DARZALEX *Faspro*®
(daratumumab and hyaluronidase-fihj)
Injection for subcutaneous use | 1,800mg/30,000units

DARZALEX *FASPRO*® + VRd is approved for a broad range of patients with newly diagnosed multiple myeloma, regardless of transplant status[1]

CEPHEUS
A CLINICAL STUDY OF DVRd VS VRd

In the treatment of transplant-ineligible patients with newly diagnosed multiple myeloma

Are your patients achieving deep responses?

52% of patients achieved MRD negativity (10^{-5}) and a complete response (CR) or better with DVRd vs 35% with VRd alone (*P*=0.0005).[1*†‡]

DARZALEX *FASPRO*® + VRd CLINICAL EVIDENCE
EXPLORE MORE IN TIE NDMM

CR=complete response; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); MRD=minimal residual disease; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*At a median follow-up of 22 months.[1]

†Primary endpoint.[1,2]

‡In the CEPHEUS trial, patients had to achieve MRD negativity (threshold of 10^{-5}) and CR or better. All MRD testing was performed with a next-generation sequencing assay (clonoSEQ).[1]

INDICATIONS

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib, lenalidomide, and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DARZALEX *FASPRO*® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase, or any of the components of the formulation.

Achievement of MRD negativity is associated with improved PFS[3,4]

Use of MRD (CR) as a trial endpoint allows for earlier assessment of potential treatment response and may help predict outcomes[5]

A prospectively planned analysis including patients with transplant-eligible, transplant-ineligible, or relapsed/refractory multiple myeloma found that achieving MRD-negative CR (10^{-5}) at 9 months was associated with significantly higher odds of remaining progression-free and alive compared with those who did not achieve MRD-negative CR at 9 months (odds ratio for PFS, 9.8; 95% CI: 5.1-14.5).[4]*

Similarly, achieving MRD-negative CR at 12 months was associated with significantly higher odds of remaining progression-free and alive compared with those who did not achieve MRD-negative CR at 12 months (odds ratio for PFS, 12.0; 95% CI: 7.3-16.6).[4]

MRD-negative CR is a strong prognostic factor for PFS across disease settings in multiple myeloma and may be useful for treatment decision-making[4]

CI=confidence interval; CR=complete response; FDA=U.S. Food and Drug Administration; MRD=minimal residual disease; PFS=progression-free survival.

*The International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i²TEAMM) group conducted a prospectively planned, pooled analysis of individual patient data from 11 randomized controlled trials comprising 4,773 patients with multiple myeloma (including transplant-eligible, transplant-ineligible, and relapsed/refractory multiple myeloma) to assess minimal residual disease as a potential intermediate clinical trial endpoint that would be reasonably likely to predict long-term clinical benefit.[4]

DARZALEX *FASPRO*® + VRd: The first and only FDA approval in NDMM based on a study with a primary endpoint of MRD negativity (≥CR, 10^{-5})[1,6]

CEPHEUS: Phase 3 study of DARZALEX *FASPRO*® + VRd vs VRd in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.[1,2]

Key eligibility criteria

- NDMM patients (TIE or refused transplant as initial therapy)
- ECOG PS 0-2
- Frailty index of 0-1*

The effectiveness of DARZALEX *FASPRO*® + VRd has not been established in patients who refused ASCT as initial therapy.

1:1 randomization (N=395)

21-day cycles
8 cycles of bortezomib treatment

VRd
V: 1.3 mg/m² BSA SC Days 1, 4, 8, 11
R: 25 mg PO Days 1–14
d: 20 mg PO Days 1, 2, 4, 5, 8, 9, 11, 12

DVRd
D: 1,800 mg SC QW Cycles 1–2, Q3W Cycles 3–8
VRd: schedule as to the left

28-day cycles until disease progression or unacceptable toxicity

Rd Cycles 9+
R: 25 mg PO Days 1–21
d: 40 mg PO Days 1, 8, 15, 22

DRd Cycles 9+
D: 1,800 mg SC Q4W
Rd: schedule as to the left

Primary endpoint
- Overall MRD (≥CR) negativity rate†

Key secondary endpoints
- Complete response (CR) or better (≥CR) rate
- Progression-free survival
- Sustained MRD-negativity (≥CR; 10^{-5}) rate (≥12 months)

