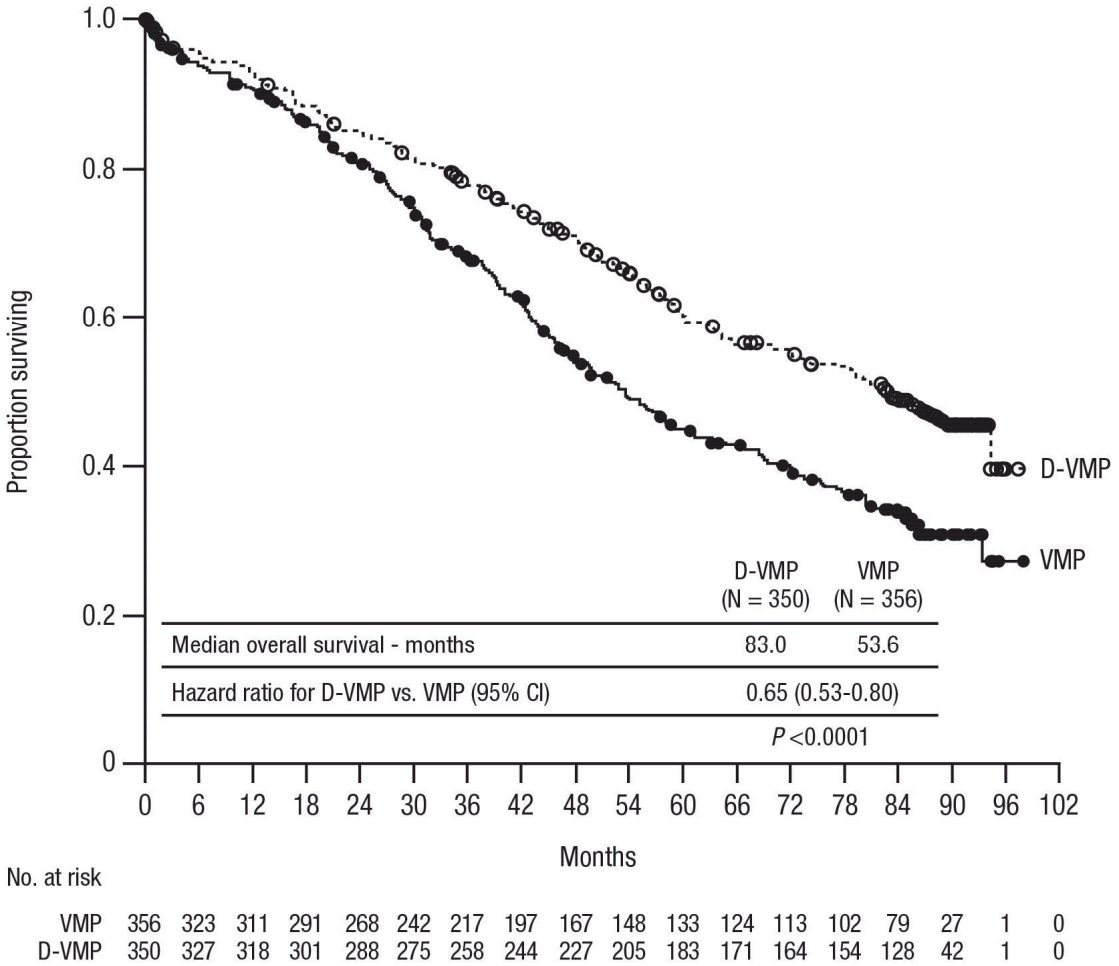
With a median follow-up of 16.5 months, the primary analysis of PFS in study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; $p < 0.0001$). Results of an updated 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 3: Kaplan-Meier curve of PFS in study MMY3007



After a median follow-up of 40 months, D-VMP has shown an OS advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. After a median follow-up of 87 months, the median OS was 83 months (95% CI: 72.5, NE) in the D-VMP arm and 53.6 months (95% CI: 46.3, 60.9) in the VMP arm.

Figure 4: Kaplan-Meier curve of OS in study MMY3007



Additional efficacy results from study MMY3007 are presented in table 8 below.

Table 8: 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 DARZALEX 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 DARZALEX infusion, the dexamethasone dose was administered intravenously as a pre-infusion medicinal product. 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 PFS.

Table 9: 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.

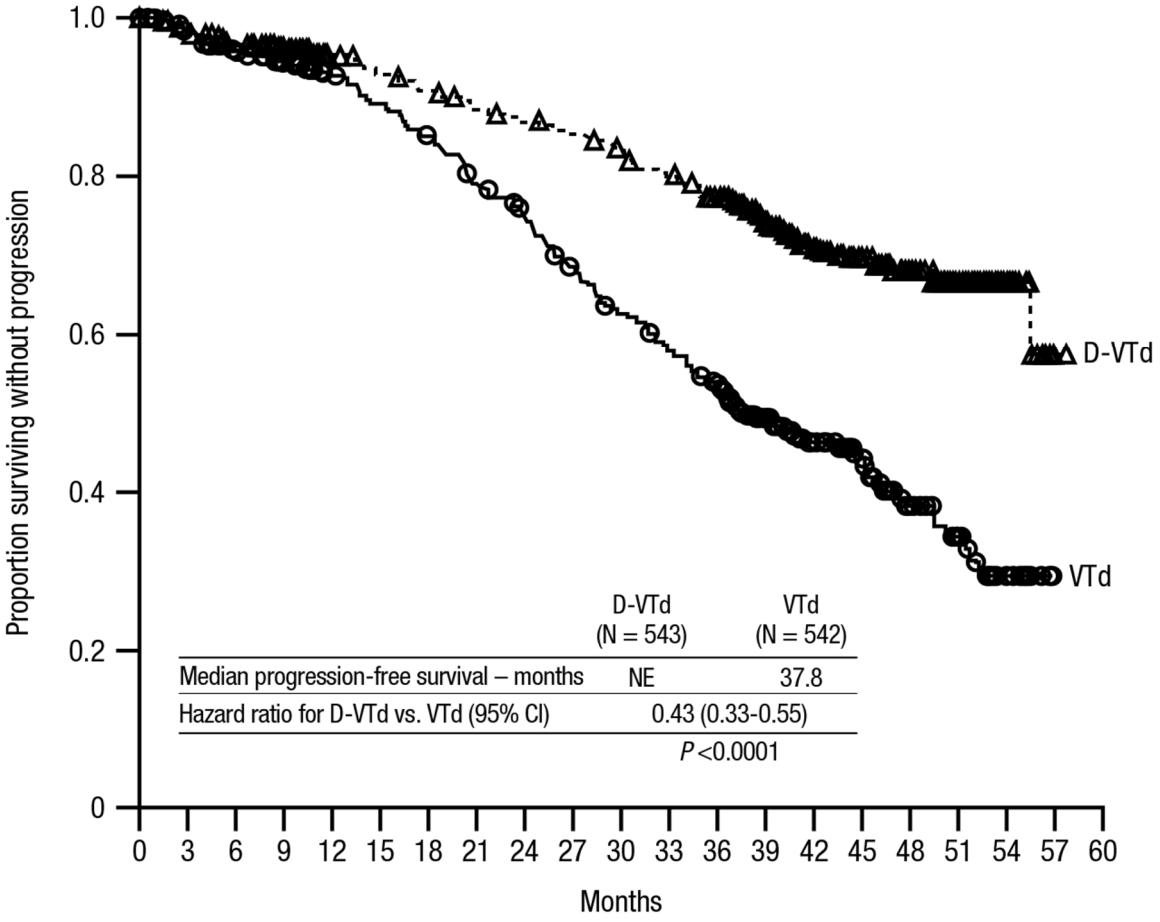
[c] Based on threshold of 10^{-5}.

[d] Regardless of response per IMWG.

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

With a median follow-up of 18.8 months, the primary analysis of PFS 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. Results of an updated PFS analysis with a median follow-up of 44.5 months, censoring patients who were randomised to daratumumab maintenance in the second randomisation, showed HR=0.43; 95% CI: 0.33, 0.55; p < 0.0001. Median PFS was not reached in the D-VTd arm and was 37.8 months in the VTd arm.

Figure 5: Kaplan-Meier curve of PFS in study MMY3006



Relapsed/refractory multiple myeloma
Monotherapy:
The clinical efficacy and safety of DARZALEX 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 DARZALEX 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 10 below.

Table 10: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	DARZALEX 16 mg/kg N=106
Overall response rate[1] (ORR: sCR+CR+VGPR+PR) [n (%)] 95% CI (%)	31 (29.2) (20.8, 38.9)
Stringent complete response (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 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 DARZALEX 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).

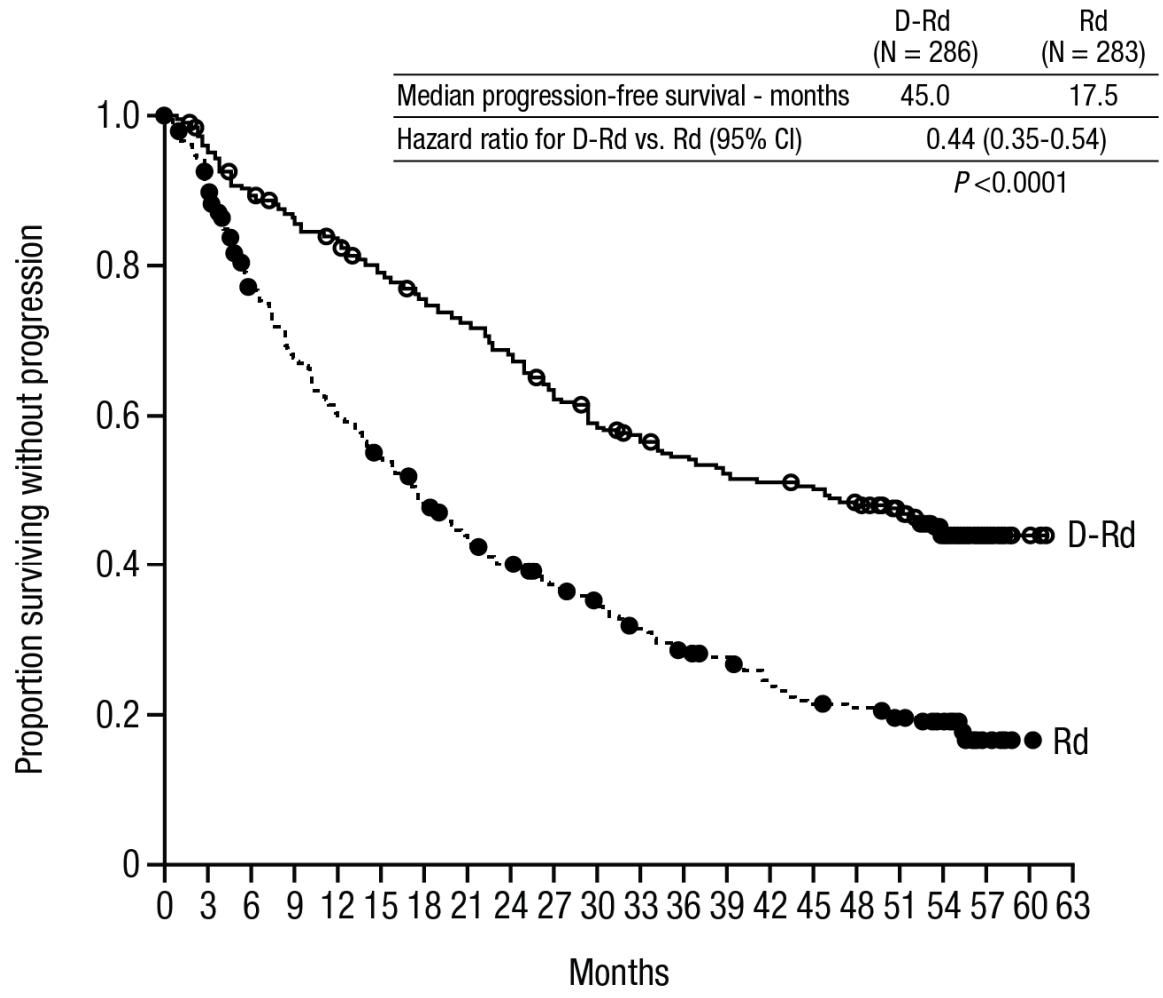
At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

Combination treatment with lenalidomide
Study MMY3003, an open-label, randomised, active-controlled phase III study, compared treatment with DARZALEX 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 DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medicinal product 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 DARZALEX 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.

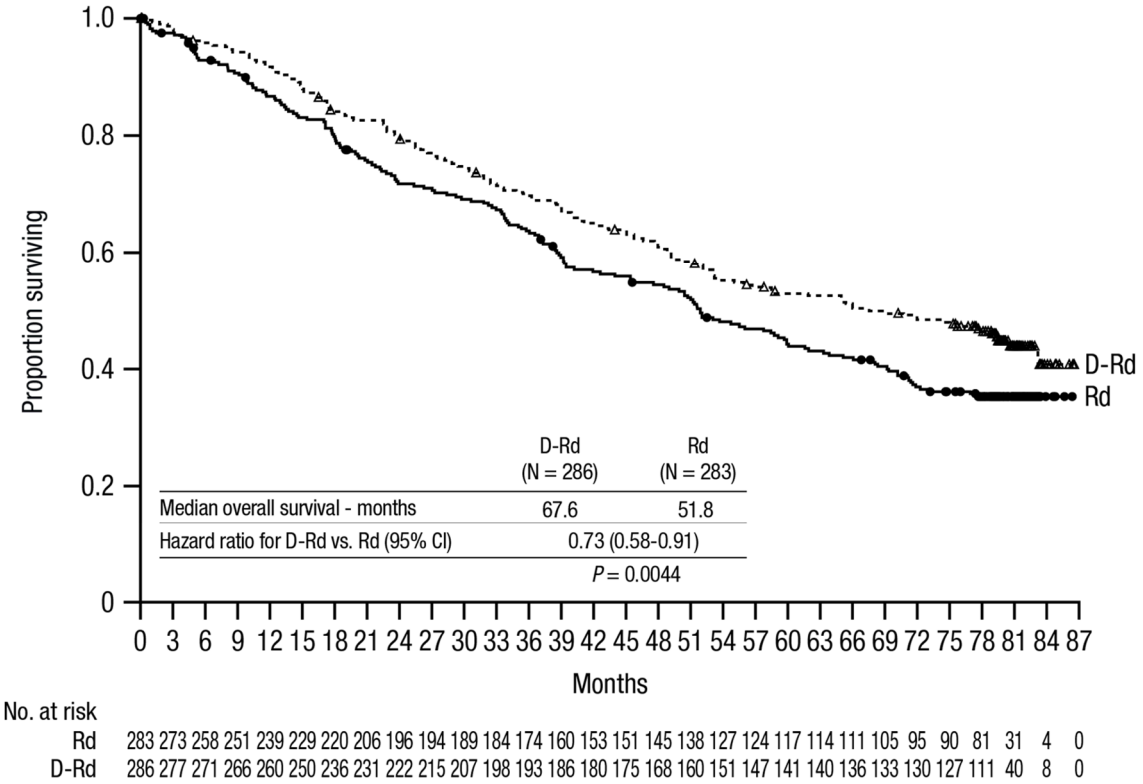
With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p < 0.0001). Results of an updated 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 6).

Figure 6: Kaplan-Meier curve of PFS in study MMY3003



After a median follow-up of 80 months, DRd has shown an OS advantage over the Rd arm (HR=0.73; 95% CI: 0.58, 0.91; p=0.0044). The median OS was 67.6 months in the DRd arm and 51.8 months in the Rd arm.

Figure 7: Kaplan-Meier curve of OS in study MMY3003



Additional efficacy results from study MMY3003 are presented in table 11 below.

Table 11: 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.

Combination treatment with bortezomib

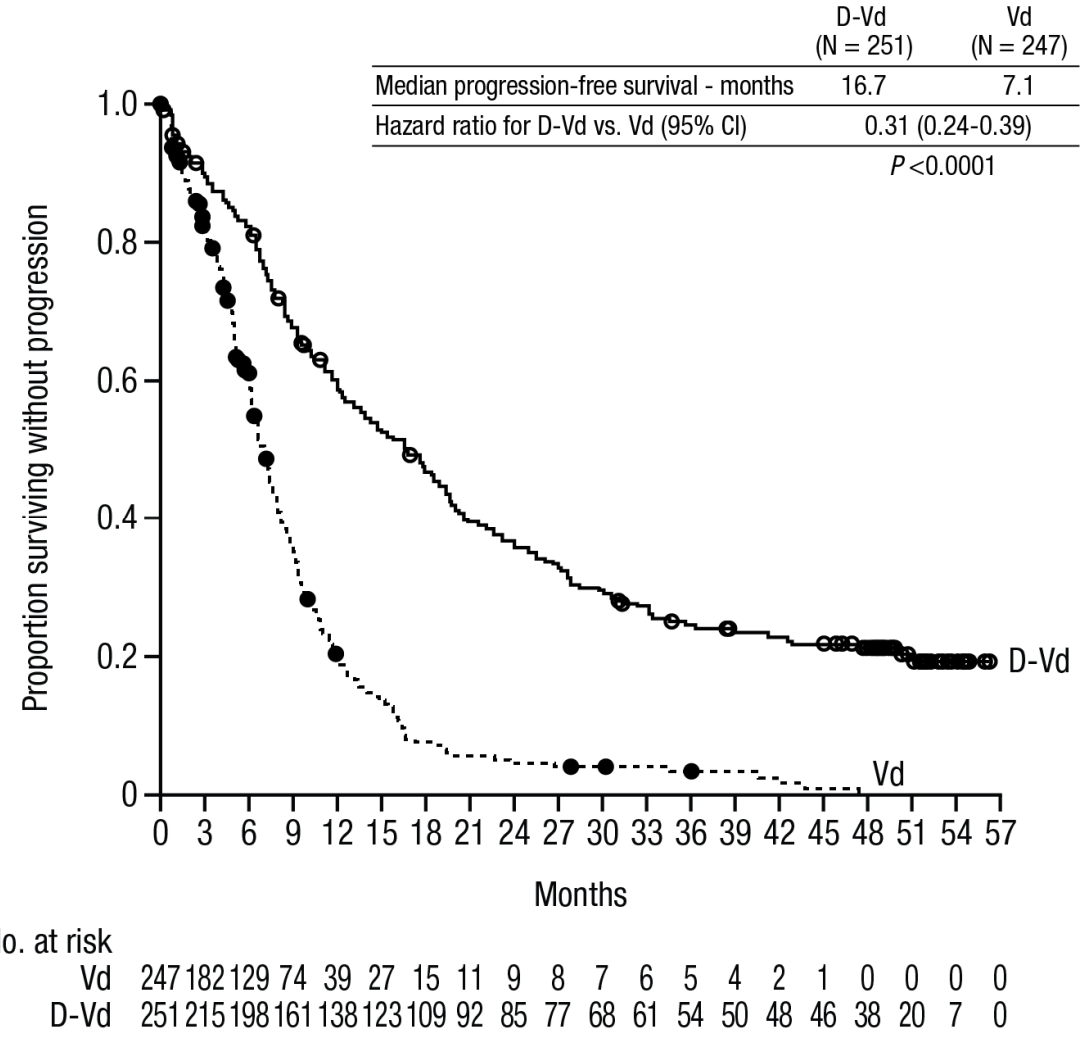
Study MMY3004, an open-label, randomised, active-controlled phase III study, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous 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 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 DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medicinal product. DARZALEX 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 DARZALEX 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.

