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EMPLICITI 300 MG
EMPLICITI 400 MG

POWDER FOR CONCENTRATE FOR SOLUTION FOR IV INFUSION

1. NAME OF THE MEDICINAL PRODUCT

Empliciti 300 mg powder for concentrate for solution for infusion.
Empliciti 400 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Empliciti 300 mg powder for concentrate for solution for infusion
Each vial contains 300 mg elotuzumab*.

Empliciti 400 mg powder for concentrate for solution for infusion
Each vial contains 400 mg elotuzumab.

After reconstitution, each mL of concentrate contains 25 mg elotuzumab.

* Elotuzumab is produced in NS0 cells by recombinant DNA technology.

Empliciti contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium free'.For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

The powder is white to off white whole or fragmented cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy (see sections 4.2 and 5.1).

Empliciti is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Elotuzumab therapy should be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

Premedication for prevention of infusion reaction
Patients must be administered with the following premedications 45-90 minutes prior to Empliciti infusion (see section 4.4):

- Dexamethasone 8 mg intravenous
- H1 blocker: diphenhydramine (25-50 mg orally or intravenous) or equivalent H1 blocker.
- H2 blocker: ranitidine (50 mg intravenous or 150 mg orally) or equivalent H2 blocker.
- Paracetamol (650-1000 mg orally).

Management of infusion reaction
If a ≥ Grade 2 infusion reaction occurs during Empliciti administration, the infusion must be interrupted. Upon resolution to ≤ Grade 1, Empliciti should be restarted at 0.5 mL/min and may be gradually increased at a rate of 0.5 mL/min every 30 minutes as tolerated to the rate at which the infusion reaction occurred. If there is no recurrence of the infusion reaction, the escalation can be resumed (see Tables 3 and 4).

In patients who experience an infusion reaction, vital signs should be monitored every 30 minutes for 2 hours after the end of the Empliciti infusion. If the infusion reaction recurs, the Empliciti infusion must be stopped and not restarted on that day (see section 4.4). Very severe infusion reactions (≥ Grade 3) may require permanent discontinuation of Empliciti therapy and emergency treatment.

Posology for administration with lenalidomide and dexamethasone
The length of each treatment cycle is 28 days, see Table 1 for the dosing schedule.
Treatment should continue until disease progression or unacceptable toxicity.

The recommended dose of Empliciti is 10 mg/kg administered intravenously every week, on days 1, 8, 15, and 22 for the first two treatment cycles and every 2 weeks thereafter on days 1 and 15.

The recommended dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles, and at least 2 hours after Empliciti infusion when administered on the same day.

The administration of dexamethasone is as follows:

- On days that Empliciti is administered, dexamethasone should be given as 28 mg orally once daily between 3 and 24 hours before Empliciti plus 8 mg intravenously between 45 and 90 minutes before Empliciti on days 1, 8, 15, and 22 of repeated 28-day cycles.
- On days that Empliciti is not administered but a dose of dexamethasone is scheduled (Days 8 and 22 of cycle 3 and all subsequent cycles), dexamethasone should be given 40 mg orally.

Table 1: Recommended dosing schedule of Empliciti in combination with lenalidomide and dexamethasone

Cycle	28-Day Cycles 1 & 2				28-Day Cycles 3+			
Day of Cycle	1	8	15	22	1	8	15	22
Premedication	✓	✓	✓	✓	✓		✓	
Empliciti (mg/kg) intravenously	10	10	10	10	10		10	
Lenalidomide (25 mg) orally	Days 1-21				Days 1-21			
Dexamethasone (mg) orally	28	28	28	28	28	40	28	40
Day of Cycle	1	8	15	22	1	8	15	22

For additional information concerning lenalidomide and dexamethasone, see the corresponding prescribing information leaflets.

Posology for administration with pomalidomide and dexamethasone
The length of each treatment cycle is 28 days, see Table 2 for the dosing schedule.
Treatment should continue until disease progression or unacceptable toxicity.

The recommended dose of Empliciti is 10 mg/kg administered intravenously every week on days 1, 8, 15, and 22 of each treatment cycle for the first two cycles and then 20 mg/kg administered on day 1 of each treatment cycle thereafter.

The recommended dose of pomalidomide is 4 mg orally once daily on days 1-21 of repeated 28-day cycles, and at least 2 hours after Empliciti infusion when administered on the same day.

The administration of dexamethasone is as follows:
- On days that Empliciti is administered, patients ≤ 75 years old give dexamethasone 28 mg orally between 3 and 24 hours before Empliciti plus 8 mg intravenously between 45 and 90 minutes before Empliciti and for patients > 75 years old give dexamethasone 8 mg orally between 3 and 24 hours before Empliciti plus 8 mg intravenously between 45 and 90 minutes before Empliciti.
- On days that Empliciti is not administered but a dose of dexamethasone is scheduled (Days 8, 15 and 22 of cycle 3 and all subsequent cycles), give 40 mg orally to patients ≤ 75 years old and 20 mg orally to patients > 75 years old.

Table 2: Recommended dosing schedule of Empliciti in combination with pomalidomide and dexamethasone

Cycle	28-Day Cycles 1 and 2				28-Day Cycles 3+			
Day of Cycle	1	8	15	22	1	8	15	22
Premedication	✓	✓	✓	✓	✓			
Empliciti (mg/kg) intravenously	10	10	10	10	20			
Pomalidomide (4 mg) orally	Days 1-21				Days 1-21			
Dexamethasone (mg) intravenously	8	8	8	8	8			
Dexamethasone (mg) orally ≤ 75 years old	28	28	28	28	28	40	40	40
Dexamethasone (mg) orally > 75 years old	8	8	8	8	8	20	20	20
Day of Cycle	1	8	15	22	1	8	15	22

For additional information concerning pomalidomide and dexamethasone, see the corresponding prescribing information leaflets.