ASCT=autologous stem cell transplant; BSA=body surface area; CR=complete response; D=DARZALEX *FASPRO*®; d=dexamethasone; DRd=DARZALEX *FASPRO*® (D) + lenalidomide (R) + dexamethasone (d); DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); ECOG PS=Eastern Cooperative Oncology Group performance status; FDA=U.S. Food and Drug Administration; MRD=minimal residual disease; NDMM=newly diagnosed multiple myeloma; PO=oral; QW=every week; Q3W=every 3 weeks; Q4W=every 4 weeks; R=lenalidomide (R); Rd=lenalidomide (R) + dexamethasone (d); SC=subcutaneous; TIE=transplant ineligible; V=bortezomib; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*Calculation of additive frailty is based on a scale of 0-5 based on age, comorbidities, and cognitive and physical conditions, with 0 indicating fit, 1 indicating intermediate fitness, and ≥2 indicating frail, per the Myeloma Geriatric Assessment score (http://www.myelomafrailtyscorecalculator.net).[2]

†FDA dictates that MRD should be assessed in patients who are in CR.[7]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®.

CEPHEUS included a broad range of patients with newly diagnosed multiple myeloma[1,2]

CEPHEUS: Patient demographic and clinical characteristics at baseline (ITT population)[2]*

DVRd and VRd treatment arms were well-balanced[2,8]

Characteristics	DVRd (n=197)	VRd (n=198)
Age		
Median (range) (years)	70 (42–79)	70 (31–80)
Distribution, no. (%)		
<65 years	36 (18.3)	35 (17.7)
65 to <70 years	52 (26.4)	53 (26.8)
≥70 years	109 (55.3)	110 (55.6)
Male sex, no. (%)†	87 (44.2)	111 (56.1)
Race, no. (%)†		
White	162 (82.2)	156 (78.8)
Black or African American	10 (5.1)	9 (4.5)
Asian	11 (5.6)	14 (7.1)
Native Hawaiian or other Pacific Islander	0	1 (0.5)
Other	1 (0.5)	2 (1.0)
Not reported	13 (6.6)	16 (8.1)
ECOG performance status score, no. (%)‡		
0	71 (36.0)	84 (42.4)
1	103 (52.3)	100 (50.5)
2	23 (11.7)	14 (7.1)

del=deletion; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); ECOG=Eastern Cooperative Oncology Group; IgA=immunoglobulin A; IgD=immunoglobulin D; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM=immunoglobulin M; ISS=International Staging System; ITT=intent-to-treat; t=translocation; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*The intention-to-treat population was defined as all patients who underwent randomization.[2]

†Sex and race were reported by the patient.[2]

‡ECOG performance status is scored on a scale of 0-5, with 0 indicating no symptoms and higher scores indicating increasing disability.[2]

Continued on next page

SELECT IMPORTANT SAFETY INFORMATION

Systemic Reactions

In a pooled safety population of 1446 patients with multiple myeloma (N=1235) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or as part of a combination therapy, 7% of patients experienced a systemic administration-related reaction (Grade 2: 3%, Grade 3: 0.8%, Grade 4: 0.1%).

In all patients (N=1639), systemic administration-related reactions occurred in 7% of patients with the first injection, 0.5% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 283 systemic administration-related reactions that occurred in 135 patients, 240 (85%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

CEPHEUS included a broad range of patients with newly diagnosed multiple myeloma[1,2] (cont)

Characteristics	DVRd (n=197)	VRd (n=198)
Frailty score, no. (%)[§]		
0 (fit)	124 (62.9)	132 (66.7)
1 (intermediate fitness)	73 (37.1)	66 (33.3)
Type of measurable disease, no. (%)		
Detected in serum only	120 (60.9)	108 (54.5)
IgG	89 (45.2)	76 (38.4)
IgA	27 (13.7)	31 (15.7)
Other[‖]	4 (2.0)	1 (0.5)
Detected in serum and urine	41 (20.8)	45 (22.7)
Detected in urine only	20 (10.2)	24 (12.1)
Detected in serum-free light chains only	16 (8.1)	21 (10.6)
ISS disease stage, no. (%)[¶]		
I	68 (34.5)	68 (34.3)
II	73 (37.1)	75 (37.9)
III	56 (28.4)	55 (27.8)
Cytogenetic risk profile, no. (%)[#]		
Standard risk	149 (75.6)	149 (75.3)
High risk	25 (12.7)	27 (13.6)
Indeterminate**	23 (11.7)	22 (11.1)
Median time since diagnosis of multiple myeloma (range) (months)	1.2 (0.4–5.8)	1.3 (0.3–8.0)

