J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

02-2025

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

**הנדון: דארזלקס 120 מ"ג/מ"ל תת עורי 1,800 מ"ג**
**Darzalex 120mg/ml S.C 1800mg**

חברת J-C Health Care Ltd מבקשת להודיעכם כי העלון לרופא של התכשיר שבנדון התעדכן ב 02-2025.

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן בטקסט ~~בחול עם קו חוצה~~, טקסט המהווה החמרה מודגש ברקע צהוב )אך קיימים עדכונים נוספים.

**ההתוויות המאושרות לתכשיר בישראל:**

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

Light chain (AL) amyloidosis
In combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.

**מרכיב פעיל:** Daratumumab

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug.

כמו כן, מצורפים לפרסום זה וניתן לקבל העתק מודפס שלהם באמצעות פנייה לבעל הרישום: J-C Health Care Ltd, קיבוץ שפיים, 6099000, טל': 09-9591111.

בברכה,

יעל לפידות מללי
רוקחת ממונה
J-C Health Care Ltd

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

**העדכון בעלון לרופא הינו:**

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Multiple myeloma
DARZALEX ~~120MG/ML S.C. 1,800MG~~ 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.
- for the treatment of adult patients with multiple myeloma in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (see section 5.1).
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Light chain (AL) amyloidosis
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

.....
Posology

*Multiple myeloma*

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

The recommended dose is 1,800 mg of DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 1.

**Table 1: DARZALEX ~~120MG/ML S.C. 1,800MG~~ dosing schedule in combination with lenalidomide , 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

For dose and schedule of medicinal products administered with DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

*Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)*

The recommended dose is 1,800 mg of DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 2.

…..

*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 5.

**Table 5: 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.

Cardiac deficiency

No clinical data are available for patients with NYHA Class IIIB and IV since they were excluded from clinical trials. Very few data on patients with Mayo cardiac stage IIIB are available. No posology can be recommended (see section 5.1).

….

**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.

….

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

## 4.8 Undesirable effects

Summary of the safety profile

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

~~With the exception of IRRs (see Table 5 below), T~~the safety profile of the DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation ~~(evaluated in 260 and 258 patients treated with the subcutaneous and intravenous formulations respectively) from the phase III study MMY3012~~ was similar to ~~that of the known safety profile of the~~ intravenous formulation with the exception of a lower rate of IRRs. In the phase III study MMY3012, ~~,~~ n~~N~~eutropenia ~~is~~ was the only adverse reaction reported at ≥ 5% higher frequency for DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation compared to intravenous daratumumab (grade 3 or 4: 13% vs 8%, respectively).

Tabulated list of adverse reactions

Table ~~5~~6 summarises the adverse reactions that occurred in patients receiving DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation or intravenous formulation of daratumumab.

The data reflects exposure to DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation (1~~,~~800 mg) in ~~490~~ 639 patients with multiple myeloma (MM). The data includ~~ing~~es 260 patients from a phase III active-controlled study (MMY3012) who received DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection as monotherapy and 149 patients from a phase III active-controlled study (MMY3013) who received DARZALEX subcutaneous formulation in combination with pomalidomide and dexamethasone (D-Pd). ~~and~~The data also reflects three open-label, clinical studies in which patients received DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX ~~120MG/ML S.C. 1,800MG~~ 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). 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).

….

**Table ~~5~~6: Adverse reactions in 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 | 37 | 2 |
| | ~~Bronchitis[a]~~Pneumonia[a] | | ~~14~~17 | ~~2~~10 |
| | ~~Pneumonia[a]~~ Bronchitis[a] | | 14 | ~~9~~1 |
| | Urinary tract infection | Common | ~~7~~6 | 1 |
| | Influenza | | 4 | 1[#] |
| | Sepsis[a] | | 4 | 3 |
| | COVID-~~19[d]~~19[g] | | 7 | 4 |
| | Cytomegalovirus infection[a] | Un~~C~~common | < 1 | < 1[#] |