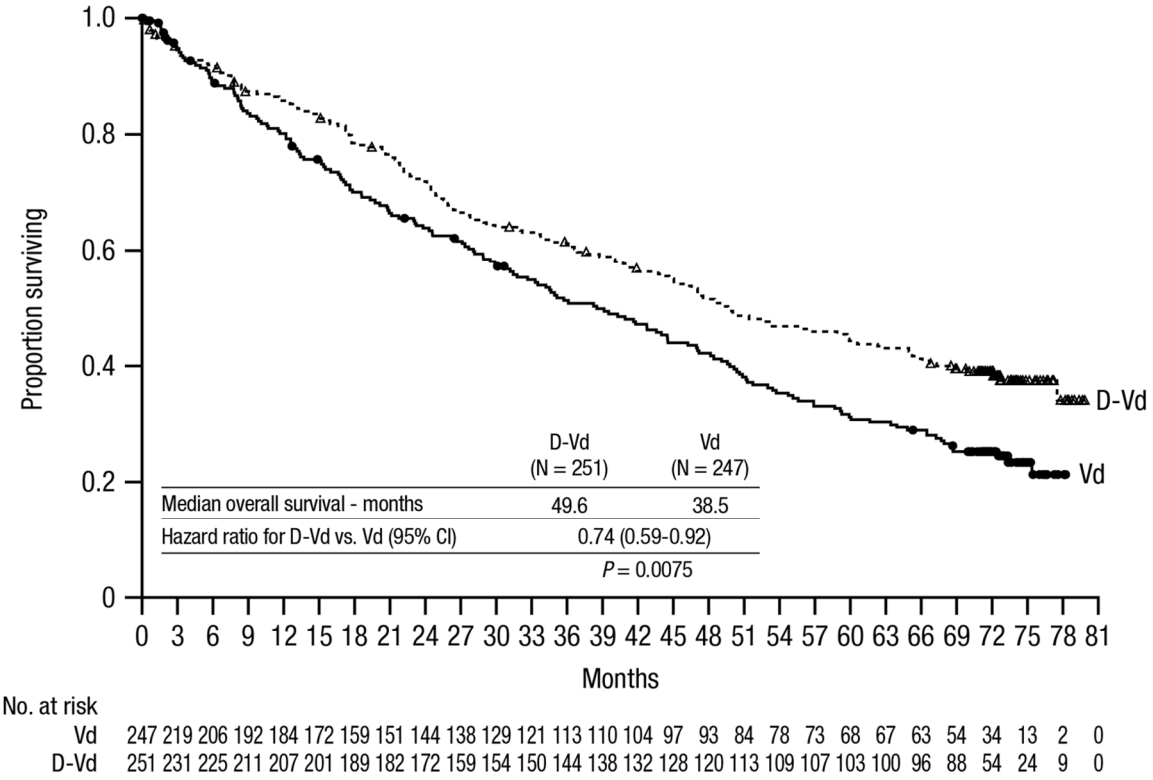
With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001). Results of 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 8).

Figure 8: Kaplan-Meier curve of PFS in study MMY3004



After a median follow-up of 73 months, DVd has shown an OS advantage over the Vd arm (HR=0.74; 95% CI: 0.59, 0.92; p=0.0075). The median OS was 49.6 months in the DVd arm and 38.5 months in the Vd arm.

Figure 9: Kaplan-Meier curve of OS in study MMY3004



Additional efficacy results from study MMY3004 are presented in table 12 below.

Table 12: 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.

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

The pharmacokinetics (PK) of daratumumab following intravenous administration of daratumumab monotherapy were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg.

In the 1 to 24 mg/kg cohorts, peak serum concentrations (C_{max}) after the first dose increased in approximate proportion to dose and volume of distribution was consistent with initial distribution into the plasma compartment. Following the last weekly infusion, C_{max} increased in a greater than dose-proportional manner, consistent with target mediated drug disposition. Increases in AUC were more than dose-proportional and clearance (CL) decreased with increasing dose. These observations suggest CD38 may become saturated at higher doses, after which the impact of target binding clearance is minimised and the clearance of daratumumab approximates the linear clearance of endogenous IgG1. Clearance also decreased with multiple doses, which may be related to tumour burden decreases.

Terminal half-life increases with increasing dose and with repeated dosing. The mean (standard deviation [SD]) estimated terminal half-life of daratumumab following the first 16 mg/kg dose was 9 (4.3) days. The estimated terminal half-life of daratumumab following the last 16 mg/kg dose increased, but there are insufficient data for a reliable estimation. Based on population PK analysis, the mean (SD) half-life associated with non-specific linear elimination was approximately 18 (9) days; this is the terminal half-life that can be expected upon complete saturation of target mediated clearance and repeat dosing of daratumumab.

At the end of weekly dosing for the recommended monotherapy schedule and dose of 16 mg/kg, the mean (SD) serum C_{max} value was 915 (410.3) micrograms/mL, approximately 2.9-fold higher than following the first infusion. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (331.5) micrograms/mL.

Four population PK analyses were performed to describe the PK characteristics of daratumumab and to evaluate the influence of covariates on the disposition of daratumumab in patients with multiple myeloma; analysis 1 (n=223) in patients receiving DARZALEX monotherapy while analysis 2 (n=694), analysis 3 (n=352) and analysis 4 (n=355) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Analysis 2 included 694 patients (n=326 for lenalidomide-dexamethasone; n=246 for bortezomib-dexamethasone; n=99 for pomalidomide-dexamethasone; n=11 for bortezomib-melphalan-prednisone; and n=12 for bortezomib-thalidomide-dexamethasone), analysis 3 included 352 patients (bortezomib-melphalan-prednisone) and analysis 4 included 355 patients (lenalidomide-dexamethasone).

Based on the population PK analysis of daratumumab monotherapy (analysis 1), daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean (SD) ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 (0.5). The mean (SD) central volume of distribution is 56.98 (18.07) mL/kg.

Three additional population PK analyses (analysis 2, analysis 3 and analysis 4) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Daratumumab concentration-time profiles were similar following the monotherapy and combination therapies. The

mean estimated terminal half-life associated with linear clearance in combination therapy was approximately 15-23 days.

Based on the four population PK analyses (analyses 1-4) body weight was identified as a statistically significant covariate for daratumumab clearance. Therefore, body weight based dosing is an appropriate dosing strategy for the multiple myeloma patients.

Simulation of daratumumab pharmacokinetics was conducted for all recommended dosing schedules in 1309 patients with multiple myeloma. The simulation results confirmed that the split and single dosing for the first dose provide similar PK, with the exception of the PK profile in the first day of the treatment.

Special populations

Age and gender
Based on four individual population PK analyses (1-4) in patients receiving daratumumab monotherapy or various combination therapies (analyses 1-4), age (range: 31-93 years) had no clinically important effect on the PK of daratumumab, and the exposure of daratumumab was similar between younger (aged < 65 years, n=518) and older (aged ≥ 65 to < 75 years n=761; aged ≥ 75 years, n=334) patients.

Gender did not affect exposure of daratumumab to a clinically relevant degree in the population PK analyses.

Renal impairment
No formal studies of daratumumab in patients with renal impairment have been conducted. Four individual population PK analyses were performed based on pre-existing renal function data in patients receiving daratumumab monotherapy, or various combination therapies (Analyses 1-4), and included a total of 441 patients with normal renal function (creatinine clearance [CRCL] ≥ 90 mL/min), 621 with mild renal impairment (CRCL < 90 and ≥ 60 mL/min), 523 with moderate renal impairment (CRCL < 60 and ≥ 30 mL/min), and 27 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 daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolised through hepatic pathways.
Four individual population PK analyses were performed in patients receiving daratumumab monotherapy or various combination therapies (Analyses 1-4), and included a total of 1404 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN]), 189 with mild hepatic impairment (TB 1.0 x to 1.5 x ULN or AST > ULN) and 8 patients with moderate (TB > 1.5 x to 3.0 x ULN; n=7), or severe (TB > 3.0 x ULN; n=1) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function.

Race
Based on four individual population PK analyses in patients receiving either daratumumab monotherapy or various combination therapies (analyses 1-4), the exposure to daratumumab was similar between white (n=1371) and non-white subjects (n=242).

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.

Carcinogenicity and mutagenicity

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

Reproductive toxicology

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

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

L-histidine
L-histidine hydrochloride monohydrate
L-methionine
Polysorbate 20 (E432)
Sorbitol (E420)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

3 years.

After dilution

From a microbiological point of view, unless the method of opening/ dilution 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 and should be no more than 24 hours at refrigerated conditions (2 °C-8 °C) protected from light, followed by 15 hours (including infusion time) at room temperature (15 °C-25 °C) and room light. If stored in the refrigerator, allow the solution to reach ambient temperature before administration.

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 after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 mL concentrate in a type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 100 mg of daratumumab. Pack size of 1 vial.

20 mL concentrate in a type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 400 mg of daratumumab. Pack size of 1 vial.

DARZALEX is also supplied as an initiation pack containing 11 vials: (6 x 5 mL vials + 5 x 20 mL vials).

6.6 Special precautions for disposal and other handling

This medicinal product is for single-use only.
Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colourless to yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Using aseptic technique, remove a volume of sodium chloride 9 mg/mL (0.9%) solution for injection from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing sodium chloride 9 mg/mL (0.9%) solution for injection (see section 4.2). Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Visually inspect parenteral medicinal products for particulate matter and discolouration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15 °C-25 °C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2 °C-8 °C) and protected from light. Do not freeze. If stored in the refrigerator, allow the solution to reach ambient temperature before administration.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused 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/1/16/1101/001
EU/1/16/1101/002
EU/1/16/1101/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2016
Date of latest renewal: 06 January 2022

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 1800 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mL vial of solution for injection contains 1800 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) using recombinant DNA technology.

Excipient 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, with a pH of 5.6 and osmolality of 343 to 395 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma

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, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma.
- 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.
- 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 were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor 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.

Smouldering multiple myeloma

DARZALEX as monotherapy is indicated for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma (see section 5.1).

Light chain (AL) amyloidosis

DARZALEX is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.

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.

The first 4 doses of DARZALEX should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.

DARZALEX is intended for use under the guidance of a healthcare professional. After receiving proper training in product preparation and subcutaneous injection technique, a patient or a patient's caregiver may administer the subsequent doses of DARZALEX after the initial 4 doses, if a healthcare professional determines that it is appropriate and with medical follow-up, as necessary. Patients should be instructed to contact their healthcare professional if there are any symptoms from subcutaneous injection or illness.

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

Multiple myeloma
Dosing schedule in combination with lenalidomide and dexamethasone or pomalidomide and dexamethasone (4-week cycle regimen) and for monotherapy

The recommended dose is 1800 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 and dexamethasone (Rd), pomalidomide and dexamethasone (Pd) (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.

Dexamethasone should be administered at 40 mg/week (or a reduced dose of 20 mg/week for patients > 75 years).

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 1800 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 1800 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.

Dexamethasone should be 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 should be administered on days 1, 2, 8, 9, 15, 16 in cycles 5 and 6.

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, lenalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)

The recommended dose is 1800 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, lenalidomide and dexamethasone ([VRd]; 4-week cycle dosing regimen)

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

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

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

[c] DARZALEX can be discontinued for patients who have achieved MRD negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months.

Dexamethasone should be administered at 40 mg on days 1-4 and days 9-12 of each 28-day cycle during induction and consolidation (cycles 1-6).

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, lenalidomide and dexamethasone (3-week cycle regimens) for treatment of newly diagnosed patients who are ineligible for ASCT

The recommended dose is 1800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 5.

Table 5: DARZALEX dosing schedule in combination with bortezomib, lenalidomide and dexamethasone ([VRd]; 3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 24[a]	every three weeks (total of 6 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 7.

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

Dexamethasone should be administered at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle of cycles 1-8. For patients > 75 years or underweight (BMI < 18.5), dexamethasone may be administered at 20 mg on days 1, 4, 8, and 11.

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 and dexamethasone (3-week cycle regimen)

The recommended dose is 1800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 6.

Table 6: DARZALEX dosing schedule in combination with bortezomib and dexamethasone (Vd) (3-week cycle dosing regimen)

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

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

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

Dexamethasone should be administered at 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 of the first 8 bortezomib treatment cycles or a reduced dose of 20 mg/week for patients > 75 years, underweight (BMI < 18.5), poorly controlled diabetes mellitus or prior intolerance to steroid therapy.

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.

Smouldering multiple myeloma
Dosing schedule for monotherapy (4-week cycle dosing regimen)

The recommended dose is 1800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 7.

Table 7: DARZALEX dosing schedule for smouldering multiple myeloma monotherapy (4-week cycle dosing regimen)[a]

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Weeks 25 onwards until disease progression or a maximum of 3 years[b]	every four weeks

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

AL amyloidosis
Dosing schedule in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle regimens)

The recommended dose is 1800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 8.

Table 8: DARZALEX 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 study, DARZALEX 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 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 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).
- Leukotriene inhibitor (oral montelukast 10 mg or equivalent) is recommended on cycle 1 day 1 for smouldering multiple myeloma patients.

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 dose 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 dose 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.

Body weight (> 120 kg)
Limited number of patients with body weight > 120 kg have been studied using flat-dose (1800 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. Use proper technique when withdrawing DARZALEX from the vial. To reduce the incidence of stopper coring, avoid the use of large diameter or blunt tip transfer needles or multiple stopper punctures. 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 name 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 8.5% (134/1573) 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 1% of patients (see section 4.8).

The median time to onset of IRRs following DARZALEX injection was 3.3 hours (range 0.08-83 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, pruritus, chills, vomiting, nausea, hypotension and blurred vision. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, tachycardia and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma) (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. For patients with smouldering multiple myeloma, pre-medication with leukotriene inhibitors on cycle 1 day 1 should be considered. 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. If ocular symptoms occur, interrupt DARZALEX and seek immediate ophthalmologic evaluation prior to restarting DARZALEX (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.

Infections

DARZALEX can cause serious, life-threatening, or fatal infections (see section 4.8).

Patients should be closely monitored for signs and symptoms of infection prior to and during treatment with DARZALEX and treated appropriately. Prophylactic antimicrobials according to treatment guidelines should be considered prior to, during or post-treatment (see section 4.2).

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 hereditary fructose intolerance (HFI) should not be given this medicinal product.

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 intravenous or subcutaneous formulations and lenalidomide, pomalidomide, thalidomide, bortezomib, melphalan, prednisone, carfilzomib, cyclophosphamide 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 or limited amount of data from the use of daratumumab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). DARZALEX is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether daratumumab is excreted in human milk.
A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from 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 neuropathy, upper respiratory tract infection, musculoskeletal pain and COVID-19. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea, atrial fibrillation and syncope.

The safety profile of the DARZALEX subcutaneous formulation was similar to that of intravenous formulation with the exception of a lower rate of IRRs. In the phase III study MMY3012, neutropenia was 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 9 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 (1800 mg) in 1187 patients with multiple myeloma (MM). The data includes 260 patients from a phase III active-controlled study (MMY3012) who received DARZALEX solution for subcutaneous injection as monotherapy, 149 patients from a phase III active-controlled study (MMY3013) who received DARZALEX subcutaneous formulation in combination with pomalidomide and dexamethasone (D-Pd), 351 patients from a phase III active-controlled study (MMY3014) who received DARZALEX subcutaneous formulation in combination with bortezomib, lenalidomide and dexamethasone (D-VRd), and 197 newly diagnosed multiple myeloma patients for whom transplant was not planned as initial therapy or who were ineligible for transplant from a phase III active-controlled study (MMY3019) who received DARZALEX subcutaneous formulation in combination with bortezomib, lenalidomide and dexamethasone (D-VRd). The data also reflects 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). Data reflect exposure to 193 patients with smouldering multiple myeloma at high risk of developing multiple myeloma from a phase III randomised study (SMM3001) in which patients received DARZALEX subcutaneous fomulation as monotherapy. Additionally, data reflect exposure to 193 patients with newly diagnosed AL amyloidosis from a phase III active-controlled study (AMY3001) in which patients received DARZALEX subcutaneous formulation in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd).

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 (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).

Table 9: Adverse reactions in multiple myeloma, including smouldering multiple myeloma at high risk of developing multiple myeloma, and AL amyloidosis 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	46	3
	COVID-19[a,g]		23	6
	Pneumonia[a]		19	11
	Bronchitis[a]		14	1
	Urinary tract infection	Common	7	1
	Sepsis[a]		4	4
	Cytomegalovirus infection[a]	Uncommon	< 1	< 1[#]
	Hepatitis B Virus reactivation[a]		< 1	< 1
Blood and lymphatic system disorders	Neutropenia[a]	Very common	42	36
	Thrombocytopenia[a]		30	18
	Anaemia[a]		26	11
	Lymphopenia[a]		12	10
	Leukopenia[a]		11	6
Immune system disorders	Hypogammaglobulinaemia[a]	Common	3	< 1[#]
	Anaphylactic reaction[b]	Rare	-	-
Metabolism and nutrition disorders	Hypokalaemia[a]	Very common	10	3
	Decreased appetite		10	< 1
	Hyperglycaemia	Common	6	3
	Hypocalcaemia		6	1
	Dehydration		2	1[#]
Psychiatric disorders	Insomnia	Very common	17	1[#]
Nervous system disorders	Peripheral neuropathy	Very common	31	4
	Headache		11	< 1[#]
	Dizziness	Common	9	< 1[#]
	Paraesthesia		9	< 1
	Syncope		3	2[#]
Cardiac disorders	Atrial fibrillation	Common	4	1
Vascular disorders	Hypertension[a]	Common	9	4
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	22	< 1[#]
	Dyspnoea[a]		18	2
	Pulmonary oedema[a]	Common	1	< 1
Gastrointestinal disorders	Diarrhoea	Very common	33	5
	Constipation		28	1
	Nausea		22	1[#]
	Abdominal pain[a]		14	1
	Vomiting		13	1[#]
	Pancreatitis[a]	Common	1	< 1
Skin and subcutaneous tissue disorders	Rash	Very common	12	1[#]
	Pruritus	Common	6	< 1[#]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[a,h]	Very common	35	3
	Arthralgia		14	1
	Muscle spasms		12	< 1[#]

General disorders and administration site conditions	Fatigue	Very common	24	4
	Oedema peripheral[a]		24	1
	Pyrexia		22	1
	Asthenia		19	2
	Injection site reactions[d,e]		10	0
	Chills	Common	8	< 1[#]
Injury, poisoning and procedural complications	Infusion-related reactions[c]			
	Daratumumab intravenous[f]	Very common	39	5
	Daratumumab subcutaneous[e]	Common	9	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=1573).

[f] Frequency based on daratumumab intravenous studies only (N=2324).

[g] Incidence is based on a subset of patients who received at least one dose of study treatment on or after 01 February 2020 (the start of the COVID-19 pandemic) from studies MMY3003, MMY3006, MMY3008 and MMY3013, and all daratumumab treated patients from studies MMY3014, MMY3019, and SMM3001 (N=1177).