In CEPHEUS, 21% of patients enrolled in the trial were aged 75 years and older[1]

del=deletion; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); ECOG=Eastern Cooperative Oncology Group; IgA=immunoglobulin A; IgD=immunoglobulin D; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM=immunoglobulin M; ISS=International Staging System; ITT=intent-to-treat; t=translocation; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

[§]Total additive frailty is scored on a scale of 0-5 based on age, comorbidities, and cognitive and physical conditions, with 0 indicating fit, 1 intermediate fitness, and ≥2 frail, per the Myeloma Geriatric Assessment score (http://www.myelomafrailtyscorecalculator.net).[2]

[‖]Includes IgD, IgM, IgE, and biclonal.[2]

[¶]ISS disease stage is based on the combination of serum β_2-microglobulin and albumin levels. Higher stages indicate more advanced disease.[2]

[#]Cytogenetic risk was assessed by fluorescence in situ hybridization. High risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).[2]

**Indeterminate includes patients with missing or unevaluable samples.[2]

SELECT IMPORTANT SAFETY INFORMATION

Systemic Reactions (cont)

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

CEPHEUS: Select key endpoints[1]

Primary analysis

At a median follow-up of ~2 years (22 months):

52% of patients achieved MRD negativity (10^{-5}) and complete response or better

vs

35% with VRd alone*†

(*P*=0.0005)

At a median follow-up of 22 months, **overall complete response or better (≥CR) rates were 76.1% in the DVRd arm** and 58.6% in the VRd arm (*P*=0.0002).‡

Interim analysis

At a median follow-up of 39 months:

Patients in the DVRd arm achieved a significantly higher rate of sustained MRD negativity (10^{-5}) vs VRd alone (42.6% vs 25.3%; *P*=0.0003).

↓40% **reduction in the risk of disease progression or death with DVRd compared with VRd alone** (HR=0.60; 95% CI: 0.41-0.88; *P*=0.0078). The median PFS had not been reached in either arm.

This is the first FDA approval in NDMM based on a study with a primary endpoint of MRD negativity (≥CR, 10^{-5})[1,2,6]

CI=confidence interval; ≥CR=complete response or better; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); FDA=U.S. Food and Drug Administration; HR=hazard ratio; MRD=minimal residual disease; NDMM=newly diagnosed multiple myeloma; PFS=progression-free survival; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*Primary endpoint.[1,2]

†MRD-negative complete response rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR.[1]

‡Secondary endpoint.[2]

SELECT IMPORTANT SAFETY INFORMATION

Systemic Reactions (cont)

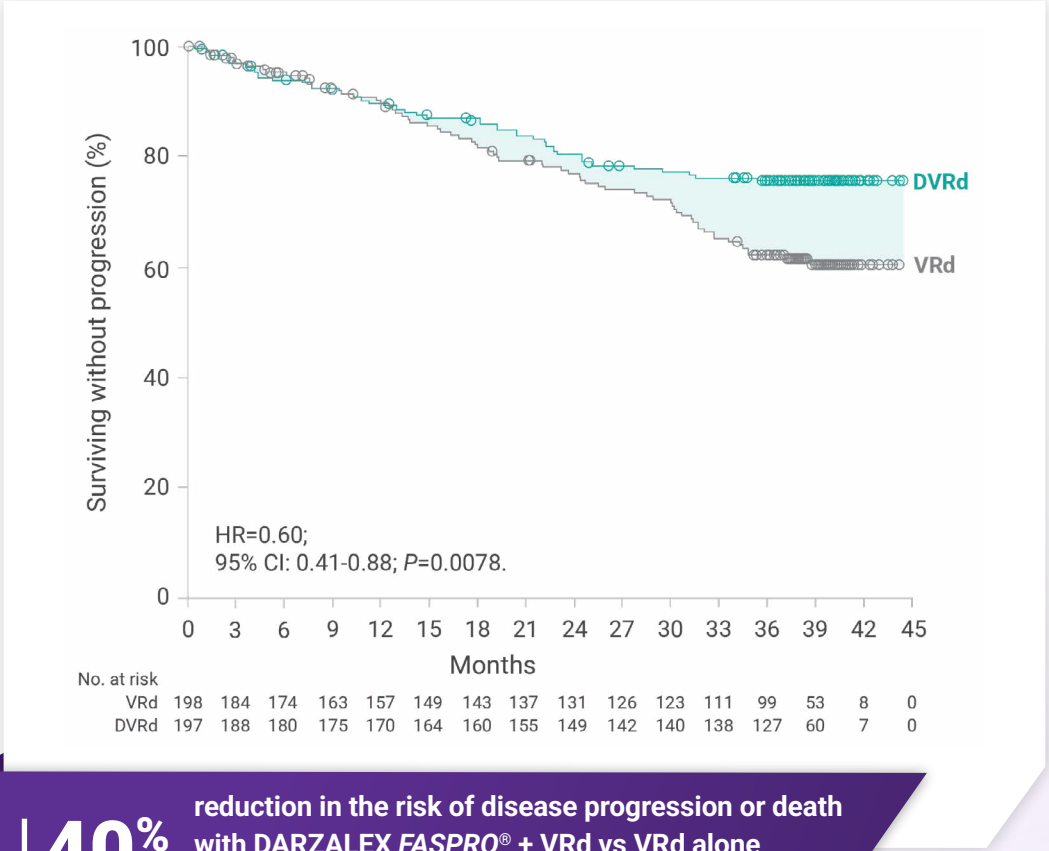
Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