See Method of administration below for instruction on infusion rates.

Dose delay, interruption, or discontinuation
If the dose of one medicine in the regimen is delayed, interrupted, or discontinued, the treatment with the other medicinal products may continue as scheduled. However, if oral or intravenous dexamethasone is delayed or discontinued, the administration of Empliciti should be based on clinical judgment (e.g. risk of hypersensitivity) (see section 4.4).

Special populations

Paediatric population
There is no relevant use of Empliciti in the paediatric population for the indication of multiple myeloma.

Elderly
No dose adjustment is required for Empliciti in patients over 65 years of age (see section 5.2). Data on the efficacy and safety of Empliciti in patients ≥ 85 years of age are very limited.

Renal impairment
No dose adjustment of Empliciti is required for patients with mild (CrCl = 60 - 89 mL/min), moderate (CrCl = 30 - 59 mL/min), severe (CrCl < 30 mL/min) renal impairment or end stage renal disease requiring dialysis (see section 5.2).

Hepatic impairment
No dose adjustment for Empliciti is required for patients with mild hepatic impairment (total bilirubin [TB] ≤ to the upper limit of normal [ULN] and AST > ULN or TB < 1 to 1.5 × ULN and any AST). Empliciti has not been studied in patients with moderate (TB > 1.5 to 3 × ULN and any AST) or severe (TB > 3 × ULN and any AST) hepatic impairment (see section 5.2).

Method of administration
Empliciti is for intravenous use only.

Infusion rate for Empliciti 10 mg/kg
The administration of the reconstituted and diluted solution must be initiated at an infusion rate of 0.5 mL/min. If the infusion is well tolerated the infusion rate may be increased in a stepwise fashion as described in Table 3. The maximum infusion rate should not exceed 5 mL/min.

Table 3: Infusion rate for Empliciti 10 mg/kg

Cycle 1, Dose 1		**Cycle 1, Dose 2**		**Cycle 1, Dose 3 and 4 and all subsequent Cycles**
Time interval	**Rate**	**Time interval**	**Rate**	**Rate**
0 - 30 min	0.5 mL/min	0 - 30 min	3 mL/min	5 mL/min*
30 - 60 min	1 mL/min	≥ 30 min	4 mL/min*	
≥ 60 min	2 mL/min*	-	-	

* Continue this rate until infusion is completed.

Infusion rate for Empliciti 20 mg/kg
The administration of reconstituted and diluted solution must be initiated at an infusion rate of 3 mL/min. If the infusion is well tolerated, the infusion rate maybe increased in a stepwise fashion as described in Table 4. The maximum infusion rate should not exceed 5 mL/min.

Patients who have escalated to 5 mL/min at 10 mg/kg dose must decrease the rate to 3 mL/min at the first infusion at 20 mg/kg.

Table 4: Infusion rate for Empliciti 20 mg/kg

Dose 1		Dose 2 and all subsequent doses
Time interval	**Rate**	**Rate**
0-30 min	3 mL/min	5 mL/min*
≥ 30 min	4 mL/min*	

* Continue this rate until infusion is completed.

For instructions on reconstitution and dilution of Empliciti 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.

The Summary of Product Characteristics for all medicinal products used in combination with Empliciti must be consulted before starting therapy.

4.4 Special warnings and precautions for use

Infusion reaction
Infusion reactions have been reported in patients receiving elotuzumab (see section 4.8).

Premedication consisting of dexamethasone, H1 blocker, H2 blocker, and paracetamol must be administered prior to Empliciti infusion (see section 4.2 Premedication). The rate of infusion reactions was much higher in patients who were not premedicated.

If any of the symptoms of infusion reaction reach Grade ≥ 2, Empliciti infusion must be interrupted and appropriate medical and supportive measures instituted. Vital signs should be monitored every 30 minutes for 2 hours after the end of the Empliciti infusion. Once the reaction has resolved (symptoms ≤ Grade 1), Empliciti can be restarted at the initial infusion rate of 0.5 mL/min. If symptoms do not recur, the infusion rate may be gradually escalated every 30 minutes to a maximum of 5 mL/min (see section 4.2 Method of administration).

Very severe infusion reactions may require permanent discontinuation of Empliciti therapy and emergency treatment. Patients with mild or moderate infusion reactions may receive Empliciti with a reduced infusion rate and close monitoring (see section 4.2 Method of administration).

Conditions for use of medicinal products used with Empliciti
Empliciti is used in combination with other medicinal products; therefore, the conditions for use applicable to those medicinal products also apply to the combination therapy. The Summary of Product Characteristics for all medicinal products used in combination with Empliciti must be consulted before starting therapy.

Infections
In clinical trials of patients with multiple myeloma, the incidence of all infections, including pneumonia, were higher in patients treated with Empliciti (see section 4.8). Patients should be monitored and infections should be managed with standard treatment.

Second primary malignancies (SPMs)
In a clinical trial of patients with multiple myeloma that compared Empliciti combined with lenalidomide and dexamethasone treatment to lenalidomide and dexamethasone treatment (CA204004), the incidence of SPMs, and specifically of solid tumours and non-melanoma skin cancer,

was higher in patient treated with Empliciti (see section 4.8). SPMs are known to be associated with lenalidomide exposure, which was extended in patients treated with Empliciti combined with lenalidomide and dexamethasone vs. lenalidomide and dexamethasone. The rate of haematologic malignancies was the same between the two treatment arms. Patients should be monitored for the development of SPMs.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction studies have not been conducted. Empliciti, as a humanised monoclonal antibody, is not expected to be metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of Empliciti.