[h] Musculoskeletal pain includes back pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.

Note: Based on 3897 multiple myeloma and AL amyloidosis 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=1573) with DARZALEX subcutaneous formulation, the incidence of any grade IRRs was 7.5% with the first injection of DARZALEX (1800 mg, week 1), 0.5% with the week 2 injection, and 1.3% with subsequent injections. Grades 3 and 4 IRRs were seen in 0.8% and 0.1% of patients, respectively.

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, pruritus, chills, vomiting, nausea, blurred vision and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, tachycardia and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma) (see section 4.4).

Injection site reactions (ISRs)
In clinical studies (N=1573) with DARZALEX subcutaneous formulation, the incidence of any grade injection site reaction was 10.2%. There were no grade 3 or 4 ISRs. The most common (> 1%) ISR at the site of injection was erythema and rash.

Infections
In patients with multiple myeloma receiving daratumumab as monotherapy, the overall incidence of infections was similar between DARZALEX subcutaneous formulation (52.9%) *versus* intravenous daratumumab groups (50.0%). 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 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 were reported:
Grade 3 or 4 infections:
Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%; DPd: 28%
Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.
Grade 5 (fatal) infections:
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%.

In patients with multiple myeloma receiving DARZALEX subcutaneous formulation combination therapy, the following were reported:
Grade 3 or 4 infections: DPd: 28%, Pd: 23%; D-VRd (transplant eligible): 35%, VRd (transplant eligible): 27%; D-VRd (transplant ineligible): 40%, VRd (transplant ineligible): 32%
Grade 5 (fatal) infections: DPd: 5%, Pd: 3%; D-VRd (transplant eligible): 2%, VRd (transplant eligible): 3%; D-VRd (transplant ineligible): 8%, VRd (transplant ineligible): 6%
Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone; VRd=bortezomib-lenalidomide-dexamethasone.

In patients with smouldering multiple myeloma at high risk of developing multiple myeloma receiving DARZALEX subcutaneous formulation monotherapy, the following were reported:
Grade 3 or 4 infections: DARZALEX subcutaneous formulation: 16%
Grade 5 infections: DARZALEX subcutaneous formulation: 1%

In patients with AL amyloidosis receiving DARZALEX subcutaneous formulation combination therapy, the following were reported:
Grade 3 or 4 infections: D-VCd: 17%, VCd: 10%
Grade 5 infections: D-VCd: 1%, VCd: 1%
Key: D=daratumumab; VCd=bortezomib-cyclophosphamide-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.

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.

<u>Other special populations</u>

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 4553 patients who received daratumumab (n=1615 subcutaneous; n=2938 intravenous) at the recommended dose, 38% were 65 to less than 75 years of age, and 15% 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=1976), 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 were 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 multiple myeloma who were eligible for autologous stem cell transplant (n=351), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia. Among patients with newly diagnosed multiple myeloma for whom transplant was not planned as initial therapy or who were ineligible for autologous stem cell transplant (n=197), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia. Among patients with smouldering multiple myeloma at high risk of developing multiple myeloma (n=193), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 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 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 reactions and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FC01.

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 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 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 multiple myeloma, including smouldering multiple myeloma at high risk of developing into multiple myeloma, and AL amyloidosis patients treated with subcutaneous daratumumab in monotherapy and combination clinical studies, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies and 8 patients tested positive for neutralising antibodies.

In multiple myeloma, including smouldering multiple myeloma at high risk of developing into multiple myeloma, and AL amyloidosis patients, the incidence of treatment-emergent anti-rHuPH20 antibodies was 8.9% (133/1491) in patients who received either monotherapy DARZALEX subcutaneous formulation or combination DARZALEX subcutaneous formulation and 1 patient tested positive for neutralising antibodies. 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 (1800 mg) *vs*. intravenous (16 mg/kg) daratumumab in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent

(IMiD) or who were double-refractory to a PI and an 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 10) and maximum C_{trough} at pre-dose cycle 3 day 1, (see section 5.2).

Table 10: 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.

After a median follow-up of 29.3 months, the median OS was 28.2 months (95% CI: 22.8, NE) in the DARZALEX subcutaneous formulation arm and was 25.6 months (95% CI: 22.1, NE) in the intravenous daratumumab arm.

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

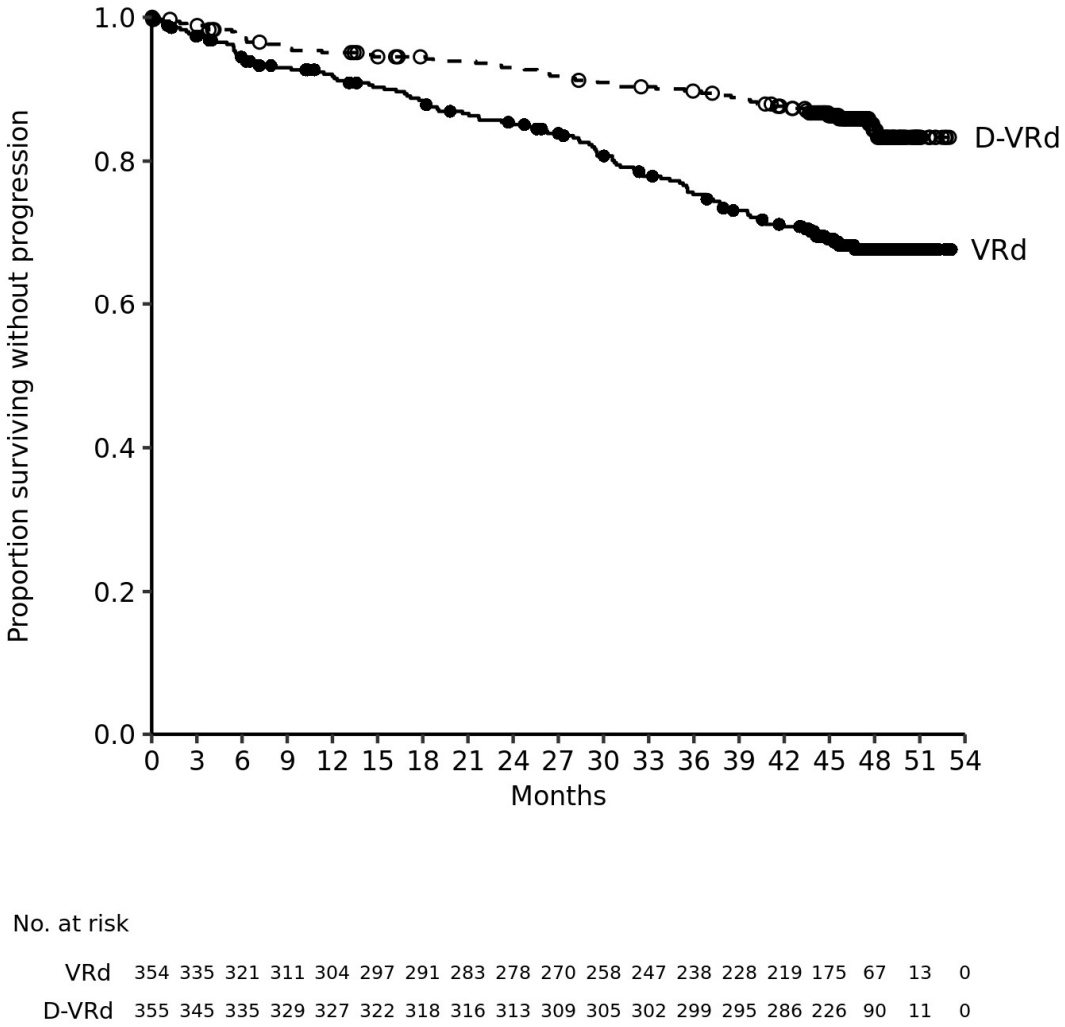
Combination treatment with bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma eligible for autologous stem cell transplant (ASCT)
Study MMY3014 was an open-label, randomised, active-controlled phase III study that compared induction and consolidation treatment with DARZALEX subcutaneous formulation (1800 mg) in combination with bortezomib, lenalidomide and dexamethasone (D-VRd), followed by maintenance with DARZALEX in combination with lenalidomide, to treatment with bortezomib, lenalidomide and dexamethasone (VRd), followed by maintenance with lenalidomide, in patients 70 years of age and younger with newly diagnosed multiple myeloma eligible for ASCT until documented disease

progression or unacceptable toxicity. An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) was permitted before treatment. Patients received DARZALEX subcutaneous formulation (1800 mg) administered subcutaneously once weekly (days 1, 8, 15, and 22) for cycles 1-2 followed by once every two weeks (days 1 and 15) for cycles 3-6. For maintenance (cycles 7+), patients received DARZALEX subcutaneous formulation (1800 mg) once every four weeks. Patients who achieved MRD negativity that was sustained for 12 months and had been treated on maintenance for at least 24 months discontinued treatment with DARZALEX subcutaneous formulation (1800 mg). Bortezomib was administered by subcutaneous (SC) 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) cycles 1-6. Lenalidomide was administered orally at 25 mg daily on days 1 to 21 during cycles 1-6. For maintenance (cycles 7+), patients received 10 mg lenalidomide daily on days 1-28 (continuously) of each cycle until documented disease progression or unacceptable toxicity. Dexamethasone (oral or intravenous) was administered at 40 mg on days 1-4 and days 9-12 of cycles 1-6. On the days of DARZALEX subcutaneous formulation (1800 mg) injection, the dexamethasone dose was administered orally or intravenously as a pre-injection medicinal product. Dose adjustments for bortezomib, lenalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 709 patients were randomised: 355 to the D-VRd arm and 354 to the VRd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 60 (range: 31 to 70 years). The majority were male (59%), 64% had an ECOG performance score of 0, 31% had an ECOG performance score of 1 and 5% had an ECOG performance score of 2. Additionally, 51% had ISS stage I, 34% had ISS stage II, 15% had ISS stage III disease, 75% had a standard cytogenetic risk, 22% had a high cytogenetic risk (del17p, t[4;14], t[14;16]), and 3% had an indeterminate cytogenetic risk.

With a median follow-up of 47.5 months, the primary analysis of PFS in study MMY3014 demonstrated an improvement in PFS in the D-VRd arm as compared to the VRd arm (HR=0.42; 95% CI: 0.30, 0.59; $p<0.0001$). The median PFS was not reached in either arm.

Figure 1: Kaplan-Meier curve of PFS in study MMY3014



Additional efficacy results from study MMY3014 are presented in table 11 below.

Table 11: Efficacy results from study MMY3014[a]

	D-VRd (n=355)	**VRd (n=354)**	**Odds ratio (95% CI)[d]**
Overall response (sCR+CR+VGPR+PR) n(%)[a]	343 (96.6%)	332 (93.8%)	
Stringent complete response (sCR)	246 (69.3%)	158 (44.6%)	
Complete response (CR)	66 (18.6%)	90 (25.4%)	
Very good partial response (VGPR)	26 (7.3%)	68 (19.2%)	
Partial response (PR)	5 (1.4%)	16 (4.5%)	
CR or better (sCR+CR)	312 (87.9%)	248 (70.1%)	3.13 (2.11, 4.65)
95% CI (%)	(84.0%, 91.1%)	(65.0%, 74.8%)	
P-value[b]			< 0.0001
Overall MRD negativity rate[a,c]	267 (75.2%)	168 (47.5%)	3.40 (2.47, 4.69)
95% CI (%)	(70.4%, 79.6%)	(42.2%, 52.8%)	
P-value[b]			< 0.0001

D-VRd=daratumumab-bortezomib-lenalidomide-dexamethasone; VRd=bortezomib-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] Patients achieved both MRD negativity (threshold of 10^{-5}) and CR or better

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

Combination treatment with bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma for whom ASCT is not planned as initial therapy or who are ineligible for ASCT

Study MMY3019 was an open-label, randomised, active-controlled phase III study that compared treatment with DARZALEX subcutaneous formulation (1800 mg) in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) to treatment with bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma for whom ASCT was not planned as initial therapy or who were not eligible for ASCT. An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) was permitted before treatment. Patients received DARZALEX subcutaneous formulation (1800 mg) administered subcutaneously once weekly (days 1, 8, and 15) for cycles 1 to 2 followed by once every three weeks for cycles 3 to 8, and once every four weeks in cycle 9 and beyond until documented disease progression or unacceptable toxicity. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m^2 body surface area twice weekly (days 1, 4, 8, and 11) of repeated 21-day (3-week) cycles 1-8. Lenalidomide was administered orally at 25 mg daily on days 1 to 14 during cycles 1-8 and on days 1-21 during cycle 9 and beyond. Dexamethasone was administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day (3-week) cycles 1-8 and days 1, 8, 15, and 22 of each 28-day (4-week) during cycle 9 and beyond. On the days of DARZALEX subcutaneous formulation (1800 mg) injection, the dexamethasone dose was administered orally or intravenously as a pre-injection medication. Dose adjustments for bortezomib, lenalidomide and dexamethasone were applied according to manufacturer's prescribing information.

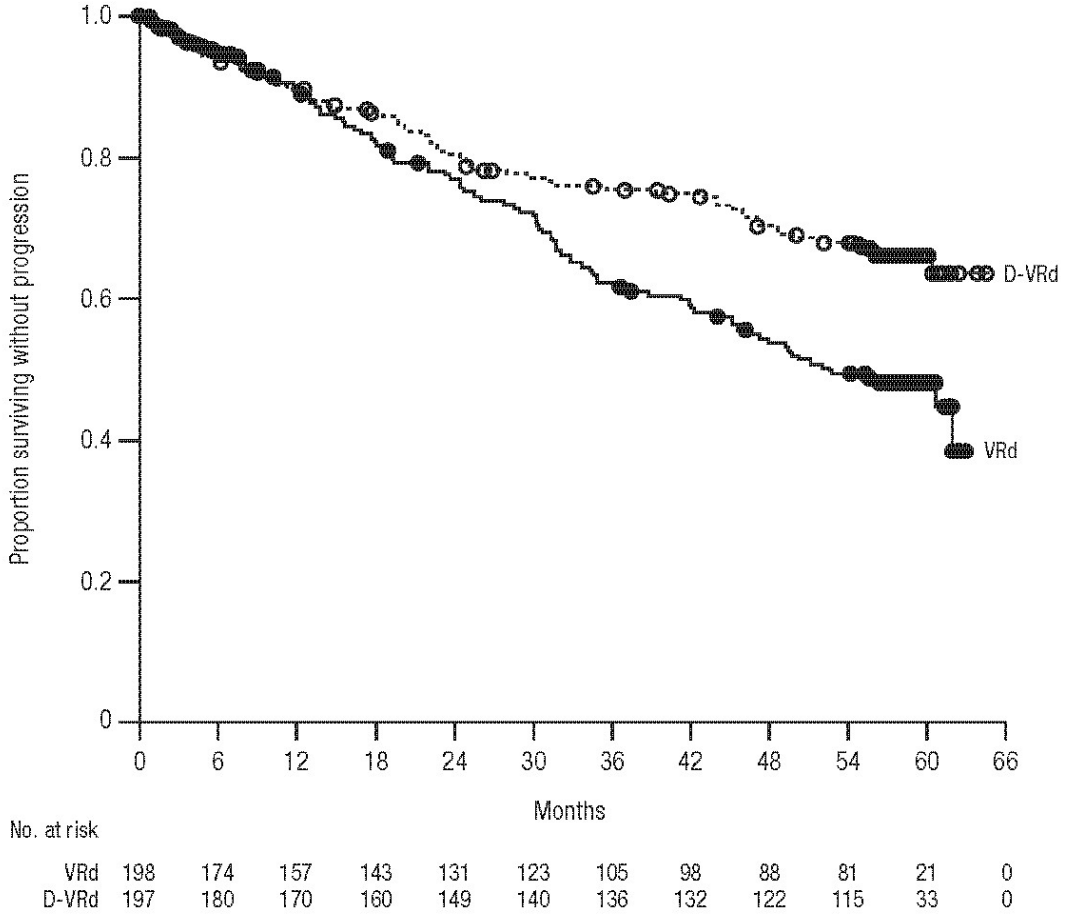
A total of 395 patients were randomised: 197 to the D-VRd arm and 198 to the VRd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 70 (range: 31 to 80 years). Fifty percent were male, 39% had an ECOG performance score of 0, 51% had an ECOG performance score of 1 and 9% had an ECOG performance score of 2. Eighteen percent were less than 70 years of age and transplant ineligible and 27% were less than 70 years of age and were transplant deferred. Additionally, 34% had ISS stage I, 38% had ISS stage II, 28% had ISS stage III disease, 75% had a standard cytogenetic risk, 13% had a high cytogenetic risk (del17p, t[4;14], t[14;16]), and 11% had an indeterminate cytogenetic risk.

With a median follow-up of 22.3 months, the primary analysis of MRD in study MMY3019 demonstrated an improvement in overall MRD negativity rate (by NGS at or below 10^{-5}) for patients reaching CR or better in the D-VRd arm as compared to the VRd arm. Overall MRD negativity rates were 53.3% (95% CI: 46.1, 60.4) in the D-VRd arm and 35.4% (95% CI: 28.7, 42.4) in the VRd arm (odds ratio [D-VRd versus VRd] 2.07 with 95% CI: 1.38, 3.10; p=0.0004).

At the time of primary MRD analysis, an improvement in overall CR or better rate was observed in the D-VRd arm as compared to the VRd arm. Overall CR or better rates were 76.6% (95% CI: 70.1, 82.4) in the D-VRd arm and 59.1% (95% CI: 51.9, 66.0) in the VRd arm (odds ratio [D-VRd versus VRd] 2.31; 95% CI: 1.48, 3.60; p=0.0002).

With a median follow-up of 39 months, an interim analysis of PFS in Study MMY3019 demonstrated an improvement in PFS in the D-VRd arm as compared to the VRd arm (HR=0.61; 95% CI: 0.42, 0.90; p=0.0104). The median PFS had not been reached in either arm. With more mature PFS data at the final PFS analysis, treatment effect for PFS was improved with a hazard ratio of 0.57 (95% CI: 0.41, 0.79). The median PFS had not been reached in the D-VRd arm and was 52.6 months in the VRd arm.

Figure 2: Kaplan-Meier curve of PFS at final analysis in study MMY3019



At the time of interim PFS analysis, an improvement in 1-year sustained MRD negativity rate (by NGS at or below 10^{-5}) for patients reaching CR or better was observed in the D-VRd arm as compared to the VRd arm. Sustained MRD negativity rates were 42.6% (95% CI: 35.6, 49.9) in the D-VRd arm and 25.3% (95% CI: 19.4, 31.9) in the VRd arm (odds ratio [D-VRd versus VRd] 2.18 with 95% CI: 1.42, 3.34; p=0.0003).

Additional efficacy results from Study MMY3019 are presented in table 12 below.