For transplant-ineligible patients with newly diagnosed multiple myeloma

DARZALEX *FASPRO*® + VRd also significantly reduced the risk of disease progression or death vs VRd alone[1]

Interim analysis

- At a median follow-up of 39 months, an interim analysis of PFS demonstrated a 40% reduction in the risk of disease progression or death with DVRd compared with VRd alone (HR=0.60; 95% CI: 0.41-0.88; *P*=0.0078). The median PFS had not been reached in either arm



↓40% **reduction in the risk of disease progression or death with DARZALEX *FASPRO*® + VRd vs VRd alone** (HR=0.60; 95% CI: 0.41-0.88; *P*=0.0078)

CI=confidence interval; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; PFS=progression-free survival; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

SELECT IMPORTANT SAFETY INFORMATION

Systemic Reactions (cont)

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

For transplant-ineligible patients with newly diagnosed multiple myeloma

DARZALEX *FASPRO*® + VRd delivers deep and durable responses[1]

Final analysis

At a median follow-up of nearly 5 years (59 months)[1,2]:

Overall Response Rates

97.0% vs 93.4% for VRd

Complete Response or Better Rates (sCR+CR; ≥CR)*

81.2% vs 61.6% for VRd

sCR
65.0% vs 44.9% for VRd

CR
16.2% vs 16.7% for VRd

Overall MRD Negativity Rates (≥CR, 10^{-5})†

60.9% vs 39.4% for VRd (95% CI: 1.58-3.55)

Sustained MRD Negativity Rates (10^{-5}, ≥12 months)‡

48.7% vs 26.3% for VRd (95% CI: 1.73-4.00)

Progression-Free Survival

↓43% **reduction in the risk of disease progression or death with DARZALEX *FASPRO*® + VRd vs VRd alone** (HR=0.57; 95% CI: 0.41-0.79; *P*=0.0005)

The median PFS had not been reached in the DVRd treatment arm and was 52.6 months in the VRd treatment arm.

CI=confidence interval; CR=complete response; ≥CR=complete response or better; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); FDA=U.S. Food and Drug Administration; HR=hazard ratio; MRD=minimal residual disease; PFS=progression-free survival; sCR=stringent complete response; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*Stringent complete response (sCR) is CR plus a normal free light chain ratio and the absence of clonal plasma cells in bone marrow as assessed by immunohistochemistry or immunofluorescence.[9]

†The overall MRD negativity rate was defined as the proportion of patients who achieved complete response or better and MRD negativity (at or below a sensitivity threshold of 10^{-5}) after randomization but prior to disease progression, subsequent antimyeloma therapy, or both.[2]

‡Sustained MRD negativity is defined as confirmed MRD-negative status at 2 examinations at least 1 year apart without MRD-positive status in between.[1]

SELECT IMPORTANT SAFETY INFORMATION

Local Reactions

In this pooled safety population of 1446 patients with multiple myeloma (N=1253) or light chain amyloidosis (N=193), injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 1.1%. The most frequent (>1%) injection-site reaction was injection-site erythema and injection-site rash. In patients with high-risk smoldering multiple myeloma (N=193), injection-site reactions occurred in 28% of patients, including Grade 2 reactions in 3%. These local reactions occurred at a median of 6 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

In the treatment of transplant-ineligible patients with newly diagnosed multiple myeloma