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

| | | | | |
|---|---|---|---|---|
| | Hepatitis B Virus reactivation[a] | ~~Uncommon~~ | < 1 | < 1 |
| **Blood and lymphatic system disorders** | Neutropenia[a] | Very common | ~~40~~39 | 33 |
| | Thrombocytopenia[a] | | ~~30~~29 | ~~18~~17 |
| | Anaemia[a] | | 27 | 12 |
| | Lymphopenia[a] | | ~~13~~14 | 11 |
| | Leukopenia[a] | | 11 | 6 |
| **Immune system disorders** | Hypogammaglobulinemia[a] | Common | 2 | < 1[#] |
| | Anaphylactic reaction[b] | Rare | - | - |
| **Metabolism and nutrition disorders** | Decreased appetite | Very common | 10 | 1 |
| | Hyperglycaemia | Common | 6 | 3 |
| | Hypocalcaemia | | 5 | 1 |
| | Dehydration | | 2 | 1[#] |
| **Psychiatric disorders** | Insomnia | Very common | ~~14~~15 | 1[#] |
| **Nervous system disorders** | Peripheral sensory neuropathy | Very common | 26 | 3 |
| | Headache | | ~~11~~10 | < 1[#] |
| | Dizziness | Common | 9 | < 1[#] |
| | Paraesthesia | | 9 | < 1 |
| | Syncope | | 3 | 2[#] |
| **Cardiac disorders** | Atrial fibrillation | Common | 3 | 1 |
| **Vascular disorders** | Hypertension[a] | ~~Very c~~Common | 9 | ~~5~~4 |
| **Respiratory, thoracic and mediastinal disorders** | Cough[a] | Very common | ~~22~~21 | < 1[#] |
| | Dyspnoea[a] | | 18 | 2 |
| | Pulmonary oedema[a] | Common | 1 | < 1 |
| **Gastrointestinal disorders** | Diarrhoea | Very common | 29 | ~~3~~4 |
| | Constipation | | 28 | 1 |
| | Nausea | | ~~23~~22 | 1[#] |
| | Vomiting | | 14 | 1[#] |
| | Pancreatitis[a] | Common | 1 | <1 |
| **Skin and subcutaneous tissue disorders** | Rash | Very c~~C~~ommon | ~~9~~10 | ~~<~~1[#] |
| | Pruritus | Common | ~~5~~6 | <1[#] |
| **Musculoskeletal and connective tissue disorders** | Back pain | Very common | ~~17~~16 | 2 |
| | Muscle spasms | | ~~12~~11 | <1[#] |
| | Arthralgia | | 10 | ~~<~~1[#] |
| | Musculoskeletal chest pain | Common | 6 | <1[#] |
| **General disorders and administration site conditions** | Fatigue | Very common | 23 | ~~3~~4 |
| | Oedema peripheral[a] | | 22 | 1 |
| | Pyrexia | | ~~22~~21 | 1 |
| | Asthenia | | 18 | 2 |
| | Chills | Common | ~~9~~8 | <1[#] |
| | ~~Injection site erythema[e]~~ | ~~Common~~ | ~~4~~ | ~~0~~ |
| | Injection site reactions[d,e] | | 8 | 0 |
| **Injury, poisoning and procedural complications** | Infusion-related reactions[c] | | | |
| | Daratumumab intravenous[f] | Very common | 39 | 5 |
| | Daratumumab subcutaneous[e] | ~~Very c~~Common | ~~11~~9 | 1[#] |

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

[#] No grade 4
[a] Indicates a grouping of terms.
[b] Based on post-marketing adverse reactions.
[c] Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
[d] Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
[e] Frequency based on daratumumab subcutaneous studies only (N=~~490~~832).
[f] Frequency based on daratumumab intravenous studies only (N=2324).
Note: Based on ~~2814~~ 3156 multiple myeloma and AL amyloidosis patients treated with daratumumab intravenous or daratumumab subcutaneous.
[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.

Description of selected adverse reactions

*Infusion-related reactions (IRRs)*
In clinical studies (monotherapy and combination treatments; N=~~490~~832) with DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation, the incidence of any grade IRRs was ~~10~~8.2% with the first injection of DARZALEX ~~120MG/ML S.C. 1,800MG~~ (1~~,~~800 mg, week 1), 0.~~2~~4% with the week 2 injection, and ~~0.8~~1.1% with subsequent injections. Grade 3 IRRs were seen in ~~1.4~~0.8% of patients. No patients had grade 4 IRRs.