Table 12: Efficacy results from the final PFS analysis of study MMY3019[a]

	D-VRd (n=197)	**VRd (n=198)**
Overall MRD negativity rate[b]	120 (60.9%)	78 (39.4%)
Odds ratio (95% CI)[c]	2.37 (1.58, 3.55)	
Sustained MRD negativity rate[d]	96 (48.7%)	52 (26.3%)
Odds ratio (95% CI)[c]	2.63 (1.73, 4.00)	
Overall CR or better (sCR+CR)	160 (81.2%)	122 (61.6%)
Odds ratio (95% CI)[c]	2.73 (1.71, 4.34)	
Overall response (sCR+CR+VGPR+PR) n (%)[a]	191 (97.0%)	184 (92.9%)
Stringent complete response (sCR)	128 (65.0%)	88 (44.4%)
Complete response (CR)	32 (16.2%)	34 (17.2%)
Very good partial response (VGPR)	23 (11.7%)	50 (25.3%)
Partial response (PR)	8 (4.1%)	12 (6.1%)

D-VRd=daratumumab-bortezomib-lenalidomide-dexamethasone; VRd=bortezomib-lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

[a] Based on intent-to-treat population, median follow-up of 59 months

[b] Patients achieved both MRD negativity (threshold of at or below 10^{-5}) and CR or better

[c] Mantel-Haenszel estimate of the common ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (< 70 years ineligible, or age< 70 years and refusal to transplant, or age ≥ 70 years) as randomised. An odds ratio > 1 indicates an advantage for D-VRd.

[d] Sustained MRD negativity is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between.

Combination therapies in multiple myeloma

MMY2040 was an open-label study evaluating the efficacy and safety of DARZALEX subcutaneous formulation 1800 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 enroled. 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 13).

Table 13: Efficacy results from study MMY2040

	D-VMP (n=67)	**D-Rd (n=65)**	**D-VRd (n=67)**
Overall response (sCR+CR+VGPR+PR), n (%)[a]	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=DARZALEX subcutaneous formulation; CI=confidence interval.

[a] Based on treated subjects.

Combination treatment with pomalidomide and dexamethasone (Pd)

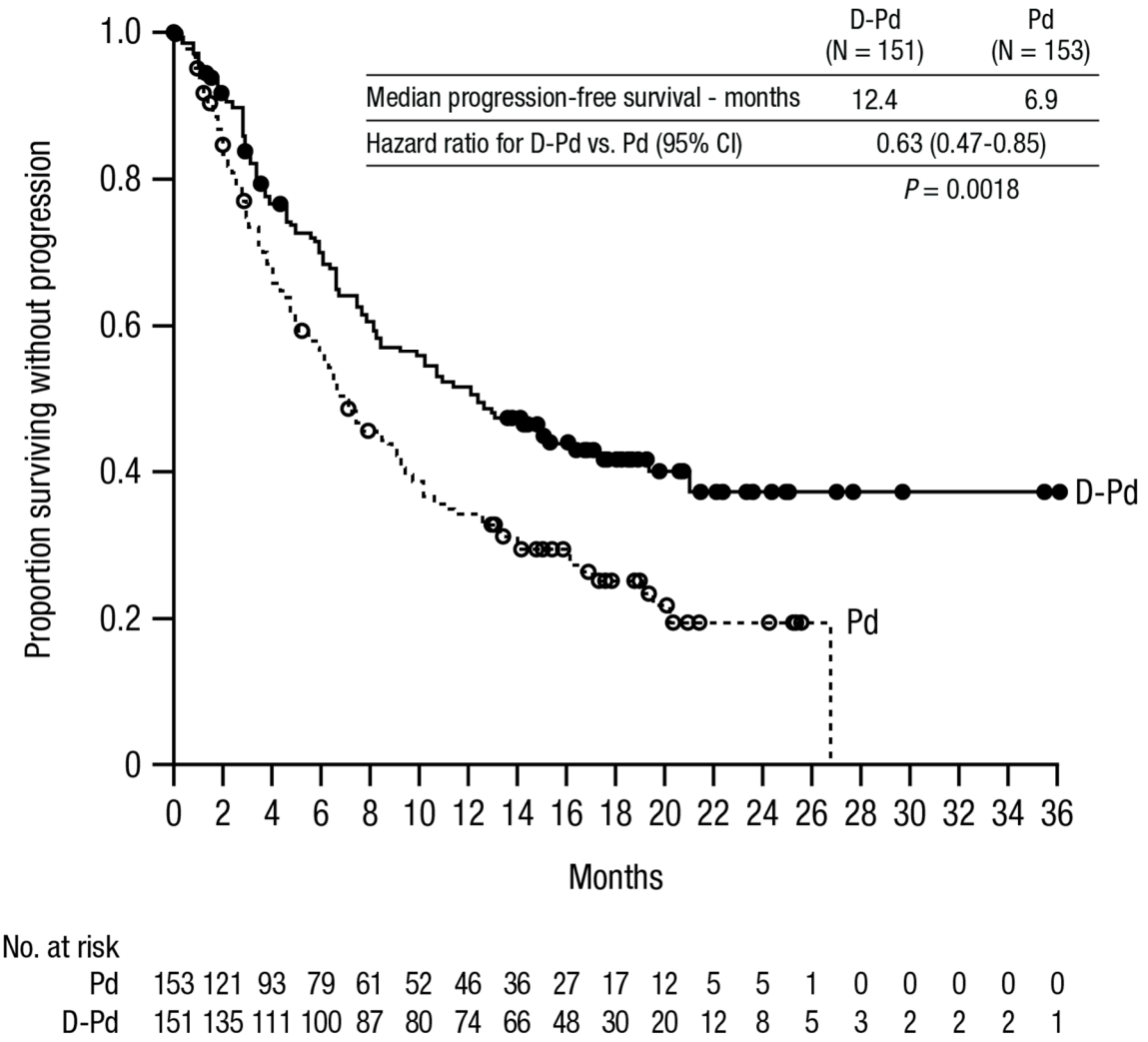
Study MMY3013 was an open-label, randomised, active-controlled phase III study that compared treatment with DARZALEX subcutaneous formulation (1800 mg) in combination with pomalidomide

and low-dose dexamethasone (D-Pd) to treatment with pomalidomide and low-dose dexamethasone (Pd) in patients with multiple myeloma who had received at least one prior line of therapy with lenalidomide and a proteasome 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 subcutaneous formulation administration days, 20 mg of the dexamethasone dose was given as a pre-administration medicinal product 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 subcutaneous formulation pre-administration medicinal product. 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. Patients with documented evidence of disease progression on or after the last regimen were included in the study. Patients who had ≥ grade 3 rash during prior therapy were excluded as per the pomalidomide Summary of Product Characteristics. 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. All patients received a prior treatment with a proteasome inhibitor (PI) and lenalidomide, and 56% of patients received prior stem cell transplantation (ASCT). Ninety-six percent (96%) of patients received prior treatment with bortezomib. The majority of patients were refractory to lenalidomide (80%), a PI (48%), or both an immunomodulator and a PI (42%). Eleven percent of patients received 1 prior line of therapy; all were refractory to lenalidomide and 32.4% were refractory to both lenalidomide and a PI. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

With a median follow-up of 16.9 months, the primary analysis of PFS in study MMY3013 showed 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.

Figure 3: Kaplan-Meier curve of PFS in study MMY3013



An additional planned follow-up analysis of OS after a median follow-up of 39.6 months was performed. At OS maturity of 57%, the median OS was 34.4 months in the D-Pd arm and 23.7 months in the Pd arm (HR [95% CI]: 0.82 [0.61, 1.11]).

Additional efficacy results from study MMY3013 are presented in table 14 below.

Table 14: 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.

Monotherapy – smouldering multiple myeloma at high risk of developing into multiple myeloma
SMM3001, an open-label, randomised, phase III study, compared efficacy and safety of treatment with DARZALEX subcutaneous formulation (1800 mg) to active monitoring in patients with smouldering multiple myeloma at high risk of developing multiple myeloma. For patients randomised to the treatment arm, DARZALEX subcutaneous formulation (1800 mg) was administered subcutaneously once weekly (days 1, 8, 15, and 22) for cycles 1 to 2 then every 2 weeks (days 1 and 15) for cycles 3 to 6, and thereafter every 4 weeks until 39 cycles or up to 36 months or until confirmed disease progression.

A total of 390 patients were randomised: 194 to the DARZALEX subcutaneous formulation arm and 196 to the active monitoring arm. The baseline demographic and disease characteristics were similar between the two study arms. The median patient age was 64 years (range: 31-86 years); 12% were ≥75 years; 48% were male; 83% Caucasian, 8% Asian, and 3% were African American. Eighty-three percent had an ECOG performance score of 0 and 17% had an ECOG performance score of 1. Median percentage of plasma cells in the bone marrow was 20% and the median time from initial diagnosis date of smouldering multiple myeloma to randomisation was 0.7 years. Eighty percent of patients had less than 3 risk factors associated with progression to multiple myeloma. Risk factors were serum M protein ≥30 g/L; IgA SMM; immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes; serum involved: uninvolved FLC ratio ≥8 and <100, clonal bone marrow plasma cells (BMPCs) >50% to <60% with measurable disease. To be eligible for enrolment in study SMM3001, patients were required to have at least one of these risk factors and BMPCs ≥10%. Nineteen percent of patients had a serum M protein ≥30 g/L, 25% had IgA SMM, 60% had immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, 72% had serum involved: uninvolved FLC ratio ≥8 and <100, and 3% clonal BMPCs >50% to <60% with measurable disease.

The primary endpoint of the study was PFS as assessed by the independent review committee (IRC). The Kaplan-Meier curve for PFS is shown in figure 4 and efficacy results from study SMM3001 are presented in table 15 below.

Figure 4: Kaplan-Meier curve of PFS in study SMM3001

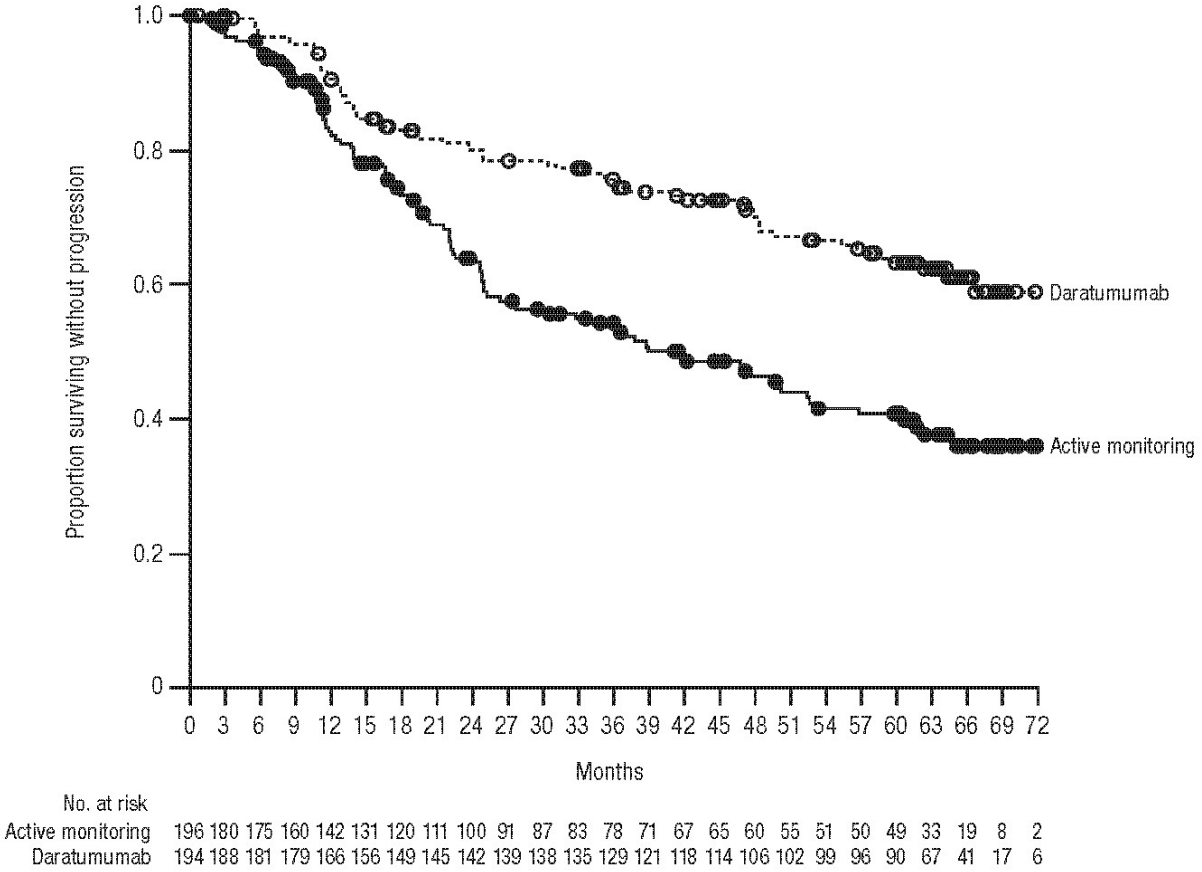


Table 15: Efficacy results from study SMM3001[a]

	DARZALEX subcutaneous formulation (n=194)	**Active monitoring (n=196)**	**Odds ratio (95% CI)[b]**
Progression-free survival (PFS), months[c]			
Median (95% CI)	NE (66.7-NE)	41.5 (26.4-53.3)	
Hazard ratio (95% CI)	0.49 (0.36, 0.67)		
P-value[d]	< 0.0001		
Overall response (sCR+CR+VGPR+PR), n(%)[a]	123 (63.4%)	4 (2.0%)	83.80 (29.69, 236.54), p<0.0001
Stringent Complete Response (sCR)	5 (2.6%)	0	
Complete response (CR)	12 (6.2%)	0	
Very good partial response (VGPR)	41 (21.1%)	2 (1.0%)	
Partial response (PR)	65 (33.5%)	2 (1.0%)	

CI=confidence interval; NE=not evaluable

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

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

[c] Median follow-up was 65.2 months.

[d] p-value based on the log-rank test stratified by the stratification factor.

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

Study AMY3001, an open-label, randomised, active-controlled phase III study, compared treatment with DARZALEX subcutaneous formulation (1800 mg) in combination with bortezomib,

cyclophosphamide and dexamethasone (D-VCd) to treatment with bortezomib, cyclophosphamide and dexamethasone (VCd) alone in patients with newly diagnosed systemic 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.

All patients enroled in study AMY3001 had newly diagnosed AL amyloidosis with at least one affected organ, measurable haematologic disease, cardiac stage I-IIIA (based on European Modification of Mayo 2004 cardiac stage), and NYHA class I-IIIA. Patients with NYHA class IIIB and IV were excluded.

Bortezomib (SC; 1.3 mg/m^2 body surface area), cyclophosphamide (oral or IV; 300 mg/m^2 body surface area; max dose 500 mg), and dexamethasone (oral or IV; 40 mg or a reduced dose of 20 mg for patients > 70 years or body mass index [BMI] < 18.5 or those who have hypervolaemia, 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 medicinal product 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. All patients had one or more affected organs and 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. Patients with grade 2 sensory or grade 1 painful peripheral neuropathy were excluded. The primary efficacy endpoint 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 16.

Table 16: 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%)	
Haematologic 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]

D-VCd=daratumumab-bortezomib-cyclophosphamide-dexamethasone; VCd=bortezomib-cyclophosphamide-dexamethasone; CI=confidence interval.

[a] All results from the planned analysis after a median follow-up of 11.4 months based on intent-to-treat population.

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

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

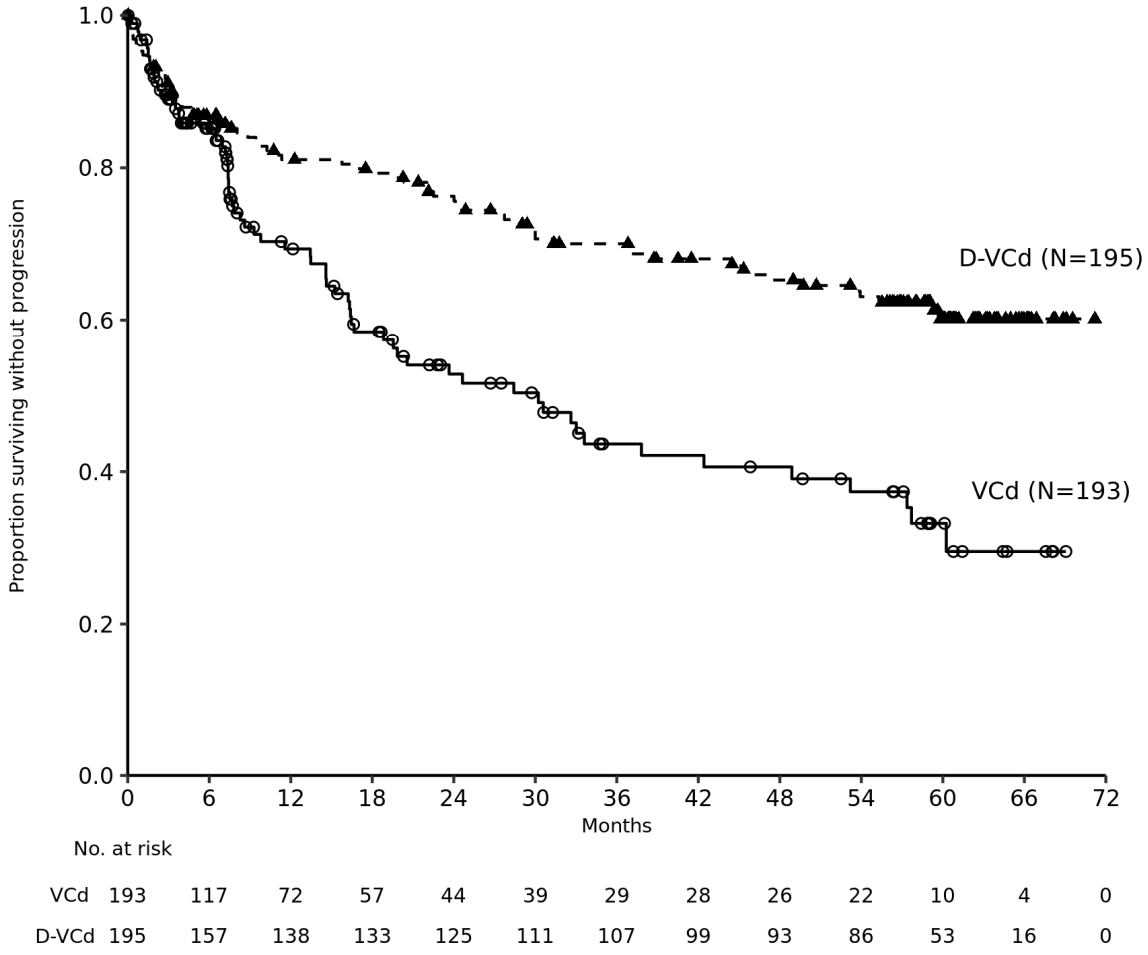
[d] Nominal p-value from inverse probability censoring weighted log-rank test.

With a median follow-up of 11.4 months, 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.

After a median follow-up of 61.4 months, the overall HemCR rates were 59.5% (95% CI: 52.2, 66.4) in the D-VCd group and 19.2% (95% CI: 13.9, 25.4) in the VCd group (odds ratio [D-VCd versus VCd] 6.03 with 95% CI: 3.80, 9.58).