Types of adverse events seen with DARZALEX *FASPRO*® + VRd were similar to those observed with the individual drugs[1]

Adverse reactions reported in ≥20% of patients who received DARZALEX *FASPRO*® + VRd in CEPHEUS

	DARZALEX *FASPRO*®-VRd (n=197)		VRd (n=195)	
Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections				
Upper respiratory tract infection*	75	4#	63	3#
COVID-19†	39**	9	25**	3
Pneumonia‡	31**	16	26**	15
Urinary tract infection†	24	4#	17	3#
Nervous system disorders				
Sensory neuropathy§	72	12#	72	10
Motor dysfunction‖	44	11#	37	7#
Dizziness†	26	2#	26	1#
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain†	62	9#	61	7#
Gastrointestinal disorders				
Diarrhea†	57	12#	59	9#
Constipation	38	2#	42	3#
Nausea	25	0	25	2#
Abdominal pain†	23**	1	17	2#

COVID-19=coronavirus 19; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*Upper respiratory tract infection includes acute sinusitis, influenza, influenza-like illness, laryngitis, nasal congestion, nasopharyngitis, parainfluenzae virus infection, pharyngitis, pharyngitis streptococcal, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection bacterial, respiratory tract infection viral, rhinitis, rhinovirus infection, sinus congestion, sinus disorder, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection, upper respiratory tract inflammation, and viral upper respiratory tract infection.[1]

†Includes other related terms.[1]

‡Pneumonia includes bronchopulmonary aspergillosis, COVID-19 pneumonia, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia cryptococcal, pneumonia influenzal, pneumonia klebsiella, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia viral, and tuberculosis.[1]

§Sensory neuropathy includes anosmia, burning sensation, dysesthesia, hyperesthesia, hyperesthesia teeth, hypoesthesia, hypoesthesia oral, neuralgia, neuropathy peripheral, oral dysesthesia, palmar-plantar erythrodysesthesia syndrome, paresthesia, paresthesia oral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, and skin burning sensation.[1]

‖Motor dysfunction includes balance disorder, essential tremor, extrapyramidal disorder, facial paralysis, gait disturbance, hypotonia, mobility decreased, motor dysfunction, muscle contractions involuntary, muscle contracture, muscle spasms, muscular weakness, myopathy, paraparesis, peripheral motor neuropathy, peroneal nerve palsy, pharyngeal paresthesia, and tremor.[1]

¶Renal impairment includes acute kidney injury, blood creatinine increased, chronic kidney disease, creatinine renal clearance decreased, glomerular filtration rate decreased, prerenal failure, renal failure, renal impairment, and renal injury.[1]

#Only Grade 3 adverse reactions occurred.[1]

**Fatal adverse reactions occurred for abdominal pain: n=1 (1%) in the DARZALEX *FASPRO*®-VRd arm; COVID-19: n=7 (4%) in the DARZALEX *FASPRO*®-VRd arm and n=5 (3%) in the VRd arm; pneumonia: n=8 (4%) in the DARZALEX *FASPRO*®-VRd arm and n=5 (3%) in the VRd arm; dyspnea: n=1 (1%) in the DARZALEX *FASPRO*®-VRd arm.[1]

Continued on next page

In the treatment of transplant-ineligible patients with newly diagnosed multiple myeloma

Types of adverse events seen with DARZALEX *FASPRO*® + VRd were similar to those observed with the individual drugs[1] (cont)

	DARZALEX *FASPRO*®-VRd (n=197)		VRd (n=195)	
Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
General disorders and administration site conditions				
Fatigue†	56	14#	53	11#
Edema†	54	4#	46	2#
Pyrexia†	24	1#	16	1#
Skin and subcutaneous tissue disorders				
Rash†	50	8#	47	7
Psychiatric disorders				
Sleep disorder†	33	3#	33	2#
Respiratory, thoracic, and mediastinal disorders				
Cough†	32	1#	21	1#
Dyspnea†	21**	2	17	1#
Renal and urinary disorders				
Renal impairment¶	26	7	25	6
Metabolism and nutrition disorders				
Decreased appetite	21	1#	20	3#
Injury, poisoning, and procedural complications				
Bruising†	20	0	12	0

COVID-19=coronavirus 19; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*Upper respiratory tract infection includes acute sinusitis, influenza, influenza-like illness, laryngitis, nasal congestion, nasopharyngitis, parainfluenzae virus infection, pharyngitis, pharyngitis streptococcal, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection bacterial, respiratory tract infection viral, rhinitis, rhinovirus infection, sinus congestion, sinus disorder, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection, upper respiratory tract inflammation, and viral upper respiratory tract infection.[1]