Empliciti may be detected in the serum protein electrophoresis (SPEP) and serum immunofixation assays of myeloma patients and could interfere with correct response classification. The presence of elotuzumab in patient's serum may cause a small peak in the early gamma region on SPEP that is IgGκ on serum immunofixation. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.
In case of detection of additional peaks on serum immunofixation, the possibility of a biclonal gammopathy should be excluded.

The Summary of Product Characteristics for all medicinal products used in combination with Empliciti must be consulted before starting therapy.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential/Contraception in the males and females
Empliciti should not be used in women of childbearing potential, unless the clinical condition of the woman requires treatment with elotuzumab. Women of childbearing potential should use effective contraception.
Male patients must use effective contraception measures during and for 180 days following treatment if their partner is pregnant or of childbearing potential and not using effective contraception.

Pregnancy
There is no human experience with elotuzumab during pregnancy. Elotuzumab will be given in combination with lenalidomide, which is contraindicated during pregnancy. No animal data are present regarding the effect on reproductive toxicity because of the lack of an adequate animal model. Empliciti should not be used during pregnancy unless the clinical condition of the woman requires treatment with elotuzumab.

The prescribing information leaflets for all medicinal products used in combination with Empliciti must be consulted before starting therapy. When Empliciti is used with lenalidomide or pomalidomide there is a risk of foetal harm, including severe life-threatening human birth defects associated with these agents and the need to follow requirements regarding pregnancy avoidance, including testing and contraception. Lenalidomide and pomalidomide are present in the blood and sperm of patients receiving the medicine. Refer to the prescribing information leaflets for requirements regarding contraception due to presence and transmission in sperm and for additional detail. Patients receiving Empliciti in combination with lenalidomide or pomalidomide should adhere to the pregnancy prevention programme of lenalidomide or pomalidomide respectively.

Breast-feeding
Elotuzumab is not expected to be excreted into human milk. Elotuzumab will be given in combination with lenalidomide or pomalidomide and breast-feeding should be stopped because of the use of lenalidomide or pomalidomide.

Fertility
Studies to evaluate the effect of elotuzumab on fertility have not been performed. Thus, the effect of elotuzumab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

On the basis of reported adverse reactions, Empliciti is not expected to influence the ability to drive or use machines. Patients experiencing infusion reactions should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of safety profile
The safety data of elotuzumab have been assessed from a total of 682 patients with multiple myeloma treated with elotuzumab in combination with lenalidomide and dexamethasone (451 patients), bortezomib and dexamethasone (103 patients) or pomalidomide and dexamethasone (128 patients) pooled across 8 clinical trials. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The most serious adverse reaction that may occur during elotuzumab treatment is pneumonia.

The most common adverse reactions (occurring in > 10% of patients) with elotuzumab treatment were infusion related reactions, diarrhoea, herpes zoster, nasopharyngitis, cough, pneumonia, upper respiratory tract infection, lymphopenia and weight decreased.

Tabulated list of adverse reactions
Adverse reactions reported in 682 patients with multiple myeloma who were treated with elotuzumab in 8 clinical trials are presented in Table 5.

These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from available data).

Table 5: Adverse reactions in patients with multiple myeloma treated with Empliciti

System Organ Class	Adverse reactions	Frequency overall	Grade 3/4 frequency
Infections and infestations	Herpes zoster[a]	Common	Uncommon
	Nasopharyngitis	Very common	None reported
	Pneumonia[b]	Very common	Common
	Upper respiratory tract infection	Very common	Common
Blood and lymphatic system disorders	Lymphopenia[c]	Very common	Common
	Leukopenia	Common	Common
Immune system disorders	Anaphylactic reaction	Uncommon	Uncommon
	Hypersensitivity	Common	Uncommon
Psychiatric disorders	Mood altered	Common	None reported
Nervous system disorders	Headache	Very common	Uncommon
	Hypoaesthesia	Common	Uncommon
Vascular disorders	Deep vein thrombosis	Common	Common
Respiratory, thoracic and mediastinal disorders	Cough[d]	Very common	Uncommon
	Oropharyngeal pain	Common	None reported
Gastrointestinal disorders	Diarrhoea	Very common	Common
Skin and subcutaneous tissue disorders	Night sweats	Common	None reported
General disorders and administration site conditions	Chest pain	Common	Common
	Fatigue	Very common	Common
	Pyrexia	Very common	Common
Investigations	Weight decreased	Very common	Uncommon
Injury, poisoning and procedural complications	Infusion related reaction	Common	Uncommon

[a] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, and herpes virus infection.

[b] The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.

[c] The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.

[d] The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.

Exposure-adjusted rates for adverse reactions (all Grades and Grade 3/4) in CA204004, a clinical trial in patients with multiple myeloma comparing Empliciti combined with lenalidomide and dexamethasone treatment (N = 318) to lenalidomide and dexamethasone treatment (N = 317), is shown in Table 6.