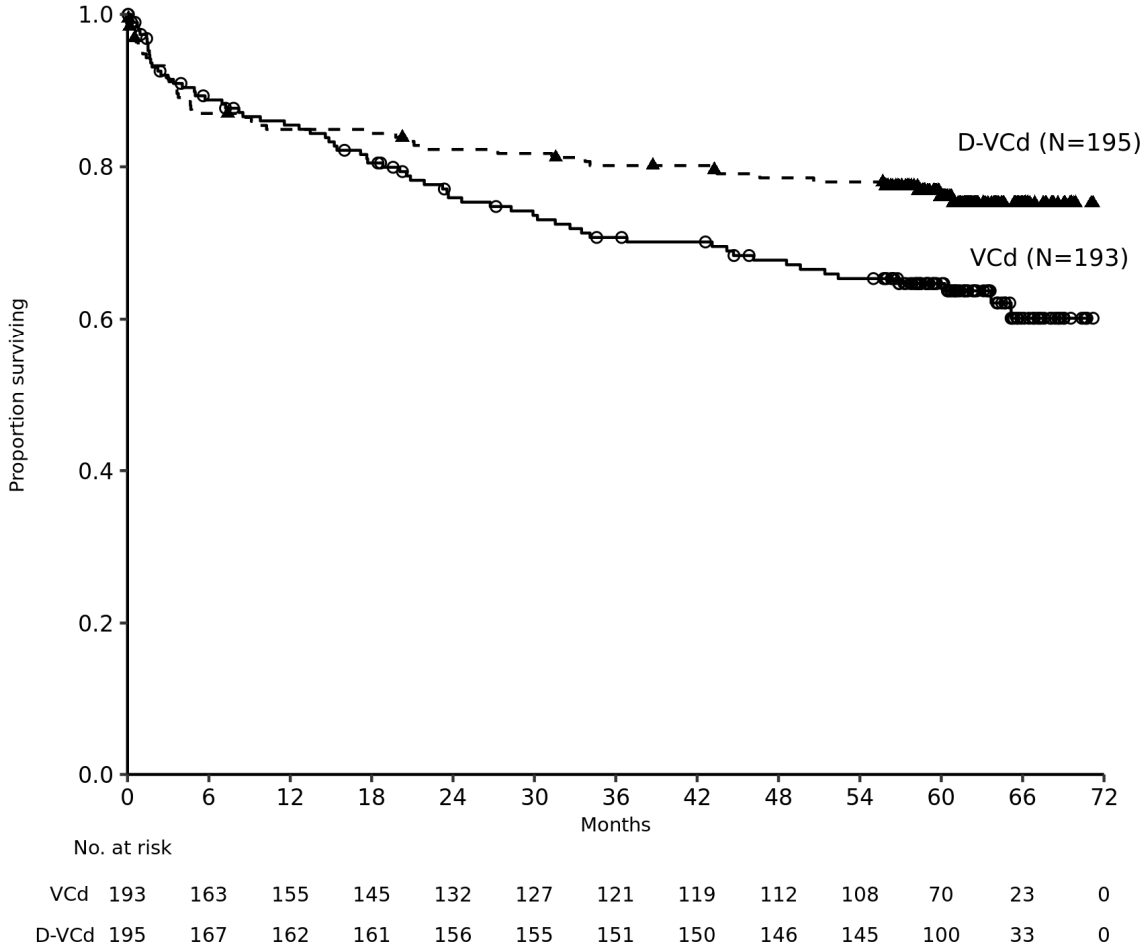
Results of a MOD-PFS analysis after a median follow-up of 61.4 months showed an improvement in MOD-PFS for patients in the D-VCd group compared with the VCd group. The hazard ratio (HR) for MOD-PFS was 0.44 (95% CI: 0.31, 0.63) and the p-value was <0.0001. The median MOD-PFS was not reached in the D-VCd arm and was 30.2 months in the VCd arm. The Kaplan-Meier estimated 60-month MOD-PFS rate was 60% (95% CI: 52, 67) in the D-VCd arm and was 33% (95% CI: 23, 44) in the VCd arm.

Figure 5: Kaplan-Meier curve of MOD-PFS in study AMY3001



After a median follow-up of 61.4 months, a total of 112 deaths were observed [n=46 (23.6%) D-VCd *vs*. n=66 (34.2%) VCd group]. The median OS was not reached for either arm; however, the HR for OS was 0.62 (95% CI: 0.42, 0.90) and the p-value was 0.0121. The 60-month OS rate was 76% (95% CI: 69, 82) in the D-VCd arm and was 65% (95% CI: 57, 71) in the VCd arm.

Figure 6: Kaplan-Meier curve of OS in study AMY3001



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

Newly diagnosed multiple myeloma

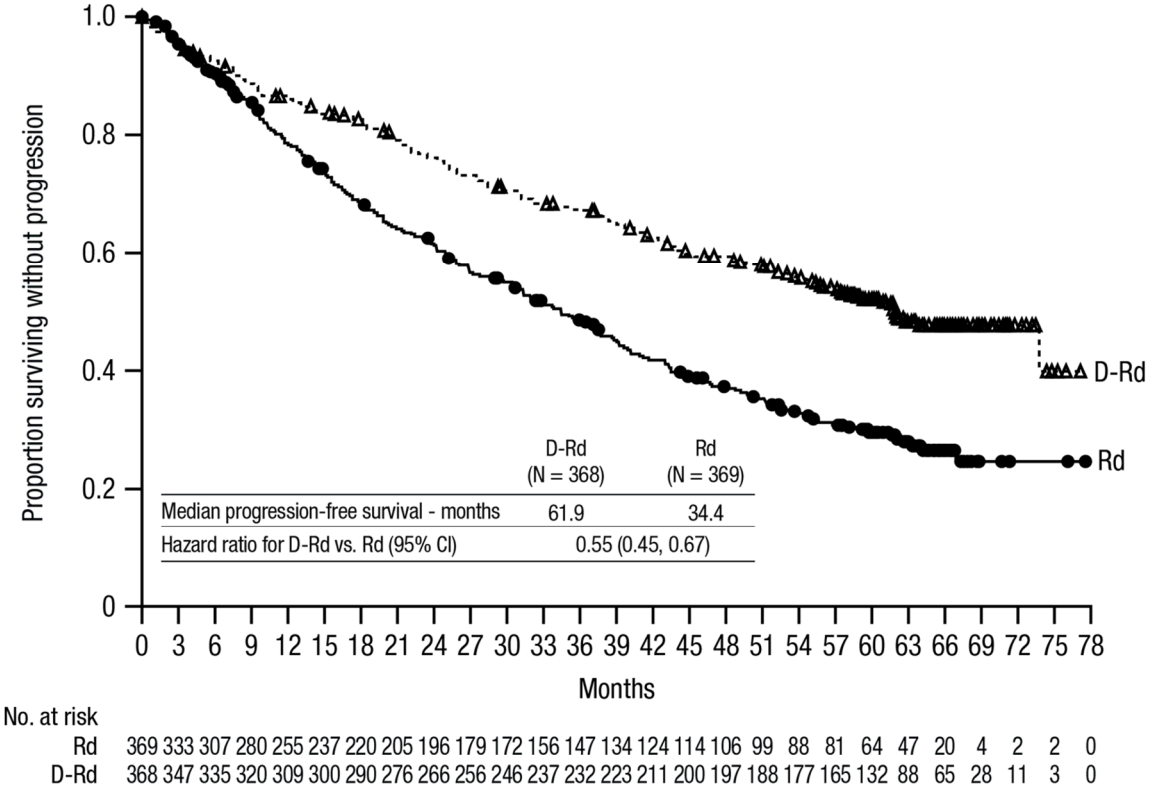
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant

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 and overall survival (OS).

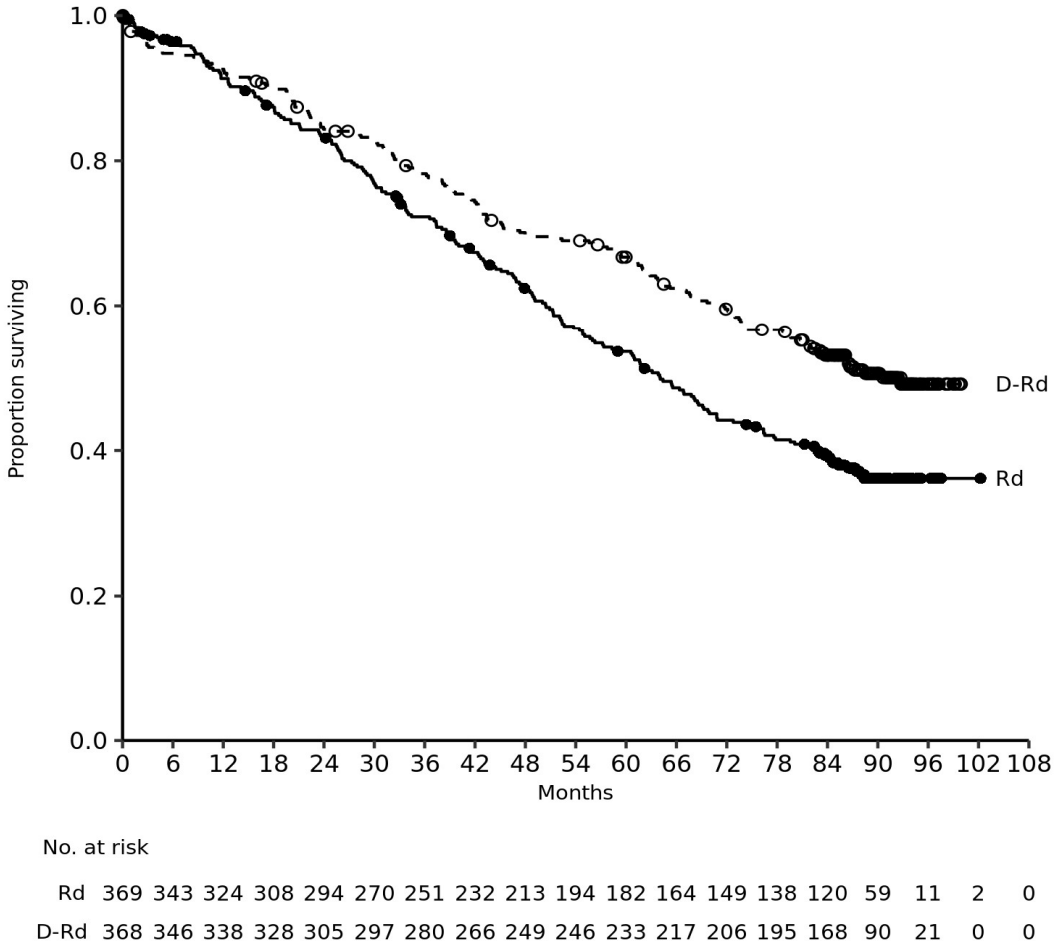
With a median follow-up of 28 months, the primary analysis of PFS in study MMY3008 showed an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (HR=0.56; 95% CI: 0.43, 0.73; p < 0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis after a median follow-up of 64 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 61.9 months in the DRd arm and 34.4 months in the Rd arm (HR=0.55; 95% CI: 0.45, 0.67).

Figure 7: Kaplan-Meier curve of PFS in study MMY3008



With a median follow-up of 56 months, DRd has shown an OS advantage over the Rd arm (HR=0.68; 95% CI: 0.53, 0.86; p=0.0013). Results of an updated OS analysis after a median of 89 months continued to show an improvement in OS for patients in the DRd arm compared to the Rd arm. Median OS was 90.3 months in the DRd arm and was 64.1 months in the Rd arm (HR= 0.67; 95% CI: 0.55, 0.82).

Figure 8: Kaplan-Meier curve of OS in study MMY3008



Additional efficacy results from study MMY3008 are presented in table 17 below.

Table 17: 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.

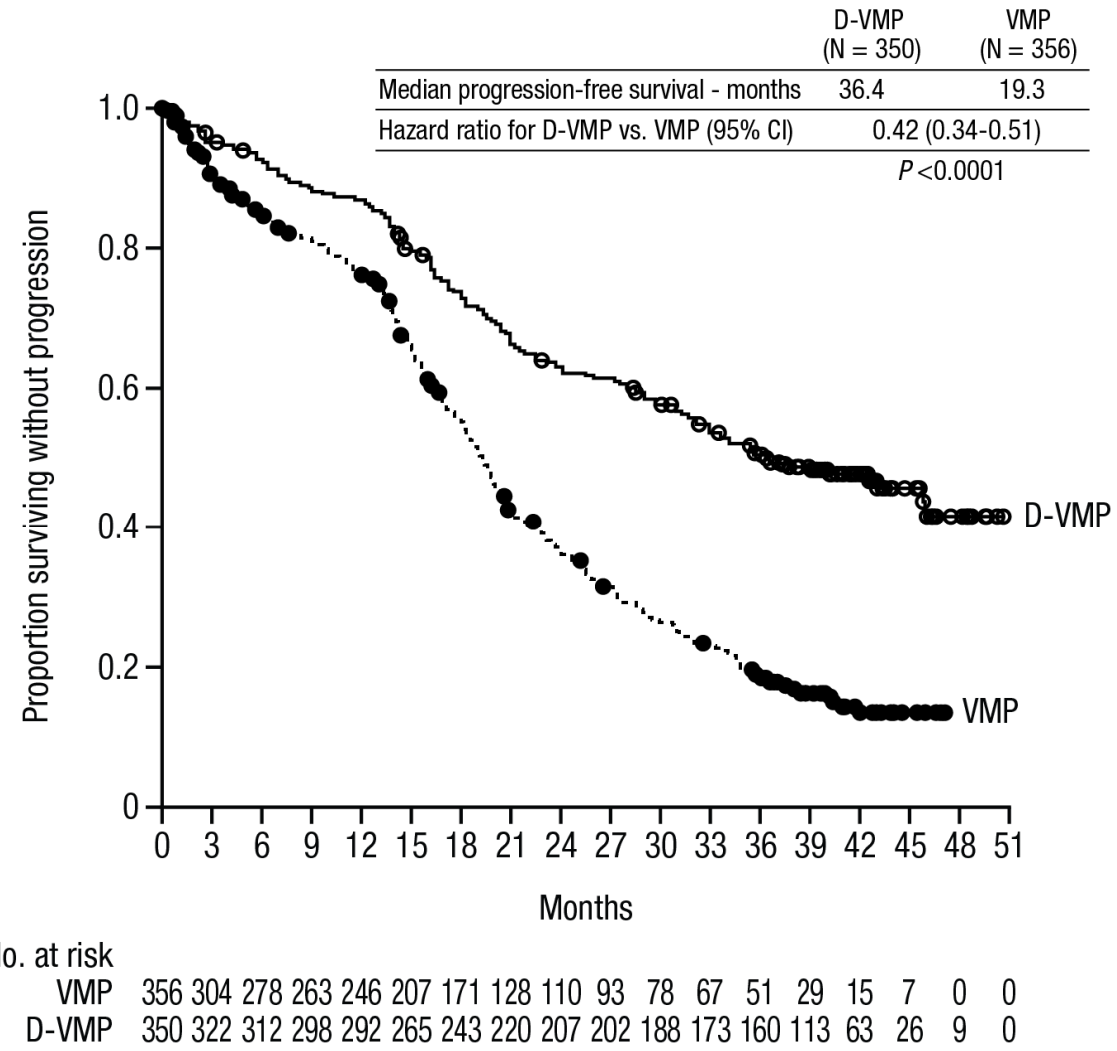
Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant

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).

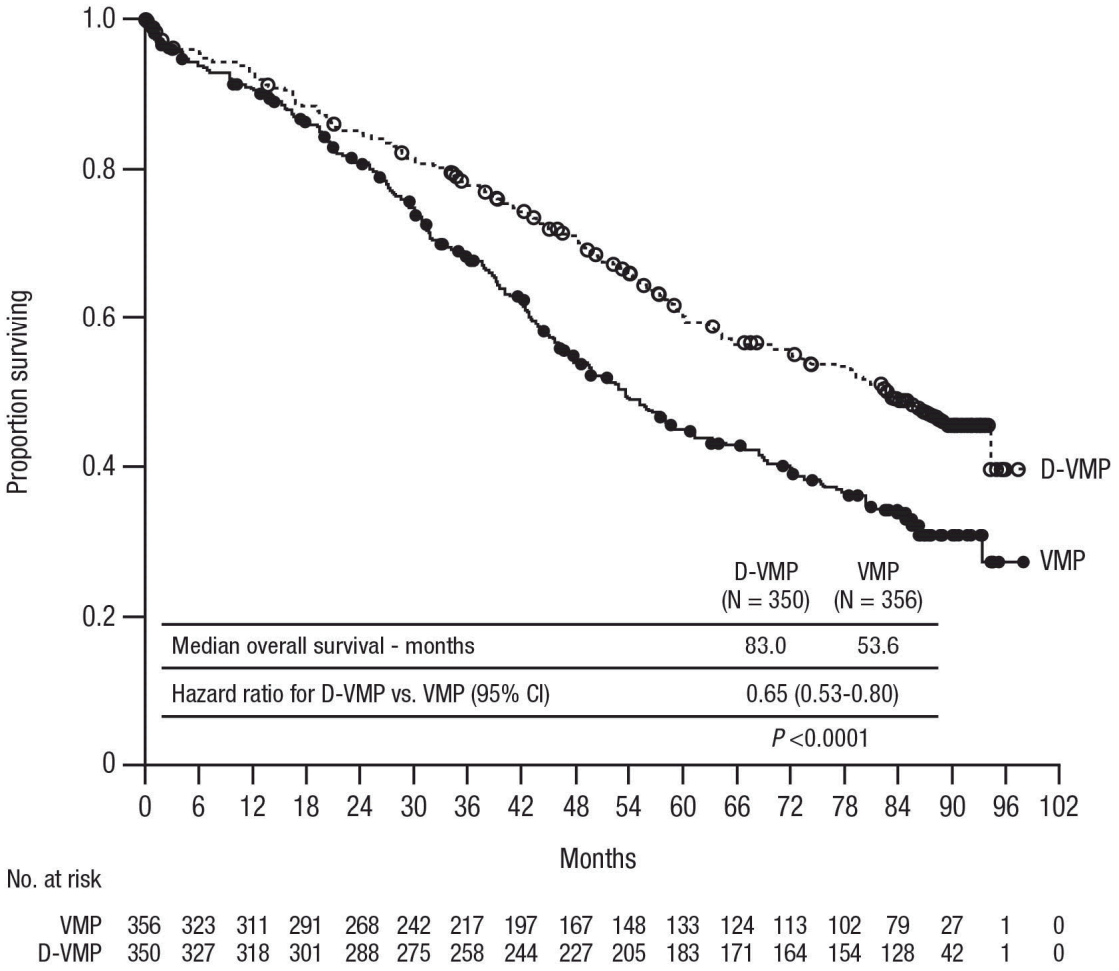
With a median follow-up of 16.5 months, the primary analysis of PFS in study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; $p < 0.0001$). Results of an updated 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 9: Kaplan-Meier curve of PFS in study MMY3007



After a median follow-up of 40 months, D-VMP has shown an OS advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. After a median follow-up of 87 months, the median OS was 83 months (95% CI: 72.5, NE) in the D-VMP arm and 53.6 months (95% CI: 46.3, 60.9) in the VMP arm.

Figure 10: Kaplan-Meier curve of OS in study MMY3007



Additional efficacy results from study MMY3007 are presented in table 18 below.

Table 18: 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 medicinal product. 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 PFS.