†Includes other related terms.[1]

‡Pneumonia includes bronchopulmonary aspergillosis, COVID-19 pneumonia, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia cryptococcal, pneumonia influenzal, pneumonia klebsiella, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia viral, and tuberculosis.[1]

§Sensory neuropathy includes anosmia, burning sensation, dysesthesia, hyperesthesia, hyperesthesia teeth, hypoesthesia, hypoesthesia oral, neuralgia, neuropathy peripheral, oral dysesthesia, palmar-plantar erythrodysesthesia syndrome, paresthesia, paresthesia oral, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, and skin burning sensation.[1]

‖Motor dysfunction includes balance disorder, essential tremor, extrapyramidal disorder, facial paralysis, gait disturbance, hypotonia, mobility decreased, motor dysfunction, muscle contractions involuntary, muscle contracture, muscle spasms, muscular weakness, myopathy, paraparesis, peripheral motor neuropathy, peroneal nerve palsy, pharyngeal paresthesia, and tremor.[1]

¶Renal impairment includes acute kidney injury, blood creatinine increased, chronic kidney disease, creatinine renal clearance decreased, glomerular filtration rate decreased, prerenal failure, renal failure, renal impairment, and renal injury.[1]

#Only Grade 3 adverse reactions occurred.[1]

**Fatal adverse reactions occurred for abdominal pain: n=1 (1%) in the DARZALEX *FASPRO*®-VRd arm; COVID-19: n=7 (4%) in the DARZALEX *FASPRO*®-VRd arm and n=5 (3%) in the VRd arm; pneumonia: n=8 (4%) in the DARZALEX *FASPRO*®-VRd arm and n=5 (3%) in the VRd arm; dyspnea: n=1 (1%) in the DARZALEX *FASPRO*®-VRd arm.[1]

Most frequent hematologic laboratory abnormalities and serious adverse reactions in CEPHEUS[1]*

Select laboratory abnormalities (≥30%) that worsened from baseline in patients who received DARZALEX *FASPRO*® + VRd in CEPHEUS

	DARZALEX *FASPRO*®-VRd†		VRd	
Laboratory abnormality	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology				
Decreased leukocytes	93	39	77	15
Decreased neutrophils	89	49	75	35
Decreased lymphocytes	87	55	72	38
Decreased platelets	81	31	73	23
Decreased hemoglobin	53	14	52	16
Chemistry				
Increased ALT	66	7	61	3
Increased creatinine	54	5	56	3
Decreased potassium	53	19	36	12
Decreased sodium	48	16	40	13
Increased AST	43	3	46	3
Increased alkaline phosphatase	43	2	31	1
Decreased corrected calcium	32	5	26	5

- The median duration of treatment was 56.3 months (0.1-64.6 months) for DARZALEX *FASPRO*® + VRd and 34.3 months (0.5-63.8 months) for VRd
- Serious adverse reactions occurred in 72% of patients who received DARZALEX *FASPRO*® + VRd. The most frequent serious adverse reactions in >5% of patients who received DARZALEX *FASPRO*® + VRd were pneumonia (19%), COVID-19 (12%), thromboembolism (7%), and diarrhea (6%)
- Fatal adverse reactions occurred in 16.8% of patients who received DARZALEX *FASPRO*® + VRd
  - Fatal adverse reactions that occurred in more than 1 patient included pneumonia (4%), COVID-19 (4%), and myocardial infarction (2%)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; COVID-19=coronavirus 19; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*A total of 395 patients (with transplant-ineligible disease or who refused transplant as initial therapy) with newly diagnosed multiple myeloma were enrolled between December 11, 2018, and October 7, 2019, with a clinical cutoff date of May 7, 2024. This time period coincided with the World Health Organization's International Health Regulation Emergency Committee declaring the 2019 novel coronavirus outbreak a Public Health Emergency of International Concern (PHEIC) in January 2020.[2,10]