Signs and symptoms of IRR may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, 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=~~490~~832) with DARZALEX ~~1,800MG daratumumab~~ subcutaneous formulation, the incidence of any grade injection site reaction was ~~8.2~~7.7%. There were no grade 3 or 4 ISRs. The most common (≥ 1%) ISR~~s~~ at the site of injection ~~were~~was erythema~~, injection site induration, pruritis~~.

*Infections*
In patients with multiple myeloma receiving ~~DARZALEX 120MG/ML S.C. 1,800MG~~ daratumumab as monotherapy, the overall incidence of infections was similar between DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation (52.9%) versus intravenous daratumumab groups (50.0%). Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation (11.7%) and intravenous daratumumab (14.3%). Most infections were manageable and rarely led to treatment discontinuation. Pneumonia was the most commonly reported ~~severe (G~~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: 2~~7~~8%, Rd: 23%; DPd: 28%
Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.
~~Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients. Fatal infections were primarily due to pneumonia and sepsis.~~
~~In patients receiving intravenous daratumumab combination therapy, fatal infections (g~~Grade 5~~)~~ (fatal) infections ~~were reported as follows~~:

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

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.~~

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

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.

…

*Elderly patients*
Of the 3~~207~~549 patients who received daratumumab (n=~~490~~ 832 subcutaneous; n=2717 intravenous) at the recommended dose, 38% were 65 to less than 75 years of age, and 1~~7~~6% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=~~1827~~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 are ineligible for autologous stem cell transplant (n=777), the most common serious adverse reaction that occurred more frequently in elderly (≥75 years of age) was pneumonia. Among patients with newly diagnosed AL amyloidosis (n=193), the most common serious adverse reaction that occurred more frequently in elderly (≥65 years of age) was pneumonia.

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

....

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

....

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed ~~at a high level~~ on the surface of cells in a variety of haematological malignancies, including clonal plasma cells in multiple myeloma ~~tumour cells~~and AL amyloidosis, 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.

....

Immunogenicity

In 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.

In multiple myeloma and AL amyloidosis patients, ~~T~~the incidence of treatment-emergent non-neutralizing anti-rHuPH20 antibodies was 7.~~8~~3% (~~35/447~~55/750)~~;~~ ); in patients who received either ~~with 7.5% (19/255) in the~~ monotherapy DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation ~~groups, and 8.3% (16/192) in the pooled~~ or combination DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation ~~groups~~. The anti-rHuPH20 antibodies did not appear to impact daratumumab exposures. The clinical relevance of the development of anti-daratumumab or anti-rHuPH20 antibodies after treatment with DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation is not known.

....

*Combination treatment with pomalidomide and deFxamethasone (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, **75% of patients having received 2–3 prior lines of therapy**. All patients received a prior treatment with a proteasome inhibitor (PI) and lenalidomide, and 56% of patients received prior stem