Table 19: 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.

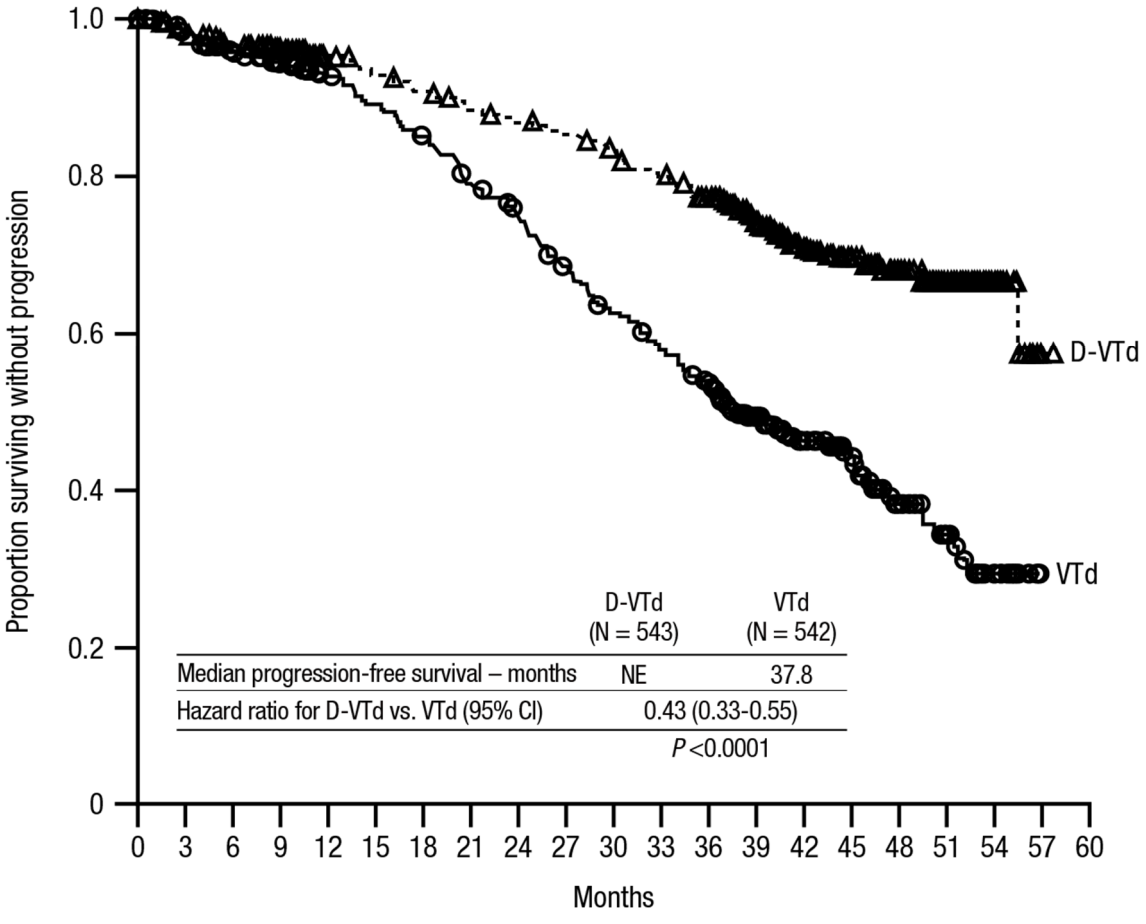
[c] Based on threshold of 10^{-5}.

[d] Regardless of response per IMWG.

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

With a median follow-up of 18.8 months, the primary analysis of PFS 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. Results of an updated PFS analysis with a median follow-up of 44.5 months, censoring patients who were randomised to daratumumab maintenance in the second randomisation, showed HR=0.43; 95% CI: 0.33, 0.55; p < 0.0001. Median PFS was not reached in the D-VTd arm and was 37.8 months in the VTd arm.

Figure 11: Kaplan-Meier curve of PFS in study MMY3006



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 20 below.

Table 20: 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 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.

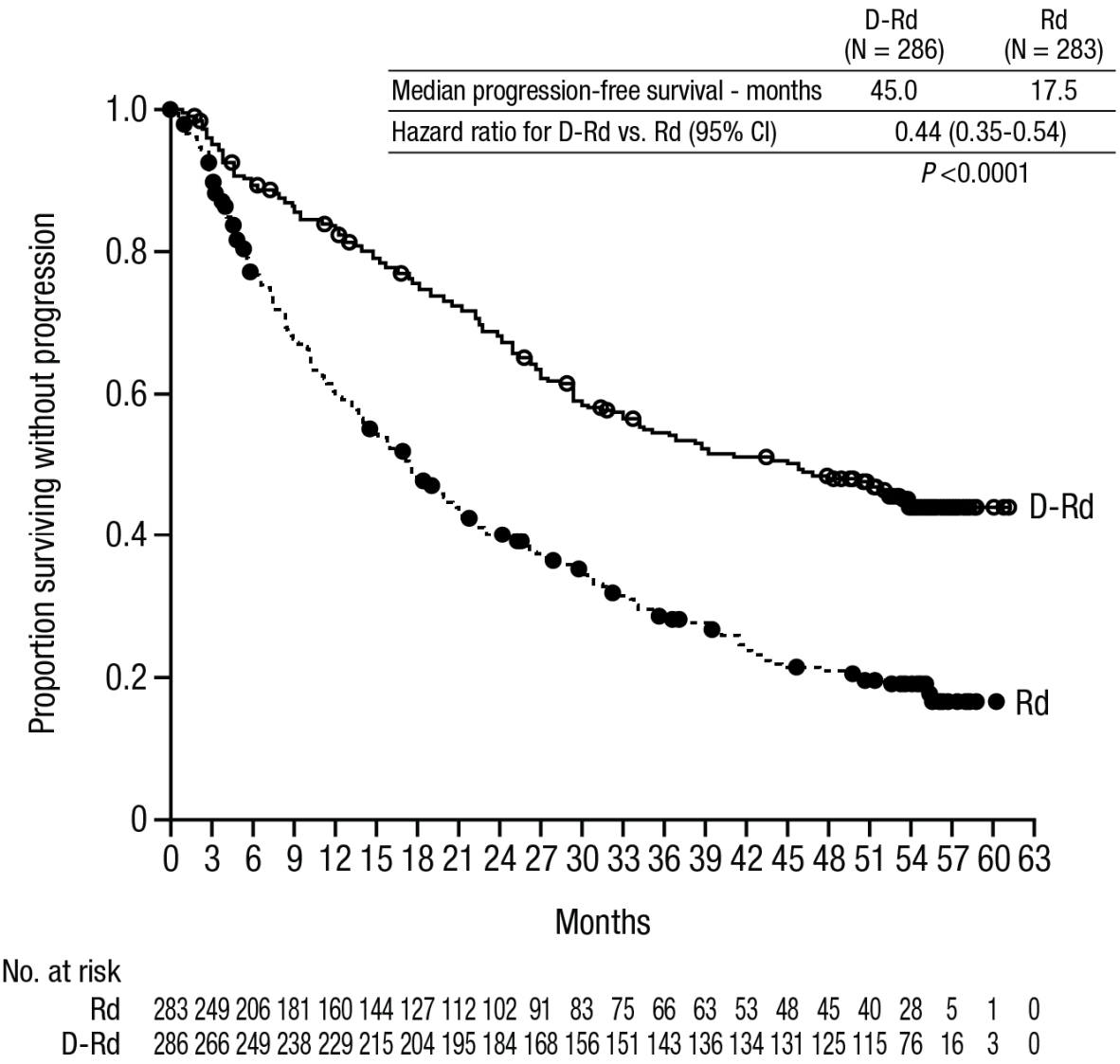
Combination treatment with lenalidomide
Study MMY3003, an open-label, randomised, active-controlled phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients

with 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 medicinal product 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.

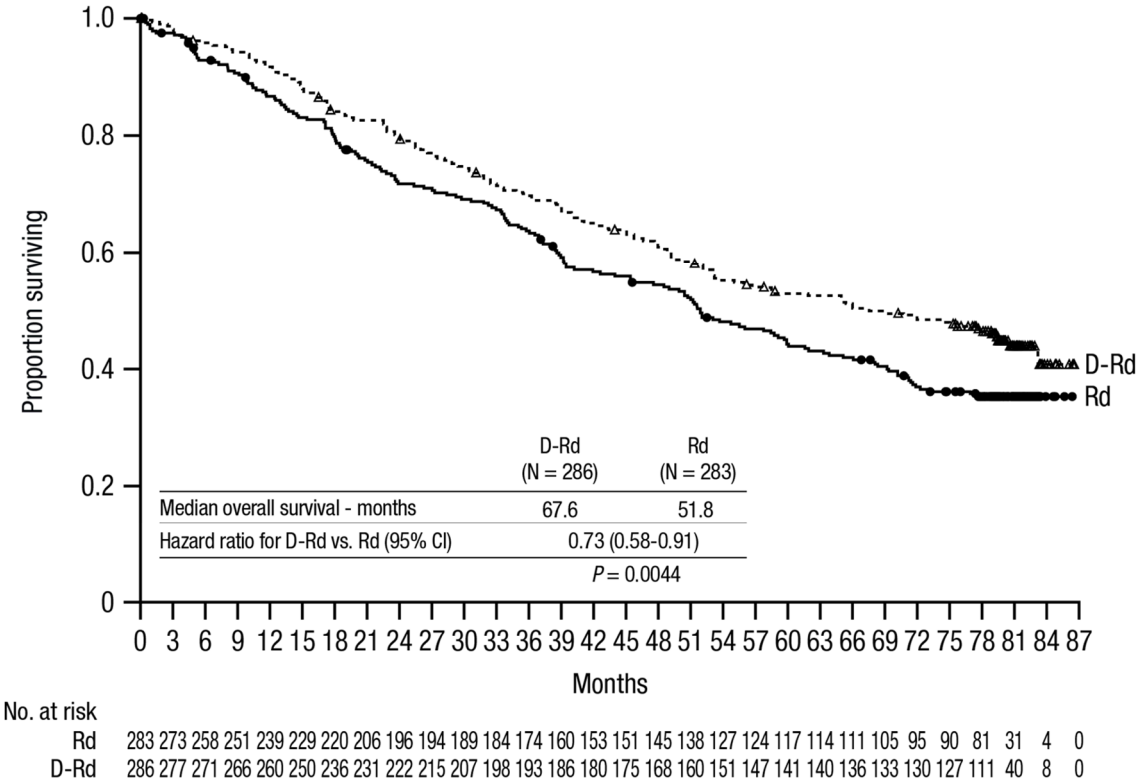
With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; $p < 0.0001$). Results of an updated 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 12).

Figure 12: Kaplan-Meier curve of PFS in study MMY3003



After a median follow-up of 80 months, DRd has shown an OS advantage over the Rd arm (HR=0.73; 95% CI: 0.58, 0.91; p=0.0044). The median OS was 67.6 months in the DRd arm and 51.8 months in the Rd arm.

Figure 13: Kaplan-Meier curve of OS in study MMY3003



Additional efficacy results from study MMY3003 are presented in table 21 below.

Table 21: 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.

Combination treatment with bortezomib

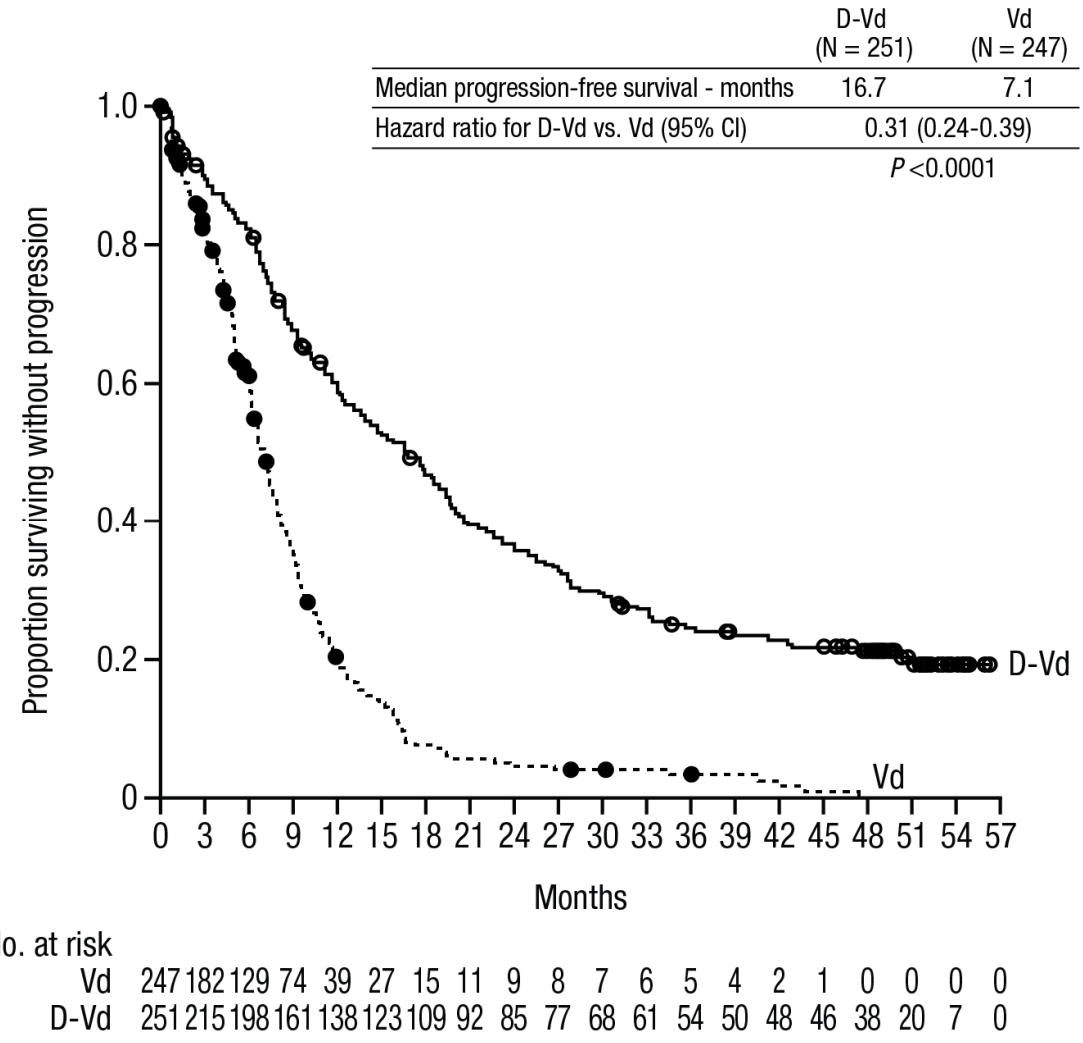
Study MMY3004, an open-label, randomised, active-controlled phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous 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 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 medicinal product. 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.

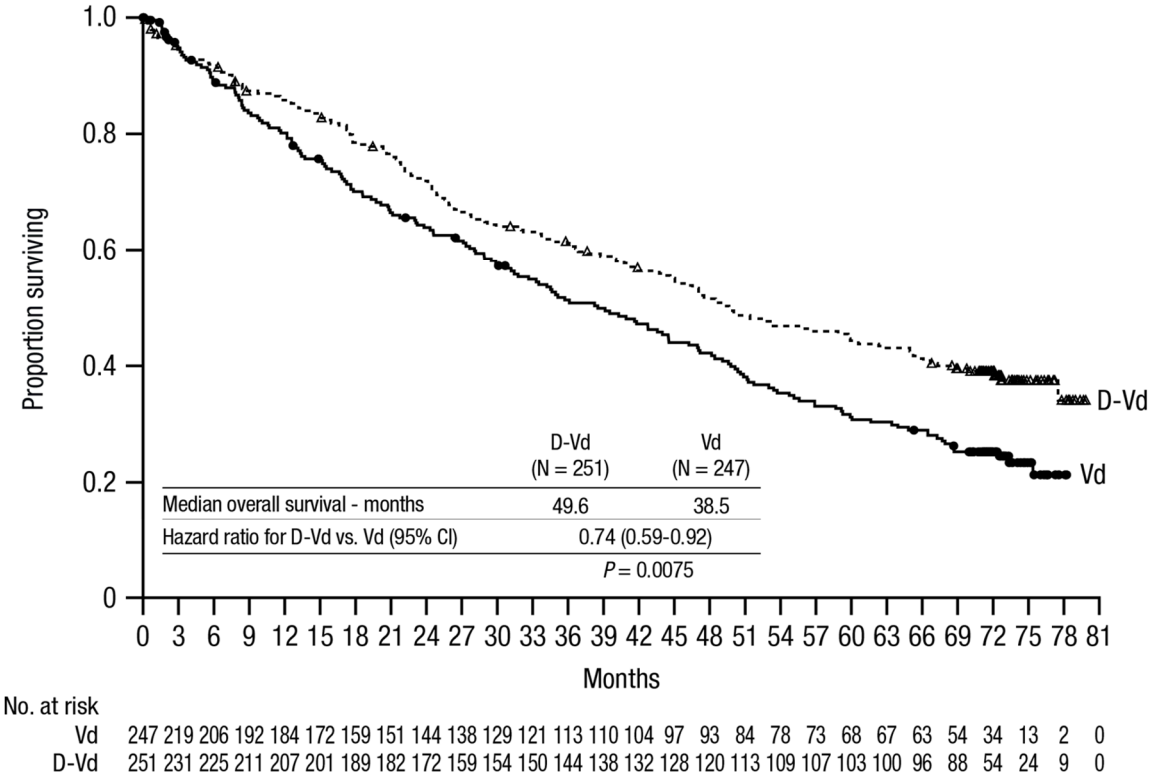
With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001). Results of 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 14).

Figure 14: Kaplan-Meier curve of PFS in study MMY3004



After a median follow-up of 73 months, DVd has shown an OS advantage over the Vd arm (HR=0.74; 95% CI: 0.59, 0.92; p=0.0075). The median OS was 49.6 months in the DVd arm and 38.5 months in the Vd arm.

Figure 15: Kaplan-Meier curve of OS in study MMY3004



Additional efficacy results from study MMY3004 are presented in table 22 below.

Table 22: 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.

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

In patients with multiple myeloma, daratumumab exposure in a monotherapy study following the recommended 1800 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).

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

Following the recommended dose of 1800 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.

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

In patients with newly diagnosed multiple myeloma eligible for ASCT, daratumumab exposure in a combination study with bortezomib, lenalidomide and dexamethasone (MMY3014) was similar to that in monotherapy, with the maximum C_{trough} (cycle 3 day 1 pre-dose) mean ± SD of 526±209 µg/mL following the recommended 1800 mg administration of DARZALEX solution for subcutaneous injection (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter).

In patients with newly diagnosed multiple myeloma for whom ASCT was not planned as initial therapy or who were ineligible for ASCT, daratumumab exposure in a combination study with bortezomib, lenalidomide and dexamethasone (MMY3019) was similar to that in monotherapy and other combination therapies following similar dosing schedule, with the maximum C_{trough} (cycle 3 day 1 pre-dose) mean ± SD of 407 ± 183 µg/mL following the recommended 1800 mg administration of DARZALEX solution for subcutaneous injection (weekly for 6 weeks, triweekly for 18 weeks, monthly thereafter).