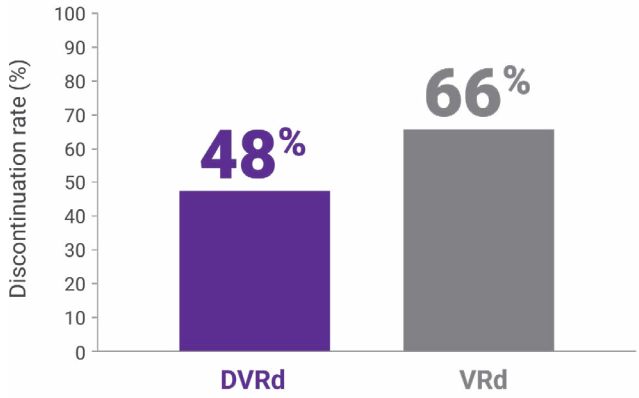
†Denominator is based on number of subjects with a baseline and post-baseline laboratory value for each laboratory test: N=197 for DARZALEX *FASPRO*® + VRd and N=194 for VRd.[1]

In the treatment of transplant-ineligible patients with newly diagnosed multiple myeloma

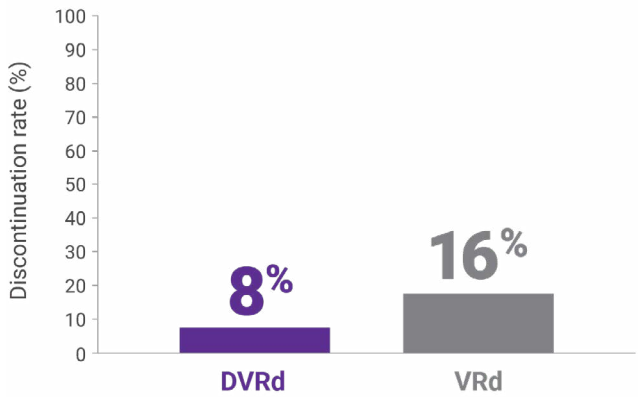
Fewer patients in the DVRd group vs VRd discontinued treatment[2]

At a median follow-up of nearly 5 years (59 months):

Overall treatment discontinuations



Treatment discontinuations due to TEAEs[1,2]



COVID-19=coronavirus 19; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

Treatment discontinuations with DVRd vs VRd were due to:

- Progressive disease: 13.7% vs 26.2%[2]
- Deaths (excluding Grade 5 TEAE): 17.3% (34/197) vs 12.3% (24/195)[8]
- COVID-19–related deaths: 7.6% (15/197) vs 4.6% (9/195)[11]
- Other*: 9.1% (18/197) vs 10.8% (21/195)[8]

*"Other" included patients who refused further treatment, physician decision, and patients who received concurrent treatment for multiple myeloma prior to disease progression.[8]

For your transplant-ineligible patients with newly diagnosed multiple myeloma

Think DARZALEX *FASPRO*® + VRd at diagnosis

Primary analysis: at a median follow-up of 22 months[1]

Deep responses

52% of patients achieved MRD negativity (10^{-5}) and complete response or better with DVRd vs 35% with VRd alone*† (*P*=0.0005)

76.1% of patients achieved an overall CR or better (≥CR) rate with DVRd vs 58.6% with VRd alone‡ (*P*=0.0002)

Interim analysis: at a median follow-up of 39 months[1]

Durable outcomes

At longer median follow-up, more patients achieved sustained MRD negativity with DVRd vs VRd alone

42.6% of patients achieved a sustained MRD negativity (10^{-5}) rate with DVRd vs 25.3% with VRd alone (*P*=0.0003)

↓40% reduction in the risk of disease progression or death with DARZALEX *FASPRO*® + VRd vs VRd alone (HR=0.60; 95% CI: 0.41-0.88; *P*=0.0078)

Final analysis: at a median follow-up of 59 months[2]

Long-term follow-up

↓43% reduction in the risk of disease progression or death with DARZALEX *FASPRO*® + VRd vs VRd alone (HR=0.57; 95% CI: 0.41-0.79; *P*=0.0005)

The median PFS had not been reached in the DVRd treatment arm and was 52.6 months in the VRd treatment arm.

CI=confidence interval; CR=complete response; DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; MRD=minimal residual disease; PFS=progression-free survival; VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*Primary endpoint.[1,2]

†MRD-negative complete response rate was defined as the proportion of patients who achieved MRD negativity (10^{-5} threshold) and ≥CR.[1]

‡Secondary endpoint.[2]

SELECT IMPORTANT SAFETY INFORMATION

Infections

DARZALEX *FASPRO*® can cause serious, life-threatening, or fatal infections. In patients who received DARZALEX *FASPRO*® in a pooled safety population including patients with smoldering multiple myeloma and light chain (AL) amyloidosis (N=1639), serious infections, including opportunistic infections, occurred in 24% of patients, Grade 3 or 4 infections occurred in 22%, and fatal infections occurred in 2.5%. The most common type of serious infection reported was pneumonia (8.5%).