Table 6: CA204004 Exposure-adjusted rates for adverse reactions for Empliciti-treated patients versus lenalidomide and dexamethasone-treated patients [includes multiple occurrences in all treated patients]

	Empliciti + Lenalidomide and Dexamethasone N = 318				Lenalidomide and Dexamethasone N = 317			
	All grades		Grade 3/4		All grades		Grade 3/4	
Adverse reaction	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**
Diarrhoea	303	59.2	19	3.7	206	49.3	13	3.1
Pyrexia	220	43.0	8	1.6	116	27.7	10	2.4
Fatigue	205	40.0	33	6.4	145	34.7	26	6.2
Cough[a]	170	33.2	1	0.2	85	20.3	-	-
Nasopharyngitis	151	29.5	-	-	116	27.7	-	-
Upper respiratory tract infection	129	25.2	2	0.4	95	22.7	4	1.0
Lymphopenia[b]	90	17.6	65	12.7	57	13.6	31	7.4
Headache	88	17.2	1	0.2	40	9.6	1	0.2
Pneumonia[c]	80	15.6	54	10.5	54	12.9	34	8.1
Leukopenia	70	13.7	19	3.7	65	15.5	21	5.0
Herpes zoster[d]	51	10.0	5	1.0	24	5.7	3	0.7
Oropharyngeal pain	45	8.8	-	-	17	4.1	-	-
Weight decreased	44	8.6	4	0.8	20	4.8	-	-
Night sweats	31	6.1	-	-	12	2.9	-	-
Chest pain	29	5.7	2	0.4	12	2.9	1	0.2
Deep vein thrombosis	26	5.1	18	3.5	12	2.9	7	1.7
Hypoaesthesia	25	4.9	1	0.2	12	2.9	-	-
Mood altered	23	4.5	-	-	8	1.9	-	-
Hypersensitivity	10	2.0	-	-	4	1.0	1	0.2

[a] The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.

[b] The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.

[c] The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.

[d] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, and herpes virus infection.

Exposure-adjusted rates for adverse reactions (all Grades and Grade 3/4) in CA204125, a clinical trial in patients with multiple myeloma comparing Empliciti combined with pomalidomide and dexamethasone treatment (N = 60) to pomalidomide and dexamethasone treatment (N = 55), is shown in Table 7.

Table 7: CA204125 Exposure-adjusted rates for adverse reactions for Empliciti-treated patients versus pomalidomide and dexamethasone-treated patients [includes multiple occurrences in all treated patients]

	Empliciti + Pomalidomide and Dexamethasone N = 60				Pomalidomide and Dexamethasone N = 55			
	All grades		Grade 3/4		All grades		Grade 3/4	
Adverse reaction	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**
Cough[a]	12	25.2	1	2.1	9	26.2	-	-
Nasopharyngitis	12	25.2	-	-	10	29.1	-	-
Upper respiratory tract infection	9	18.9	-	-	10	29.1	1	2.9
Leukopenia	13	27.3	9	18.9	3	8.7	2	5.8
Lymphopenia[b]	10	21.0	6	12.6	1	2.9	1	2.9
Pneumonia[c]	6	12.6	4	8.4	9	26.2	8	23.3
Herpes zoster[d]	5	10.5	-	-	3	8.7	-	-
Infusion related reaction	2	4.2	1	2.1	1	2.9	-	-
Chest pain	2	4.2	-	-	1	2.9	-	-
Night sweats	1	2.1	-	-	-	0.0	-	-
Hypoaesthesia	1	2.1	-	-	1	2.9	-	-
Mood altered	1	2.1	-	-	1	2.9	-	-

[a] The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.

[b] The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.

[c] The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.

[d] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, herpes virus infection and ophthalmic herpes zoster.

Description of selected adverse reactions

Infusion reactions

In the clinical trials of patients with multiple myeloma infusion reactions were reported in approximately 10% of premedicated patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) and 3% of premedicated patients treated with Empliciti combined with pomalidomide and dexamethasone (N=60) (see section 4.4). The rate of mild to moderate infusion reactions was > 50% in patients who were not premedicated. All reports of infusion reaction were ≤ Grade 3. Grade 3 infusion reactions occurred in 1% of patients. In study CA204004, the most common symptoms of an infusion reaction included fever, chills, and hypertension. Five percent (5%) of patients required interruption of the administration of Empliciti for a median of 25 minutes due to infusion reaction, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had the reaction during the first dose. In study CA204125, all of the reported infusion reactions occurred during the first treatment cycle and were ≤ Grade 2.

Infections
The incidence of infections, including pneumonia, was higher with Empliciti treatment than with control (see section 4.4). In a clinical trial of patients with multiple myeloma (CA204004), infections were reported in 81.4% of patients in the Empliciti combined with lenalidomide and dexamethasone arm (N = 318) and 74.4% in lenalidomide and dexamethasone arm (N = 317). Grade 3-4 infections were noted in 28% and 24.3% of Empliciti combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone treated patients, respectively. Fatal infections were infrequent and were reported in 2.5% of Empliciti combined with lenalidomide and dexamethasone and 2.2% of lenalidomide and dexamethasone treated patients. The incidence of pneumonia was higher in the Empliciti combined with lenalidomide and dexamethasone arm compared to lenalidomide and dexamethasone arm reported at 15.1% vs. 11.7% with a fatal outcome at 0.6% vs. 0%, respectively.

In a clinical trial of patients with multiple myeloma (CA204125), infections were reported in 65% of patients in the Empliciti combined with pomalidomide and dexamethasone arm (N = 60) and 65.5% in the pomalidomide and dexamethasone arm (N = 55). Grade 3-4 infections were noted in 13.3% and 21.8% of Empliciti combined with pomalidomide and dexamethasone and pomalidomide and dexamethasone treated patients, respectively. Fatal infections (i.e. Grade 5 infections) were reported in 5% of Empliciti combined with pomalidomide and dexamethasone and 3.6% of pomalidomide and dexamethasone treated patients.

Second Primary Malignancies
The incidence of SPMs was higher with Empliciti treatment than with control (see section 4.4). In the clinical trial of patients with multiple myeloma (CA204004), invasive SPMs have been observed in 6.9% of patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) and 4.1% of patients treated with lenalidomide and dexamethasone (N = 317). Second Primary Malignancies are known to be associated with lenalidomide exposure which was extended in patients treated with Empliciti combined with lenalidomide and dexamethasone vs. lenalidomide and dexamethasone. The rate of haematologic malignancies were the same between the two treatment arms (1.6%). Solid tumours were reported in 2.5% and 1.9% of Empliciti combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone treated patients, respectively. Non-melanoma skin cancer was reported in 3.1% and 1.6% of patients treated with Empliciti combined with lenalidomide and dexamethasone and lenalidomide and dexamethasone, respectively.