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

In patients with smouldering multiple myeloma at high risk of developing multiple myeloma, daratumumab exposure in a monotherapy study (SMM3001) was similar to that in multiple myeloma

monotherapy with the maximum C_{trough} (cycle 3 day 1 pre-dose) mean ± SD of 654 ± 243 µg/mL following the recommended 1800 mg administration of DARZALEX solution for subcutaneous injection (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter).

Absorption and distribution

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

The model predicted mean estimate of the volume of distribution for the central compartment was 5.25 L (36.9% CV) and peripheral compartment (V2) was 3.78 L in daratumumab monotherapy, and the modelled mean estimate of the volume of distribution for V1 was 4.36 L (28.0% CV) and V2 was 2.80 L when daratumumab was administered in combination with pomalidomide and dexamethasone in multiple myeloma patients. In AL amyloidosis patients, the model estimated apparent volume of distribution after subcutaneous 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 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) in daratumumab monotherapy and 4.32 mL/h (43.5% CV) when daratumumab is administered in combination with pomalidomide and dexamethasone in multiple myeloma patients. In AL amyloidosis patients, the apparent clearance after subcutaneous administration is 210 mL/day (4.1% CV). The model-based geometric mean 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 multiple myeloma patients and 27.5 days (74.0% CV) in AL amyloidosis patients. For the monotherapy and combination regimens, the steady state is achieved at approximately 5 months into every 4 weeks dosage at the recommended dose and schedule (1800 mg; once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter).

Population PK analyses were conducted using data from DARZALEX solution for subcutaneous injection monotherapy and combination therapy multiple myeloma studies, including smouldering myeloma, and the predicted PK exposures are summarised in table 23. Daratumumab exposures were similar between patients treated with DARZALEX solution for subcutaneous injection monotherapy and combination therapies.

Table 23: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1800 mg) or intravenous daratumumab (16 mg/kg) monotherapy in patients with multiple myeloma, including smouldering multiple myeloma

PK parameters	Cycles	subcutaneous daratumumab Median (5^{th}; 95^{th} percentile) in multiple myeloma	subcutaneous daratumumab Median (5^{th}; 95^{th} percentile) in smouldering multiple myeloma	intravenous daratumumab Median (5^{th}; 95^{th} percentile)
C_{trough} (µg/mL)	Cycle 1, 1st weekly dose	123 (36; 220)	155 (104;235)	112 (43; 168)
	Cycle 2, last weekly dose (cycle 3 day 1 C_{trough})	563 (177; 1063)	690 (269; 1034)	472 (144; 809)
C_{max} (µg/mL)	Cycle 1, 1st weekly dose	132 (54; 228)	158 (106; 241)	256 (173; 327)
	Cycle 2, last weekly dose	592 (234; 1114)	780 (340; 1152)	688 (369; 1061)
$AUC_{0\text{-}7\ days}$ (µg/mL•day)	Cycle 1, 1st weekly dose	720 (293; 1274)	861 (529; 1325)	1187 (773; 1619)
	Cycle 2, last weekly dose	4017 (1515; 7564)	5043 (2242; 7426)	4019 (1740; 6370)

The predicted PK expsosures for 526 patients with transplant eligible multiple myeloma who received DARZALEX solution for subcutaneous injection in combination with VRd are summarised in table 24.

Table 24: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1800 mg) in combination with VRd in patients with transplant eligible multiple myeloma

PK parameters	Cycles	subcutaneous daratumumab Median (5^{th}; 95^{th} percentile)
C_{trough} (µg/mL)	Cycle 1, 1st weekly dose	113 (66; 171)
	Cycle 2, last weekly dose (cycle 3 day 1 C_{trough})	651 (413; 915)
C_{max} (µg/mL)	Cycle 1, 1st weekly dose	117 (67; 179)
	Cycle 2, last weekly dose	678 (431; 958)
$AUC_{0\text{-}7\ days}$ (µg/mL•day)	Cycle 1, 1st weekly dose	643 (322; 1027)
	Cycle 2, last weekly dose	4637 (2941; 6522)

A population PK analysis, using data from DARZALEX solution for subcutaneous injection combination therapy in AL amyloidosis patients, was conducted with data from 211 patients. At the recommended dose of 1800 mg, predicted daratumumab concentrations were slightly higher, but generally within the same range, in comparison with multiple myeloma patients.

Table 25: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1800 mg) in patients with AL amyloidosis

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

Special populations

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

Gender had a statistically significant effect on PK parameters 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 subcutaneous 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 subcutaneous formulation monotherapy or various combination therapies in patients with multiple myeloma or AL amyloidosis. 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 with multiple myeloma receiving DARZALEX subcutaneous formulation monotherapy or various combination therapies in patients with multiple myeloma and 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 subcutaneous formulation monotherapy or various combination therapies, the daratumumab exposure was similar across races.

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

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

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 22000 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 (E432)
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

3 years.

During the shelf-life, the product in unpunctured vials may be stored at ambient 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 24 hours at refrigerated conditions (2 °C-8 °C), followed by no more than 12 hours at 15 °C-25 °C 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 1800 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, 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.

Unopened vial

Remove the DARZALEX solution for subcutaneous injection vial from refrigerated storage (2 °C-8 °C) and equilibrate to ambient temperature (≤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.

Prepared syringe

Prepare the dosing syringe in controlled and validated aseptic conditions. Withdraw 15 mL from the vial into a syringe using an 18G - 22G transfer needle with a regular bevel to minimise the risk of stopper coring. Insert the needle into the vial at a 90°angle within the ring of the stopper and minimise the number of punctures to prevent fragmentation of the stopper. Inspect the content of the syringe to ensure the absence of particulate matter, discolouration or other foreign particles.
Once transferred from the vial into the syringe, store DARZALEX solution for subcutaneous injection for up to 24 hours refrigerated followed by up to 12 hours at 15 °C-25 °C and ambient light (see section 6.3). If stored in the refrigerator, allow the solution to reach ambient temperature before administration.

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: 06 January 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCEAND MANUFACTURE RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Biogen Inc.
5000 Davis Drive
Research Triangle Park
North Carolina
27709
United States

FUJIFILM Diosynth Biotechnologies Denmark ApS
Biotek Alle 1
Hillerod, 3400
Denmark

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy
Cork
Ireland

Samsung Biologics Co, Ltd.
300, Songdo bio-daero
Yeonsu-gu
Incheon, Republic of Korea

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of DARZALEX (daratumumab) in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, aiming at increasing awareness about the Important Identified Risk of "Interference for blood typing (minor antigen) (Positive Indirect Coombs test)" and providing guidance on how to manage it.

The MAH shall ensure that in each MS where DARZALEX (daratumumab) is marketed, all HCPs and patients who are expected to prescribe, dispense and receive this product have access to/are provided with the below.

The HCPs and Blood Banks educational materials, shall contain the following key elements:

- The guide for HCPs and Blood Banks, to advice about the risk of interference for blood typing and how to minimise it;
- The Patient Alert Card.

The Guide for HCP and Blood Banks shall contain the following key elements:

- All patients should be typed and screened prior to start treatment with daratumumab; alternatively, phenotyping may also be considered;
- Daratumumab-mediated positive indirect Coombs test (interfering with cross-matching of blood) may persist for up to 6 months after the last product's infusion, therefore, the HCP should advise the patient to carry the Patient Alert Card until 6 months after the treatment has ended;
- Daratumumab bound to Red Blood Cells (RBCs) may mask the 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;
- The 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, genotyping may also be considered;
- In case of urgent need for transfusion, non-cross matched ABO/RhD compatible RBC units can be administered as per local bank practices;
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the interference with indirect antiglobulin tests;
- Reference to the need to consult the Summary of Product Characteristics (SmPC);
- Reference to the need of giving the Patient Alert Card to the patients and to advise them to consult the Package Leaflet (PL).

The Patient Alert Card, shall contain the following key elements:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using DARZALEX (daratumumab), and that this treatment is associated with the Important Identified Risk of Interference for blood typing (minor antigen) (Positive Indirect Coombs test), which might persist for up to 6 months after the last product's infusion, and a clear reference that the patient should continue to carry this card until 6 months after the treatment has ended;
- Contact details of the DARZALEX (daratumumab) prescriber;
- Reference to the need to consult the Package Leaflet (PL).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INITIATION PACK COMPRISING 11 PACKS (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 (E432), sorbitol (E420), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
Initiation pack: 11 vials (6 x 5 mL vials + 5 x 20 mL vials)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (100 mg/400 mg) FOR 1 VIAL COMPONENT AS INTERMEDIATE PACK/COMPONENT OF AN INITIATION PACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 (E432), sorbitol (E420), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial, 100 mg/5 mL
1 vial, 400 mg/20 mL
Component of an initiation pack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (100 mg/400 mg) (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 (E432), sorbitol (E420), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial, 100 mg/5 mL
1 vial, 400 mg/20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/001
EU/1/16/1101/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab
For intravenous use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/5 mL
400 mg/20 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 1800 mg solution for injection
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 15 mL vial contains 1800 mg of daratumumab (120 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 (E432), sorbitol (E420), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

darzalex

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DARZALEX 1800 mg solution for injection
daratumumab
Subcutaneous use
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DARZALEX is and what it is used for
2. What you need to know before you are given DARZALEX
3. How DARZALEX is given
4. Possible side effects
5. How to store DARZALEX
6. Contents of the pack and other information

1. What DARZALEX is and what it is used for

What DARZALEX is
DARZALEX is a cancer medicine that contains the active substance daratumumab. It belongs to a group of medicines called "monoclonal antibodies". Monoclonal antibodies are proteins that have been designed to recognise and attach to specific targets in the body. Daratumumab has been designed to attach to specific cancer cells in your body, so that your immune system can destroy the cancer cells.

What DARZALEX is used for
DARZALEX is used in adults 18 years or older, who have a type of cancer called "multiple myeloma". This is a cancer of your bone marrow.

2. What you need to know before you are given DARZALEX

You must not be given DARZALEX
- if you are allergic to daratumumab or any of the other ingredients of this medicine (listed in section 6).

Do not use DARZALEX if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given DARZALEX.

Warnings and precautions
Talk to your doctor or nurse before you are given DARZALEX.

Infusion-related reactions
DARZALEX is given as an infusion (drip) into a vein. Before and after each infusion of DARZALEX, you will be given medicines which help to lower the chance of infusion-related reactions (see "Medicines given during treatment with DARZALEX" in section 3). These reactions can happen during the infusion or in the 3 days after the infusion.
In some cases you may have a severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). Some serious allergic reactions and other severe infusion-related reactions have resulted in death.

Tell your doctor or nurse straight away if you get any of the infusion-related reactions or related symptoms listed at the top of section 4.

If you get infusion-related reactions, you may need other medicines, or the infusion may need to be slowed down or stopped. When these reactions go away, or get better, the infusion can be started again.
These reactions are most likely to happen with the first infusion. If you have had an infusion-related reaction once it is less likely to happen again. Your doctor may decide not to use DARZALEX if you have a strong infusion reaction.

Decreased blood cell counts
DARZALEX can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop any symptoms of infection such as fever, trouble breathing, cough, burning or pain when you urinate, or any symptoms of decreased platelet counts such as bruising or bleeding.

Blood transfusions
If you need a blood transfusion, you will have a blood test first to match your blood type. DARZALEX can affect the results of this blood test. Tell the person doing the test that you are using DARZALEX.

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

Children and adolescents
Do not give DARZALEX to children or adolescents below 18 years of age. This is because it is not known how the medicine will affect them.

Other medicines and DARZALEX
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines you can get without a prescription, and herbal medicines.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.
If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Contraception
Women who are being given DARZALEX should use effective contraception during treatment and for 3 months after treatment.

Breast-feeding
You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. This is because the medicine may pass into the mother’s milk and it is not known how it will affect the baby.

Driving and using machines
You may feel tired after taking DARZALEX which may affect your ability to drive or use machines.

DARZALEX contains sorbitol
Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you have HFI.

DARZALEX contains polysorbate
This medicine contains 0.4 mg of polysorbate 20 in each mL, which is equivalent to 2.0 mg per 5 mL vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

This medicine contains 0.4 mg of polysorbate 20 in each mL, which is equivalent to 8.0 mg per 20 mL vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How DARZALEX is given

How much is given
Your doctor will work out your dose and schedule of DARZALEX. The dose of DARZALEX will depend on your body weight.

The usual starting dose of DARZALEX is 16 mg per kg of body weight. DARZALEX may be given alone or together with other medicines used to treat multiple myeloma.
When given alone, DARZALEX is given as follows:
- once a week for the first 8 weeks
- then once every 2 weeks for 16 weeks
- then once every 4 weeks after that as long as your condition does not worsen.

When DARZALEX is given together with other medicines your doctor may change the time between doses as well as how many treatments you will receive.

In the first week your doctor may give you the DARZALEX dose split over two consecutive days.

How the medicine is given
DARZALEX will be given to you by a doctor or nurse. It is given as a drip into a vein ("intravenous infusion") over several hours.

Medicines given during treatment with DARZALEX
You may be given medicines to lower the chance of getting shingles.

Before each infusion of DARZALEX you will be given medicines which help to lower the chance of infusion-related reactions. These may include:
- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

After each infusion of DARZALEX you will be given medicines (such as corticosteroids) to lower the chance of infusion-related reactions.

People with breathing problems
If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD), you will be given medicines to inhale which help your breathing problems:
- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids).

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

If you forget your appointment to have DARZALEX
It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.
If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related reactions
Tell your doctor or nurse straight away if you get any of the following signs of an infusion-related reaction during or in the 3 days after the infusion. You may need other medicines, or the infusion may need to be slowed down or stopped.

These reactions include the following symptoms:

Very common (may affect more than 1 in 10 people):
- chills
- sore throat, cough
- feeling sick (nausea)
- vomiting
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems.

Common (may affect up to 1 in 10 people):
- chest discomfort
- dizziness or lightheadedness (hypotension)
- itching
- wheezing.

Rare (may affect up to 1 in 1000 people):
- severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 2.
- eye pain
- blurred vision.

If you get any of the infusion-related reactions above, tell your doctor or nurse straight away.

Other side effects
Very common (may affect more than 1 in 10 people):
- fever
- feeling very tired
- diarrhoea
- abdominal pain
- constipation
- decreased appetite
- difficulty sleeping
- headache
- feeling dizzy
- nerve damage that may cause tingling, numbness, or pain
- high blood pressure

- skin rash
- muscle spasms
- swollen hands, ankles or feet
- feeling weak
- muscle and joint pain (including back pain and chest muscle pain)
- lung infection (pneumonia)
- bronchitis
- infections of the airways – such as nose, sinuses or throat
- low number of red blood cells which carry oxygen in the blood (anaemia)
- low number of white blood cells which help fight infections (neutropenia, lymphopenia, leukopenia)
- low number of a type of blood cell called platelets which help to clot blood (thrombocytopenia)
- low level of potassium in the blood (hypokalaemia)
- unusual feeling in the skin (such as a tingling or crawling feeling)
- COVID-19.

Common (may affect up to 1 in 10 people):
- irregular heart beat (atrial fibrillation)
- build up of fluid in the lungs making you short of breath
- urinary tract infection
- severe infection throughout the body (sepsis)
- dehydration
- fainting
- chills
- high level of sugar in the blood
- low level of calcium in the blood
- low level of antibodies called 'immunoglobulins' in the blood which help fight infections (hypogammaglobulinaemia)
- inflamed pancreas
- itching
- type of herpes virus infection (cytomegalovirus infection).

Uncommon (may affect up to 1 in 100 people):
- inflamed liver (hepatitis).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DARZALEX

DARZALEX will be stored at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C-8 °C). Do not freeze.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What DARZALEX contains
- The active substance is daratumumab. One mL of concentrate contains 20 mg daratumumab. Each vial of 5 mL concentrate contains 100 mg of daratumumab. Each vial of 20 mL concentrate contains 400 mg of daratumumab.
- The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 (E432), sorbitol (E420), and water for injections (see "DARZALEX contains sorbitol" in section 2).

What DARZALEX looks like and contents of the pack
DARZALEX is a concentrate for solution for infusion and is a colourless to yellow liquid.
DARZALEX is supplied as a carton pack containing 1 glass vial.
DARZALEX is also supplied as an initiation pack containing 11 vials: (6 x 5 mL vials + 5 x 20 mL vials).

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

This medicinal product is for single-use only.
Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colourless to yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Using aseptic technique, remove a volume of sodium chloride 9 mg/mL (0.9%) solution for injection from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing sodium chloride 9 mg/mL (0.9%) solution for injection. Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Visually inspect parenteral medicinal products for particulate matter and discolouration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15 °C-25 °C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2 °C-8 °C) and protected from light. Do not freeze.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

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

Package leaflet: Information for the patient

DARZALEX 1800 mg solution for injection
daratumumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DARZALEX is and what it is used for
2. What you need to know before you are given DARZALEX
3. How DARZALEX is given
4. Possible side effects
5. How to store DARZALEX
6. Contents of the pack and other information

1. What DARZALEX is and what it is used for

What DARZALEX is
DARZALEX is a medicine that contains the active substance daratumumab. It belongs to a group of medicines called "monoclonal antibodies". Monoclonal antibodies are proteins that have been designed to recognise and attach to specific targets in the body. Daratumumab has been designed to attach to specific abnormal blood cells in your body, so that your immune system can destroy these cells.

What DARZALEX is used for
DARZALEX is used in adults 18 years or older, who have a type of cancer called "multiple myeloma". This is a cancer of your bone marrow.

DARZALEX is used in adults 18 years or older, who have a type of blood and bone marrow disorder called "smouldering multiple myeloma" that can become multiple myeloma.

DARZALEX is also used in adults 18 years or older, who have a type of blood disorder called "AL amyloidosis." In AL amyloidosis, abnormal blood cells make excessive amounts of abnormal proteins that deposit in various organs, causing these organs to not function properly.

2. What you need to know before you are given DARZALEX

You must not be given DARZALEX
- if you are allergic to daratumumab or any of the other ingredients of this medicine (listed in section 6).

Do not use DARZALEX if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given DARZALEX.

Warnings and precautions
Talk to your doctor or nurse before you are given DARZALEX.

Infusion-related reactions
DARZALEX is given as a subcutaneous injection using a small needle to inject the medicine under your skin. Before and after each injection, you will be given medicines which help to lower the chance of infusion-related reactions (see "Medicines given during treatment with DARZALEX" in section 3). These reactions are most likely to happen with the first injection and most reactions occur on the day of injection. If you have had an infusion-related reaction once it is less likely to happen again. However, delayed reactions can happen up to 3-4 days after the injection. Your doctor may decide not to use DARZALEX if you have a strong reaction after the injection.

In some cases you may have a severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 4.

Tell your doctor or nurse straight away if you get any of the infusion-related reactions or related symptoms listed at the top of section 4. If you get infusion-related reactions, you may need other medicines to treat your symptoms, or the injections may need to be stopped. When these reactions go away, or get better, the injection can be started again.

Decreased blood cell counts
DARZALEX can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop any symptoms of infection such as fever, trouble breathing, cough, burning or pain when you urinate, or any symptoms of decreased platelet counts such as bruising or bleeding.