Monitor patients for signs and symptoms of infection prior to and during treatment with DARZALEX *FASPRO*® and treat appropriately. Administer prophylactic antimicrobials according to guidelines.

Important Safety Information

CONTRAINDICATIONS

DARZALEX *FASPRO*® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase, or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®.

Systemic Reactions

In a pooled safety population of 1446 patients with multiple myeloma (N=1235) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or as part of a combination therapy, 7% of patients experienced a systemic administration-related reaction (Grade 2: 3%, Grade 3: 0.8%, Grade 4: 0.1%).

In all patients (N=1639), systemic administration-related reactions occurred in 7% of patients with the first injection, 0.5% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 283 systemic administration-related reactions that occurred in 135 patients, 240 (85%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

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Important Safety Information (cont)

Local Reactions

In this pooled safety population of 1446 patients with multiple myeloma (N=1253) or light chain amyloidosis (N=193), injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 1.1%. The most frequent (>1%) injection-site reaction was injection-site erythema and injection-site rash. In patients with high-risk smoldering multiple myeloma (N=193), injection-site reactions occurred in 28% of patients, including Grade 2 reactions in 3%. These local reactions occurred at a median of 6 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

Infections

DARZALEX *FASPRO*® can cause serious, life-threatening, or fatal infections. In patients who received DARZALEX *FASPRO*® in a pooled safety population including patients with smoldering multiple myeloma and light chain (AL) amyloidosis (N=1639), serious infections, including opportunistic infections, occurred in 24% of patients, Grade 3 or 4 infections occurred in 22%, and fatal infections occurred in 2.5%. The most common type of serious infection reported was pneumonia (8.5%).

Monitor patients for signs and symptoms of infection prior to and during treatment with DARZALEX *FASPRO*® and treat appropriately. Administer prophylactic antimicrobials according to guidelines.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX *FASPRO*® until recovery of neutrophils. In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX *FASPRO*® until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX *FASPRO*® and for 3 months after the last dose.

The combination of DARZALEX *FASPRO*® with lenalidomide, thalidomide, or pomalidomide is contraindicated in pregnant women because lenalidomide, thalidomide, and pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide, or pomalidomide prescribing information on use during pregnancy.

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Important Safety Information (cont)

Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks 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.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX *FASPRO*®.

Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (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. This interference can impact the determination of complete response and of disease progression in some DARZALEX *FASPRO*®-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, sleep disorder, headache, rash, renal impairment, motor dysfunction, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, musculoskeletal pain, decreased appetite, urinary tract infection, abdominal pain, upper respiratory tract infection, peripheral neuropathy, peripheral sensory neuropathy, constipation, pneumonia, edema, dizziness, bruising, and COVID-19.

The most common hematology laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Indications

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib, lenalidomide, and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant

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Indications (cont)

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent

Please click here to read full Prescribing Information for DARZALEX *FASPRO*®.

cp-143279v12

References: 1. DARZALEX *FASPRO*® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Usmani SZ, Facon T, Hungria V, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nat Med*. 2025;31(4):1195-1202. **3.** Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv*. 2020;4(23):5988-5999. **4.** Shi Q, Paiva B, Pederson LD, et al. Minimal residual disease–based end point for accelerated assessment of clinical trials in multiple myeloma: a pooled analysis of individual patient data from multiple randomized trials. *J Clin Oncol*. 2025;43(11):1289-1301. Published online February 12, 2025. doi:10.1200/JCO-24-02020 **5.** Data on file. RF-462016. Janssen Biotech, Inc. **6.** Data on file. RF-433969. Janssen Biotech, Inc. **7.** Data on file. RF-140179. Janssen Biotech, Inc. **8.** Usmani SZ, Facon T, Hungria V, et al. Daratumumab SC + bortezomib/lenalidomide/dexamethasone in patients with transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: results of the phase 3 CEPHEUS study. Presented at: 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. **9.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115. **10.** World Health Organization. COVID 19 Public Health Emergency of International Concern (PHEIC) Global research and innovation forum: towards a research roadmap. Presented February 11-12, 2020. **11.** Usmani SZ, Facon T, Hungria V, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nat Med*. 2025;31(4):1195-1202. [supplementary appendix].