There were no SPM events reported in patients treated in the Empliciti combined with pomalidomide and dexamethasone study arm (N = 60) and 1 (1.8%) in patients treated in the pomalidomide and dexamethasone arm (N = 55) in study CA204125.

Deep vein thrombosis
In a clinical trial of patients with multiple myeloma (CA204004), deep vein thromboses were reported in 7.2% of patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) and 3.8% of patients treated with lenalidomide and dexamethasone (N = 317). Among, patients treated with aspirin, deep vein thromboses were reported in 4.1% of patients treated with Empliciti combined with lenalidomide and dexamethasone (E-Ld) and 1.4% of patients treated with lenalidomide and dexamethasone (Ld). The rates of deep vein thromboses observed between treatment arms were similar for patients given prophylaxis with low molecular weight heparin (2.2% in both treatment arms), and for patients given vitamin K antagonists the rates were 0% for patients treated with E-Ld and 6.7% for patients treated with Ld.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity to Empliciti.
Of 390 patients across four clinical studies who were treated with Empliciti and evaluable for the presence of anti-product antibodies, 72 patients (18.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in 19 of 299 patients in CA204004. In the majority of patients, immunogenicity occurred early in treatment and was transient resolving by 2 to 4 months. There was no clear causal evidence of altered pharmacokinetic, efficacy, or toxicity profiles with anti-product antibody development based on the population pharmacokinetic and exposure-response analyses.

Of the 53 patients in CA204125 treated with Empliciti and evaluable for the presence of anti-product antibodies, 19 patients (36%) tested positive , of whom 1 patient tested persistent positive, for treatment-emergent anti-product antibodies by an ECL assay. In these 19 patients, anti-product antibodies occurred within the first 2 months of the initiation of Empliciti treatment. Anti-product antibodies resolved by 2 to 3 months in 18 (95%) of these 19 patients. Neutralizing antibodies were detected in 2 of 53 patients.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

One patient was reported to be overdosed with 23.3 mg/kg of elotuzumab in combination with lenalidomide and dexamethasone. The patient had no symptoms, did not require any treatment for the overdose, and was able to continue on elotuzumab therapy.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC23.

Mechanism of action
Elotuzumab is an immunostimulatory humanised, IgG1 monoclonal antibody that specifically targets the SLAMF7 (signaling lymphocyte activation molecule family member 7) protein. SLAMF7 is highly expressed on multiple myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on natural killer cells (NK), normal plasma cells, and other immune cells including some T cell subsets, monocytes, B cells, macrophages, and pDCs (plasmacytoid dendritic cells), but is not detected on normal solid tissues or haematopoietic stem cells.

Elotuzumab directly activates natural killer cells through both the SLAMF7 pathway and Fc receptors enhancing anti-myeloma activity *in vitro*. Elotuzumab also targets SLAMF7 on myeloma cells and through interactions with Fc receptors on specific immune cells, promotes the killing of myeloma cells through NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and macrophage-mediated antibody-dependant cellular phagocytosis (ADCP). In nonclinical models, elotuzumab has demonstrated synergistic activity when combined with lenalidomide, pomalidomide or bortezomib.

Clinical efficacy and safety
Empliciti in combination with lenalidomide and dexamethasone (CA204004)
CA204004 is a randomised, open-label study was conducted to evaluate the efficacy and safety of Empliciti in combination with lenalidomide and dexamethasone (E-Ld) in patients with multiple myeloma who have received one to three prior therapies. All patients had documented progression following their most recent therapy. Patients who were refractory to lenalidomide were excluded and 6% of patients had prior lenalidomide treatment. Patients had to recover after transplant for a minimum of 12 weeks from autologous stem cell transplant (SCT), and 16 weeks from allogeneic SCT. Patients with cardiac amyloidosis or plasma cell leukemia were excluded from this study.

Eligible patients were randomised in a 1:1 ratio to receive either Empliciti in combination with lenalidomide and dexamethasone or lenalidomide and dexamethasone (Ld). Treatment was administered in 4-week cycles until disease progression or unacceptable toxicity. Elotuzumab 10 mg/kg was administered intravenously each week for the first 2 cycles and every 2 weeks thereafter. Prior to Empliciti infusion, dexamethasone was administered as a divided dose: an oral dose of 28 mg and an intravenous dose of 8 mg. In the control group and on weeks without Empliciti, dexamethasone 40 mg was administered as a single oral dose weekly. Lenalidomide 25 mg was taken orally once daily for the first 3 weeks of each cycle. Assessment of tumour response was conducted every 4 weeks.

A total of 646 patients were randomised to receive treatment: 321 to Empliciti in combination with lenalidomide and dexamethasone and 325 to lenalidomide and dexamethasone.

Demographics and baseline characteristics were well balanced between treatment arms. The median age was 66 years (range 37 to 91); 57% of patients were older than 65 years; 60% of patients were male; Whites comprised 84% of the study population, Asians 10%, and blacks 4%. The International Staging System (ISS) Stage was I in 43%, II in 32% and III in 21% of patients. The high risk cytogenetic categories of del17p and t(4;14) were present in 32% and 9% of patients, respectively. The median number of prior therapies was 2. Thirty-five percent (35%) of patients were refractory (progression during or within 60 days of last therapy) and 65% were relapsed (progression after 60 days of last therapy). Prior therapies included: stem cell transplant (55%), bortezomib (70%) melphalan (65%), thalidomide (48%), and lenalidomide (6%).