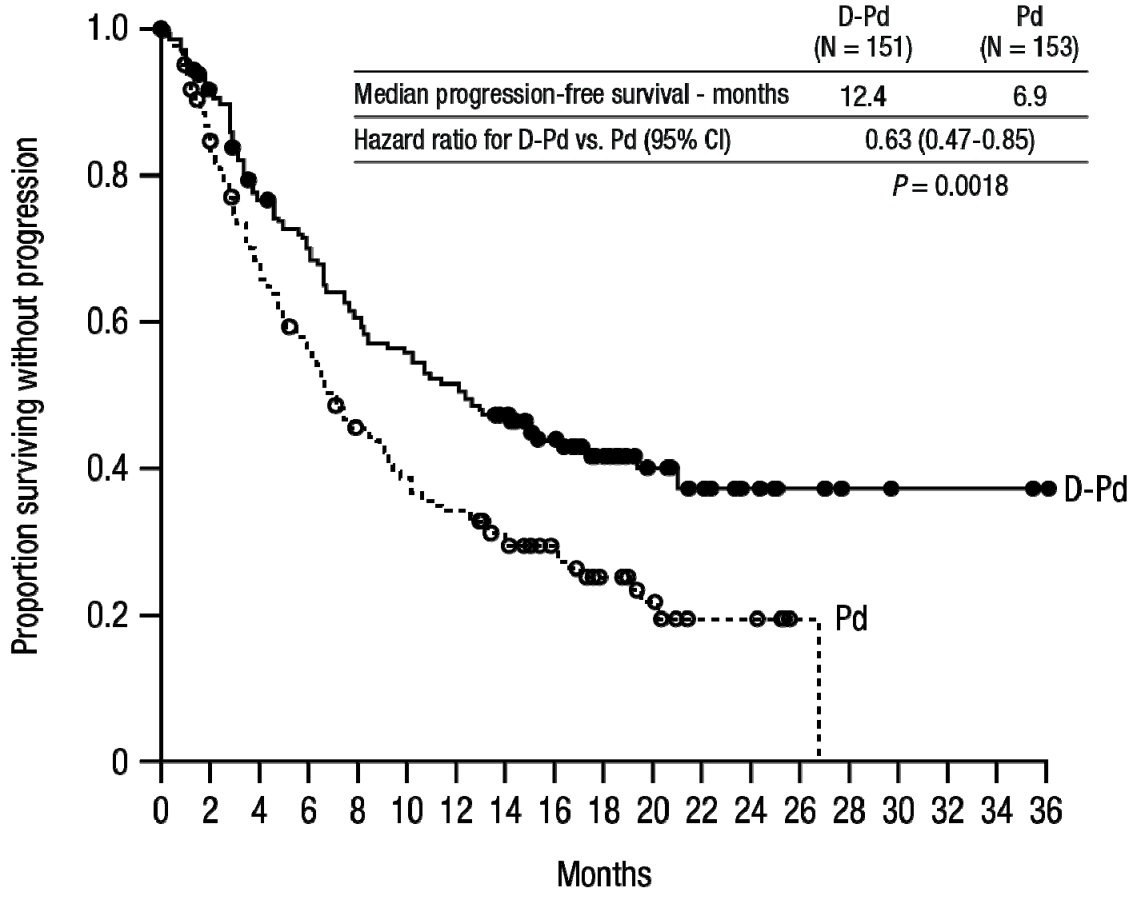
J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

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 1: 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 9 below.

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

**Table 9: Efficacy results from study MMY3013[a]**

| | D-Pd (n=151) | Pd (n=153) |
|---|---|---|
| **Overall response (sCR+CR+VGPR+PR) n(%)[a]** | 104 (68.9%) | 71 (46.4%) |
| P-value[b] | <0.0001 | |
| Stringent complete response (sCR) | 14 (9.3%) | 2 (1.3%) |
| Complete response (CR) | 23 (15.2%) | 4 (2.6%) |
| Very good partial response (VGPR) | 40 (26.5%) | 24 (15.7%) |
| Partial response (PR) | 27 (17.9%) | 41 (26.8%) |
| **MRD negativity rate[c] n(%)** | 13 (8.7%) | 3 (2.0%) |
| 95% CI (%) | (4.7%, 14.3%) | (0.4%, 5.6%) |
| P-value[d] | 0.0102 | |

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

[a] Based on intent-to-treat population

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

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

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

In responders, the median time to response was 1 month (range: 0.9 to 9.1 months) in the D-Pd group and 1.9 months (range: 0.9 to 17.3 months) in the Pd group. The median duration of response had not been reached in the D-Pd group (range: 1 to 34.9+ months) and was 15.9 months (range: 1+ to 24.8 months) in the Pd group.

*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 enrolled in study AMY3001 had newly diagnosed AL amyloidosis with at least one affected organ, measurable hematologic 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 hypervolemia, poorly controlled diabetes mellitus or prior intolerance to steroid therapy) were administered weekly on days 1, 8, 15, and 22 of repeated 28-day [4-week] cycles. On the days of DARZALEX dosing, 20 mg of the dexamethasone dose was given as a pre-injection 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

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

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 hematologic complete response (HemCR) rate as determined by the Independent Review Committee assessment based on International Concensus Criteria. Study AMY3001 demonstrated an improvement in HemCR in the D-VCd arm as compared to the VCd arm. Efficacy results are summarised in table 10.