Blood transfusions
If you need a blood transfusion, you will have a blood test first to match your blood type. DARZALEX can affect the results of this blood test. Tell the person doing the test that you are using DARZALEX.

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

Children and adolescents
Do not give DARZALEX to children or adolescents below 18 years of age. This is because it is not known how the medicine will affect them.

Other medicines and DARZALEX
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines you can get without a prescription, and herbal medicines.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.
If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Contraception
Women who are being given DARZALEX should use effective contraception during treatment and for 3 months after treatment.

Breast-feeding
You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known how it will affect the baby.

Driving and using machines
You may feel tired after taking DARZALEX which may affect your ability to drive or use machines.

DARZALEX solution for subcutaneous injection contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 15 mL, that is to say essentially 'sodium-free'.

DARZALEX solution for subcutaneous injection contains sorbitol
Sorbitol is a source of fructose. If your doctor has told you that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take this medicine.

DARZALEX solution for subcutaneous injection contains polysorbate
This medicine contains 0.4 mg of polysorbate 20 in each mL, which is equivalent to 6.0 mg per 15 mL vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How DARZALEX is given

How much is given
The dose of DARZALEX solution for subcutaneous injection is 1800 mg.

DARZALEX may be given alone or together with other medicines used to treat multiple myeloma, or with other medicines used to treat AL amyloidosis. DARZALEX is usually given as follows:
- once a week for the first 8 weeks
- then once every 2 weeks for 16 weeks
- then once every 4 weeks after that as long as your condition does not worsen.

When DARZALEX is given together with other medicines your doctor may change the time between doses as well as how many treatments you will receive.

How the medicine is given
DARZALEX will be given to you by a doctor or nurse as an injection under your skin (subcutaneous injection) over approximately 3 to 5 minutes. It is given in the stomach area (abdomen), not in other sites of the body, and not into areas of the abdomen where the skin is red, bruised, tender, hard or where there are scars.

If you experience pain during the injection, the doctor or nurse may interrupt the injection and give you the remaining injection in another area of your abdomen.

Your doctor will decide if you or your caregiver can administer DARZALEX after proper training.

Always use this medicine exactly as the doctor or nurse has told you. Check with the doctor, pharmacist or nurse if you are not sure. If you feel unwell talk to your doctor or pharmacist. Talk to your doctor about when you will have your injections and follow-up appointments.

Medicines given during treatment with DARZALEX
You may be given medicines to lower the chance of getting shingles.

Before each injection of DARZALEX you will be given medicines which help to lower the chance of infusion-related reactions. These may include:
- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

After each injection of DARZALEX you will be given medicines (such as corticosteroids) to lower the chance of infusion-related reactions.

People with breathing problems
If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD), you will be given medicines to inhale which help your breathing problems:
- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids).

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

If you forget your appointment to have DARZALEX
It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.
If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related reactions
Tell your doctor or nurse straight away if you get any of the following symptoms within 3-4 days after the injection. You may need other medicines, or the injection may need to be interrupted or stopped.

These reactions include the following symptoms:

Very common (may affect more than 1 in 10 people):
- chills
- sore throat, cough
- feeling sick (nausea)
- vomiting
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems.

Common (may affect up to 1 in 10 people):
- chest discomfort
- dizziness or lightheadedness (hypotension)
- itching
- wheezing.

Rare (may affect up to 1 in 1000 people):
- severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 2.
- eye pain
- blurred vision.

If you get any of the infusion-related reactions above, tell your doctor or nurse straight away.

Injection site reactions
Skin reactions at or near the injection site (local), including injection site reactions, can happen with DARZALEX solution for subcutaneous injection. These reactions are very common (may affect more than 1 in 10 people). Symptoms at the site of injection may include redness of the skin, itching, swelling, pain, bruising, rash, bleeding.

Other side effects
Very common (may affect more than 1 in 10 people):
- fever
- feeling very tired
- diarrhoea
- constipation
- abdominal pain
- decreased appetite
- difficulty sleeping
- headache
- nerve damage that may cause tingling, numbness, or pain
- rash
- muscle spasms
- muscle and joint pain (including back pain and chest muscle pain)
- swollen hands, ankles or feet
- feeling weak
- lung infection (pneumonia)
- bronchitis
- infections of the airways – such as nose, sinuses or throat
- low number of red blood cells which carry oxygen in the blood (anaemia)
- low number of white blood cells which help fight infections (neutropenia, lymphopenia, leukopenia)
- low number of a type of blood cell called platelets which help to clot blood (thrombocytopenia)
- low level of potassium in the blood (hypokalaemia)
- COVID-19.

Common (may affect up to 1 in 10 people):
- irregular heart beat (atrial fibrillation)
- build up of fluid in the lungs making you short of breath
- urinary tract infection
- severe infection throughout the body (sepsis)
- dehydration
- high level of sugar in the blood
- low level of calcium in the blood
- low level of antibodies called 'immunoglobulins' in the blood which help fight infections (hypogammaglobulinaemia)
- feeling dizzy
- fainting
- chills
- itching
- unusual feeling in the skin (such as a tingling or crawling feeling)
- inflamed pancreas
- high blood pressure.

Uncommon (may affect up to 1 in 100 people):
- inflamed liver (hepatitis)
- type of herpes virus infection (cytomegalovirus infection).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DARZALEX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C-8 °C). Do not freeze.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What DARZALEX contains
- The active substance is daratumumab. One mL of solution contains 120 mg daratumumab. One vial of 15 mL solution for injection contains 1800 mg of daratumumab.
- The other ingredients are recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 (E432), sorbitol (E420), and water for injections (see "DARZALEX contains sodium and sorbitol" in section 2).

What DARZALEX looks like and contents of the pack
DARZALEX solution for subcutaneous injection is a colourless to yellow liquid.
DARZALEX solution for subcutaneous injection is supplied as a carton pack containing 1 single-dose glass vial.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

DARZALEX solution for subcutaneous injection should be administered by a healthcare professional.

To prevent medication errors, 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. DARZALEX solution for injection should be given by subcutaneous injection only, using the dose specified. DARZALEX subcutaneous formulation is not intended for intravenous administration.

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

- 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.
- 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.
- 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. Withdraw 15 mL from the vial into a syringe using an 18G - 22G transfer needle with a regular bevel to minimise the risk of stopper coring. Insert the needle into the vial at a 90°angle within the ring of the stopper and minimise the number of punctures to prevent fragmentation of the stopper. Inspect the content of the syringe to ensure the absence of particulate matter, discolouration or other foreign particles.
- 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 is not used immediately, store the solution of DARZALEX for up to 24 hours refrigerated followed by up to 12 hours at 15 °C-25 °C and

ambient light. If stored in the refrigerator, allow the solution to reach ambient temperature before administration.

Administration

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

Traceability

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

The following information is intended for Patients and Caregivers only:
Instructions for Use

Your healthcare provider will administer the initial injections of DARZALEX subcutaneously (under the skin), hereafter referred to as DARZALEX. Afterwards you and your doctor may decide that you or a caregiver may inject DARZALEX. If this happens, you or a caregiver will get training from your healthcare provider on how to prepare and inject DARZALEX. Talk to your doctor if you have any questions about giving yourself an injection.

Storage

Storage of unopened vial

Store in refrigerator at 2 °C to 8 °C. Once the vial of DARZALEX is removed from the refrigerator, it should **not** be returned to the refrigerator.

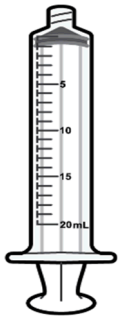
Keep the medication out of the sight and reach of children.

Supplies

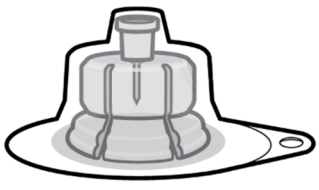
You will need:



Vial of Medication (contains 16.6 mL)



Luer Lock Syringe



20 mm Vial Adapter in Sterile Blister



Luer Lock 25G Subcutaneous Administration Set

You will also need:

• Antiseptic wipes • Cotton pad or gauze pad • Gloves

• Adhesive bandage • Sharps container • Surgical tape

1. Inspect carton and check the vial



Allow medication to come to room temperature

Take the box with the vial out of the refrigerator.

Check the box with the vial to make sure it has not passed its expiration date.

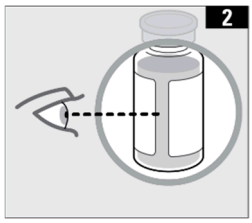
Do not use the medication if the expiration date has passed.

Let the box with the vial stand for about 30 minutes.

This will let the liquid come to a comfortable temperature for injection (room temperature).

Keep out of direct sunlight.

Do not shake the box with the vial.



Check the liquid in the vial

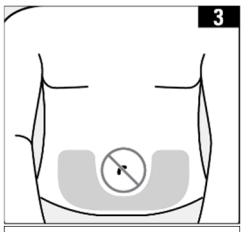
Remove the vial from the box.

Do not shake the vial.

The liquid in the vial should be clear and colourless to light yellow.

Do not use if the liquid is discoloured or cloudy or contains any foreign particles and contact your healthcare provider for assistance.

2. Prepare for the injection



* Areas in grey are recommended injection sites.

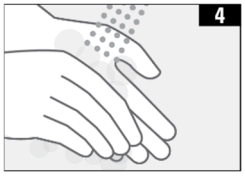
Choose an injection site on the abdomen

DARZALEX is given by injection under the skin (subcutaneously).

Inject around the belly (abdomen) **at least 7.5 cm away from the navel (belly-button).**

Use a different injection site for each injection.

Do not inject into skin that is tender, bruised, red, scaly, thick or hard. Avoid areas with scars or stretch marks.

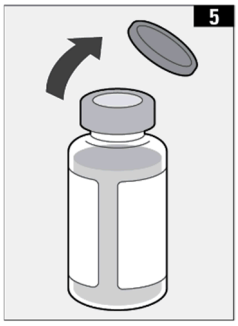


Wash hands and put on gloves

Wash your hands very well with soap and warm water.

Put on gloves. Keep gloves on until dose has been administered and materials have been discarded.

3. Prepare vial and syringe



Remove cap

Lift the thin grey cap up to remove it from the top of the vial.

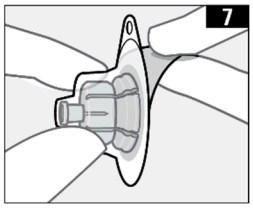
Do not remove the rubber stopper.



Clean rubber stopper

Clean the rubber stopper with an antiseptic wipe.

Put the vial on a flat surface.



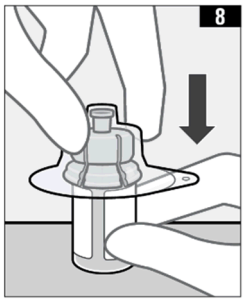
Prepare vial adapter

Hold sterile blister as shown.

Peel back and remove paper backing.

Do not touch vial adapter at any time.

This may result in contamination.



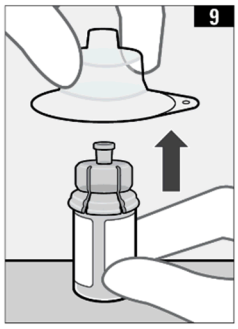
Connect vial adapter to vial

Place vial on a flat surface and hold by the base.

Centre vial adapter over the grey rubber stopper.

Push vial adapter straight down onto vial top until it snaps securely into place.

Do not place vial adapter on at an angle or liquid may leak upon transfer to the syringe.



Remove sterile blister

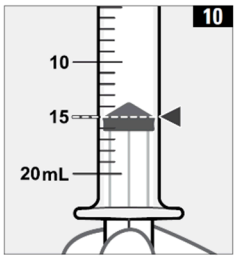
Do not remove sterile blister from vial adapter until you are ready to attach the syringe to the vial adapter.

Keep vial vertical to prevent leakage.

Hold base of vial and pull up on the sterile blister to remove.

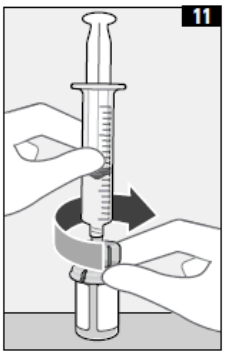
Do not touch the exposed opening on vial adapter.

This may result in contamination.



Fill the syringe with air

Pull the plunger down until the top line of the black rubber plunger is lined up with the 15 mL marker (see image).

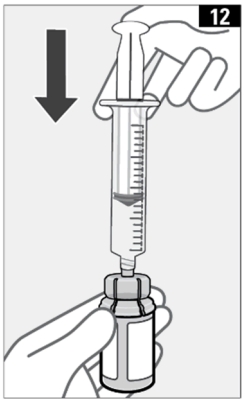


Connect syringe to vial adapter

Firmly hold the bottom of the vial adapter.

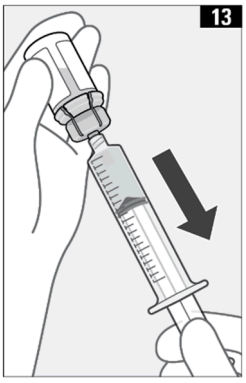
Attach the syringe to the vial adapter by twisting the tip of the syringe clockwise onto the vial adapter.

Do not over-tighten.



Inject all of the air into the vial

Inject all of the air from the syringe into the vial, this will make the transfer of liquid from the vial to the syringe easier.



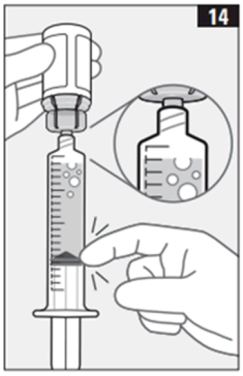
Transfer all liquid from vial to the syringe

Turn the vial and syringe upside-down.

Firmly grip the vial and syringe, then pull the syringe plunger to transfer **all** liquid into the syringe.

Due to the medication's thickness, you may feel resistance when transferring from vial to syringe.

Check to make sure the vial is empty.



Remove any air pockets or air bubbles

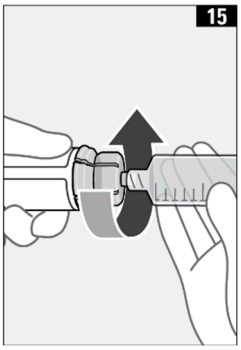
Hold the syringe pointing up.

Tap the side of the syringe until the air bubbles go to the top.

Push the plunger up until the air bubbles have been pushed out of the syringe back into the vial.

Check if air pockets or bubbles remain.

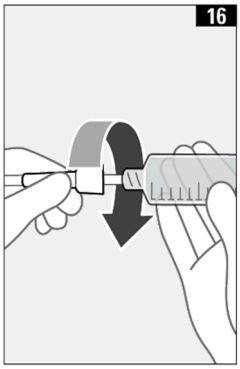
Repeat steps if necessary.



Remove syringe from vial adapter

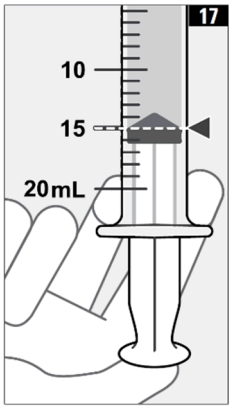
When all of the liquid has been transferred to the syringe and air bubbles have been removed, gently twist the syringe off of the vial adapter. There may be a small amount of liquid in the vial, this is normal.

See Disposal steps on how to discard vial with the vial adapter in sharps container.



Attach syringe to subcutaneous administration set

Twist to attach the Luer Lock 25G subcutaneous administration set to the syringe.



Push syringe plunger to 15 mL

Do not remove needle protection cap.

Hold the needle over a sharps container or disposable cup to collect liquid from the needle.

Hold the syringe with the tip pointing up.

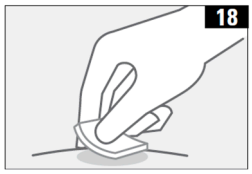
Slowly push the plunger until the top line of the black rubber plunger is lined up with the 15 mL marker **to set a 15 mL dose.**

Do not push the plunger past 15 mL because you will not receive the full dose.

You will see liquid come out of the needle. This is normal.
Dispose of the liquid per local regulations.

Place the syringe on a flat surface.

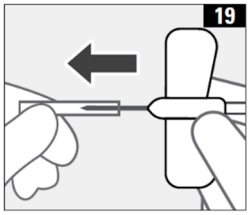
4. Inject medication



Clean injection site on the abdomen

Wipe the chosen injection site with an antiseptic wipe and allow it to dry.

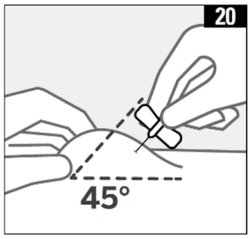
Do not touch, fan, or blow on the injection site after you have cleaned it.



Remove the needle protection cap

Remove the needle protection cap from the subcutaneous administration set needle by pulling it straight off.

Do not touch the needle or let the needle touch anything.



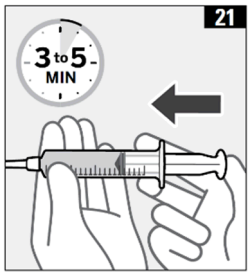
Pinch skin and insert needle

Gently pinch the cleaned skin at the injection site.

Push the needle into the pinched skin at around 45 degrees to the belly (abdomen).

Release the fold of skin.

You may secure the needle to the injection site with surgical tape.

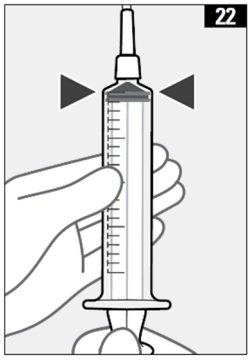


Inject 15 mL dose

Push the plunger steadily until the entire dose is delivered from the syringe. This should take approximately 3 to 5 minutes.

You may feel resistance when pushing the plunger. This is normal. Continue to push the plunger slowly.

If you feel pain at the injection site, pause or slow down the injection. If the pain persists, stop the injection and contact your healthcare provider.



Confirm the dose is complete

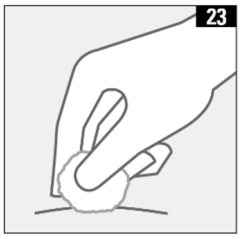
After 3 to 5 minutes, check that the plunger is fully pressed down as far as it will go in the barrel of the syringe.

This means the dose is complete.

If the plunger is not fully to the end of the barrel of the syringe, continue to press until the dose is complete.

After delivering the full dose, carefully remove the subcutaneous administration set needle from the injection site.

Do not recap the needle.



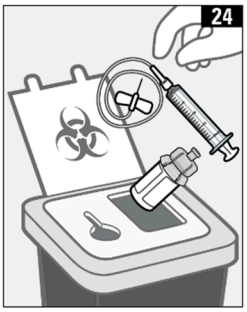
After the injection

There may be a small amount of liquid at the injection site.

This is normal.

You can press a cotton ball or gauze gently over the injection site and hold for 10 seconds.

Do not rub the skin at the injection site. You may cover the injection site with a bandage, if necessary.



Disposal

Do not recap needle before disposing.

Used syringe, subcutaneous administration set and vial with vial adapter should be placed in a puncture-resistant container, like a sharps container.

Dispose of your sharps container according to your local regulations.

Antiseptic wipes and other supplies can be disposed of in your garbage.