The primary endpoints of this study, progression-free survival (PFS), as assessed by hazard ratio, and overall response rate (ORR) were determined based on assessments made by a blinded Independent Review Committee (IRC). Efficacy results are presented in Table 8 and Figure 1. The median number of treatment cycles was 19 for the Empliciti arm and 14 for the comparator arm.

Table 8: CA204004 Efficacy results

	E-Ld N = 321	Ld N = 325
PFS (ITT)		
Hazard Ratio [97.61% CI]	0.68 [0.55, 0.85]	
Stratified log-rank test p-value[a]	0.0001	
1-Year PFS rate (%) [95% CI]	68 [63, 73]	56 [50, 61]
2-Year PFS rate (%) [95% CI]	39 [34, 45]	26 [21, 31]
3-Year PFS rate[b] (%) [95% CI]	23 [18, 28]	15 [10, 20]
Median PFS in months [95% CI]	18.5 [16.5, 21.4]	14.3 [12.0, 16.0]
Response		
Overall Response (ORR)[c] n (%) [95% CI]	252 (78.5) [73.6, 82.9]	213 (65.5) [60.1, 70.7]
p-value[d]	0.0002	
Complete Response (CR + sCR)e n (%)	14 (4.4)[f]	24 (7.4)
Very Good Partial Response (VGPR) n (%)	91 (28.3)	67 (20.6)
Partial Response (RR/PR) n (%)	147 (45.8)	122 (37.5)
Combined Responses (CR+sCR+VGPR) n (%)	105 (32.7)	91 (28.0)
Overall Survival[g]		
Hazard Ratio [95% CI]	0.77 [0.61, 0.97]	
Stratified log-rank test p-value	0.0257[h]	
Median OS in months [95% CI]	43.7 [40.34, NE]	39.6 [33.25,NE]

a p-value based on the log-rank test stratified by B2 microglobulins (<3.5 mg/L versus ≥ 3.5 mg/L), number of prior lines of therapy (1 versus 2 or 3), and prior immunomodulatory therapy (no versus prior thalidomide only versus other).

b A pre-specified analysis for 3-year PFS rate was performed based on a minimum follow-up time of 33 months.

c European Group for Blood and Marrow Transplantation (EBMT) criteria.

d p-value based on the Cochran-Mantel-Haenszel chi-square test stratified by B2 microglobulins (<3.5 mg/L versus ≥ 3.5 mg/L), number of prior lines of therapy (1 versus 2 or 3), and prior immunomodulatory therapy (no versus prior thalidomide only versus other).

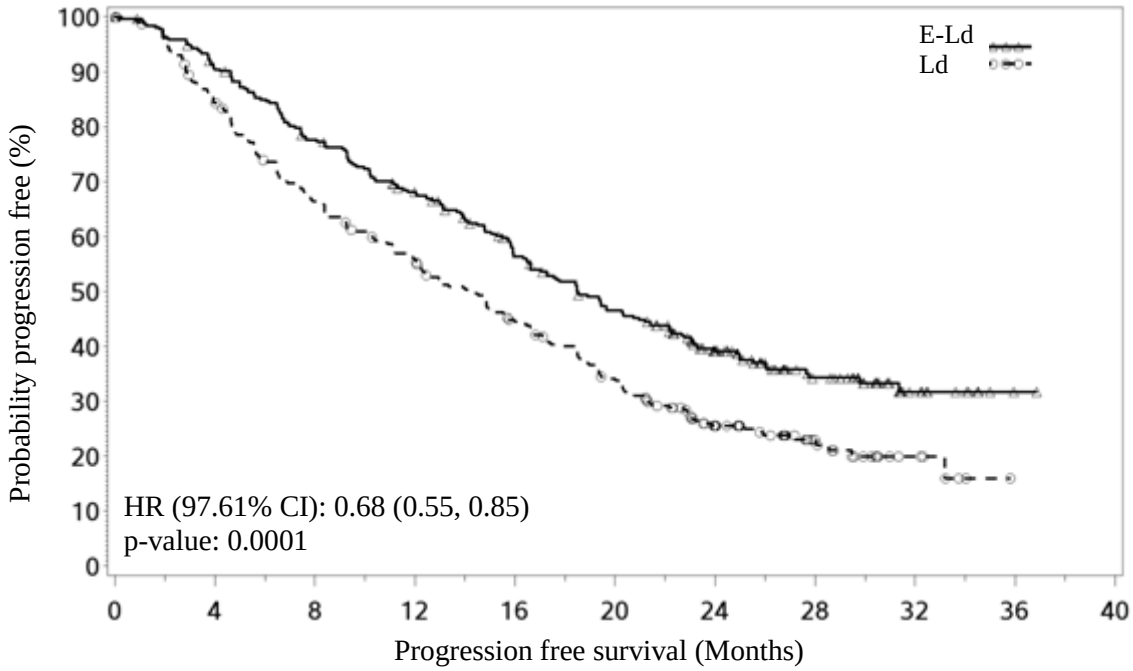
e Complete response (CR) + stringent complete response (sCR).

f Complete response rates in Empliciti group may be underestimated due to interference of elotuzumab monoclonal antibody with immunofixation assay and serum protein electrophoresis assay.

g A pre-specified interim analysis for OS was performed based on a minimum follow-up time of 35.4 months.

h The interim OS analysis did not meet the protocol-specified early stopping boundary for OS (p ≤ 0.014).

Figure 1: CA204004 Progression free survival



Number of subjects at risk

E-Ld	321	282	240	206	164	133	87	43	12	1
Ld	325	262	204	168	130	97	53	24	7	

Improvements observed in PFS were consistent across subsets regardless of age (< 65 versus ≥ 65), risk status, presence or absence of cytogenetic categories del17p or t(4;14), ISS stage, number of prior therapies, prior immunomodulatory exposure, prior bortezomib exposure, relapsed or refractory status or renal function as shown in Table 9.