**Table 10: Efficacy results from study AMY3001[a]**

| | D-VCd (n=195) | VCd (n=193) | P value |
|---|---|---|---|
| Hematologic complete response (HemCR), n (%) | 104 (53.3%) | 35 (18.1%) | <0.0001[b] |
| Very good partial response (VGPR), n (%) | 49 (25.1%) | 60 (31.1%) | |
| Partial response (PR), n (%) | 26 (13.3%) | 53 (27.5%) | |
| Hematologic VGPR or better (HemCR + VGPR), n (%) | 153 (78.5%) | 95 (49.2%) | <0.0001[b] |
| Major organ deterioration progression-free survival (MOD-PFS), Hazard ratio with 95% CI[c] | 0.58 (0.36, 0.93) | | 0.0211[d] |

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

[a] Based on intent-to-treat population

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

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

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

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.

The median follow-up for the study is 11.4 months. The median major organ deterioration progression-free survival (MOD-PFS) was not reached for patients in either arm.

Overall survival (OS) data were not mature. A total of 56 deaths were observed [n=27 (13.8%) D-VCd vs. n=29 (15%) VCd group].

.....

## 5.2 Pharmacokinetic properties

In patients with multiple myeloma, ~~D~~daratumumab exposure in a monotherapy study following the recommended 1~~,~~800 mg administration of DARZALEX ~~120MG/ML S.C. 1,800MG~~ 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 1~~,~~800 mg DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection, peak concentrations ($C_{max}$) increased 4.8-fold and total exposure ($AUC_{0\text{-}7\ days}$)

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

increased 5.4-fold from first dose to last weekly dose (8th dose). Highest trough concentrations for DARZALEX ~~120MG/ML S.C. 1,800MG~~ 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, ~~T~~the simulated trough concentrations following 6 weekly doses of 1~~,~~800 mg DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection for combination therapy were similar to 1~~,~~800 mg DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection monotherapy.

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).

Absorption and distribution

At the recommended dose of 1~~,~~800 mg, in multiple myeloma patients, the absolute bioavailability of DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection is 69%, with an absorption rate of 0.012 hour-1, with peak concentrations occurring at 70 to 72 h (Tmax). 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 modeled 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~~, suggesting that daratumumab is primarily localised to the vascular system with limited extravascular tissue distribution.~~ 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~~ing~~ that daratumumab is primarily localised to the vascular system with limited extravascular tissue distribution.

Metabolism and elimination

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

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).

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

A population PK analysis was conducted using data from DARZALEX ~~120MG/ML S.C. 1,800MG~~ solution for subcutaneous injection monotherapy and combination therapy multiple myeloma studies, and the predicted PK exposures are summarised in table 147.

**Table 147: Daratumumab exposure following administration of DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation (1,800 mg) or intravenous daratumumab (16 mg/kg) monotherapy in patients with multiple myeloma**

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

A population PK analysis, using data from DARZALEX 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 18: 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, $1^{st}$ weekly dose | 138 (86; 195) |
| | Cycle 2, last weekly dose (cycle 3 day 1 $C_{trough}$) | 662 (315; 1037) |
| $C_{max}$ (µg/mL) | Cycle 1, $1^{st}$ weekly dose | 151 (88; 226) |
| | Cycle 2, last weekly dose | 729 (390; 1105) |
| $AUC_{0\text{-}7\ days}$ (µg/mL•day) | Cycle 1, $1^{st}$ weekly dose | 908 (482; 1365) |
| | Cycle 2, last weekly dose | 4855 (2562; 7522) |

Special populations

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

Gender had a statistically significant effect on PK parameters in patients with multiple myeloma but not in patients with AL amyloidosis~~, with~~. S~~s~~lightly 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 ~~120MG/ML S.C. 1,800MG~~ 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 ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation monotherapy or various combination therapies in patients with multiple

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

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 ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation in patients with hepatic impairment have been conducted.
Population PK analyses were performed in patients with multiple myeloma receiving DARZALEX ~~120MG/ML S.C. 1,800MG~~ 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 ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation monotherapy or various combination therapies, the daratumumab exposure was similar across races.

*Body weight*
The flat-dose administration of DARZALEX ~~120MG/ML S.C. 1,800MG~~ subcutaneous formulation 1~~,~~800 mg as monotherapy achieved adequate exposure for all body-weight subgroups. In patients with multiple myeloma, ~~T~~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.

....