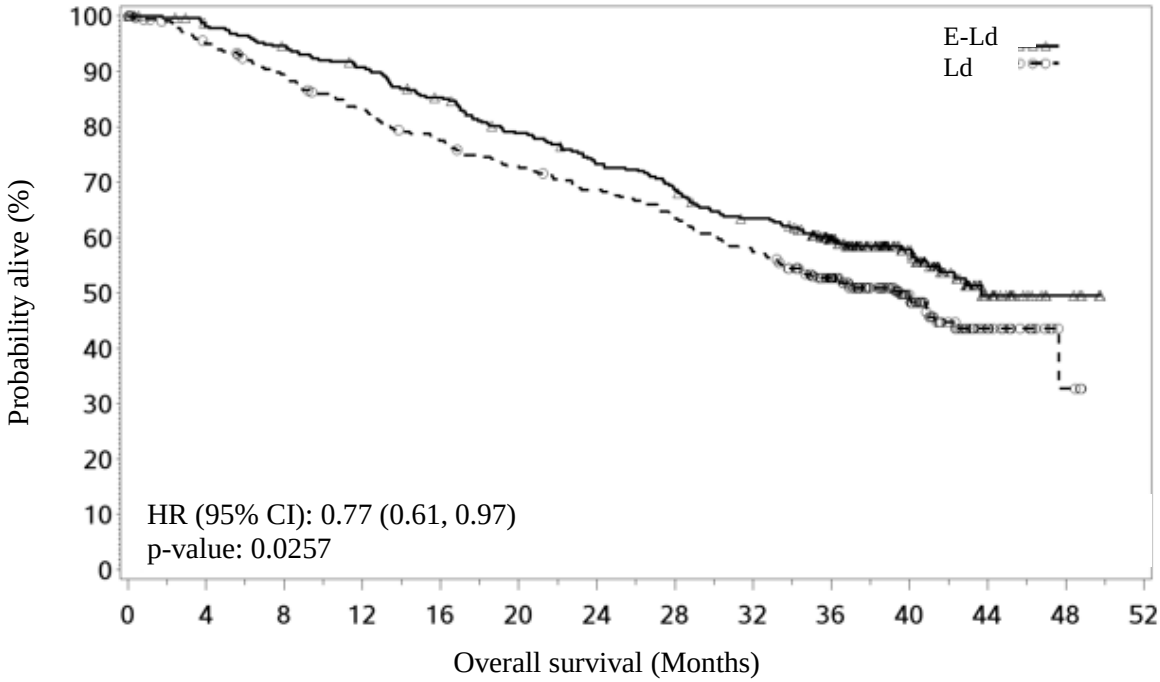
Table 9: CA204004 Efficacy results for subsets

Subset description	E-Ld N = 321 Median PFS (months) [95% CI]	Ld N = 325 Median PFS (months) [95% CI]	HR [95% CI]
Age			
< 65 years	19.4 [15.9, 23.1]	15.7 [11.2, 18.5]	0.74 [0.55, 1.00]
≥ 65 years	18.5 [15.7, 22.2]	12.9 [10.9, 14.9]	0.64 [0.50, 0.82]
Risk factors			
High risk	14.8 [9.1, 19.6]	7.2 [5.6, 11.2]	0.63 [0.41, 0.95]
Standard risk	19.4 [16.5, 22.7]	16.4 [13.9, 18.5]	0.75 [0.59, 0.94]
Cytogenetic category			
Presence of del17p	19.6 [15.8, NE]	14.9 [10.6, 17.5]	0.65 [0.45, 0.93]
Absence of del17p	18.5 [15.8, 22.1]	13.9 [11.1, 16.4]	0.68 [0.54, 0.86]
Presence of t(4;14)	15.8 [8.4, 18.4]	5.5 [3.1, 10.3]	0.55 [0.32, 0.98]
Absence of t(4;14)	19.6 [17.0, 23.0]	14.9 [12.4, 17.1]	0.68 [0.55, 0.84]
ISS Stage			
I	22.2 [17.8, 31.3]	16.4 [14.5, 18.6]	0.61 [0.45, 0.83]
II	15.9 [9.5, 23.1]	12.9 [11.1, 18.5]	0.83 [0.60, 1.16]
III	14.0 [9.3, 17.3]	7.4 [5.6, 11.7]	0.70 [0.48, 1.04]

Prior therapies			
Lines of prior therapy = 1	18.5 [15.8, 20.7]	14.5 [10.9, 17.5]	0.71 [0.54, 0.94]
Lines of prior therapy = 2 or 3	18.5 [15.9, 23.9]	14.0 [11.1, 15.7]	0.65 [0.50, 0.85]
Prior thalidomide exposure	18.4 [14.1, 23.1]	12.3 [9.3, 14.9]	0.61 [0.46, 0.80]
No prior immunomodulatory exposure	18.9 [15.8, 22.2]	17.5 [13.0, 20.0]	0.78 [0.59, 1.04]
Prior bortezomib exposure	17.8 [15.8, 20.3]	12.3 [10.2, 14.9]	0.67 [0.53, 0.84]
No prior bortezomib exposure	21.4 [16.6, NE]	17.5 [13.1, 21.3]	0.70 [0.48, 1.00]
Response to therapy			
Relapsed	19.4 [16.6, 22.2]	16.6 [13.0, 18.9]	0.75 [0.59, 0.96]
Refractory	16.6 [14.5, 23.3]	10.4 [6.6, 13.3]	0.55 [0.40, 0.76]
Renal function			
Baseline CrCl < 60 mL/min	18.5 [14.8, 23.3]	11.7 [7.5, 17.4]	0.56 [0.39, 0.80]
Baseline CrCl ≥ 60 mL/min	18.5 [15.9, 22.2]	14.9 [12.1, 16.7]	0.72 [0.57, 0.90]

The 1-, 2- and 3-year rates of overall survival for Empliciti in combination with lenalidomide and dexamethasone treatment were 91%, 73%, and 60% respectively, compared with 83%, 69%, and 53% respectively, for lenalidomide and dexamethasone treatment (See Figure 2).

Figure 2: CA204004 Overall survival



Number of subjects at risk

E-Ld	321	308	296	283	264	242	224	210	191	152	84	23	5
Ld	325	298	278	255	237	222	208	193	174	134	69	22	3

Empliciti in combination with pomalidomide and dexamethasone (CA204125)
CA204125 is a randomised, open-label study conducted to evaluate the efficacy and safety of Empliciti in combination with pomalidomide and dexamethasone (E-Pd) in patients with refractory or relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and had disease progression on or within 60 days of their last therapy. Patients were refractory if they had progressed on or within 60 days of treatment with lenalidomide and a PI and on or within 60 days of their last treatment, or relapsed and refractory if

they had achieved at least a partial response to previous treatment with lenalidomide and a PI but progressed within 6 months and had developed progressive disease on or within 60 days after completing their last treatment. Patients with Grade 2 or higher peripheral neuropathy were excluded from the clinical studies with E-Pd.

A total of 117 patients were randomised in a 1:1 ratio to receive treatment: 60 to elotuzumab in combination with pomalidomide and dexamethasone (E-Pd) and 57 to pomalidomide and dexamethasone (Pd). Treatment was administered in 4-week cycles (28-day cycle) until disease progression or unacceptable toxicity. Elotuzumab 10 mg/kg was administered intravenously each week for the first 2 cycles and 20 mg/kg every 4 weeks thereafter.

Dexamethasone was administered on day 1, 8, 15 and 22 of each cycle. On weeks with Empliciti infusion, dexamethasone was administered before Empliciti as a divided dose: subjects ≤ 75 years an oral dose of 28 mg and an intravenous dose of 8 mg, and in subjects > 75 years an oral dose of 8 mg and an intravenous dose of 8 mg. On weeks without an Empliciti infusion and in the control group, dexamethasone was administered in subjects ≤ 75 years as an oral dose of 40 mg and in subjects > 75 years as an oral dose of 20 mg dexamethasone. Assessment of tumour response was conducted every 4 weeks.

Demographics and baseline characteristics were balanced between treatment arms. The median age was 67 years (range 36 to 81); 62% of patients were older than 65 years; 57% of patients were male; whites comprised 77% of the study population, Asians 21%, and blacks 1%. The International Staging System (ISS) Stage was I in 50%, II in 38% and III in 12% of patients. The chromosomal abnormalities as determined by the FISH of del(17p), t(4;14) and t(14;16) were present in 5%, 11% and 7% of patients, respectively. Eleven (9.4%) patients had high-risk myeloma. The median number of prior therapies was 3. Eighty-seven percent (87%) of the patients were refractory to lenalidomide, 80% refractory to a PI and 70% were refractory to both lenalidomide and a PI. Prior therapies included stem cell transplant (55%), bortezomib (100%), lenalidomide (99%), cyclophosphamide (66%), melphalan (63%), carfilzomib (21%), ixazomib (6%), and daratumumab (3%).

The median number of treatment cycles was 9 for the E-Pd arm and 5 for the Pd arm.
The primary endpoint was investigator assessed PFS by modified International Myeloma Working Group (IMWG) criteria. The median PFS per ITT was 10.25 months (95% CI: 5.59, NE) in the E-Pd arm and 4.67 months (95% CI: 2.83, 7.16) in the Pd arm. PFS and ORR were also assessed by the IRC.

PFS results per the investigator and IRC are summarised in Table 10 (minimum follow-up of 9.1 months). Kaplan-Meier curve for PFS per the investigator is provided in Figure 3.

Table 10: CA204125 Efficacy results

	Investigator Assessed		**IRC Assessed**[f]	
	E-Pd N = 60	**Pd N = 57**	**E-Pd N = 60**	**Pd N = 57**
PFS (ITT)				
Hazard Ratio [95% CI]	0.54 [0.34, 0.86]		0.51 [0.32, 0.82]	
Stratified log-rank test p-value[a]	0.0078		0.0043	
Median PFS in months [95% CI]	10.25 [5.59, NE]	4.67 [2.83, 7.16]	10.25 [6.54, NE]	4.70 [2.83,7.62]
Response				
Overall Response (ORR)[b] n (%) [95% CI]	32 (53.3) [40.0, 66.3]	15 (26.3) [15.5, 39.7]	35 (58.3) [44.9, 70.9]	14 (24.6) [14.1, 37.8]

p-value[c]	0.0029		0.0002	
Complete Response (CR + sCR)[d] n (%)	5 (8.3)[e]	1 (1.8)	0 (0.0)[e]	0 (0.0)
Very Good Partial Response (VGPR) n (%)	7 (11.7)	4 (7.0)	9 (15.0)	5 (8.8)
Partial Response (RR/PR) n (%)	20 (33.3)	10 (17.5)	26 (43.3)	9 (15.8)
Combined Responses (CR+sCR+VGPR) n (%)	12 (20.0)	5 (8.8)	9 (15.0)	5 (8.8)

[a] p-value based on the log-rank test stratified by stage of disease at study entry (International Staging System I-II vs III) and number of prior lines of therapy (2-3 vs ≥ 4) at randomization.

[b] modified International Myeloma Working Group (IMWG) criteria.

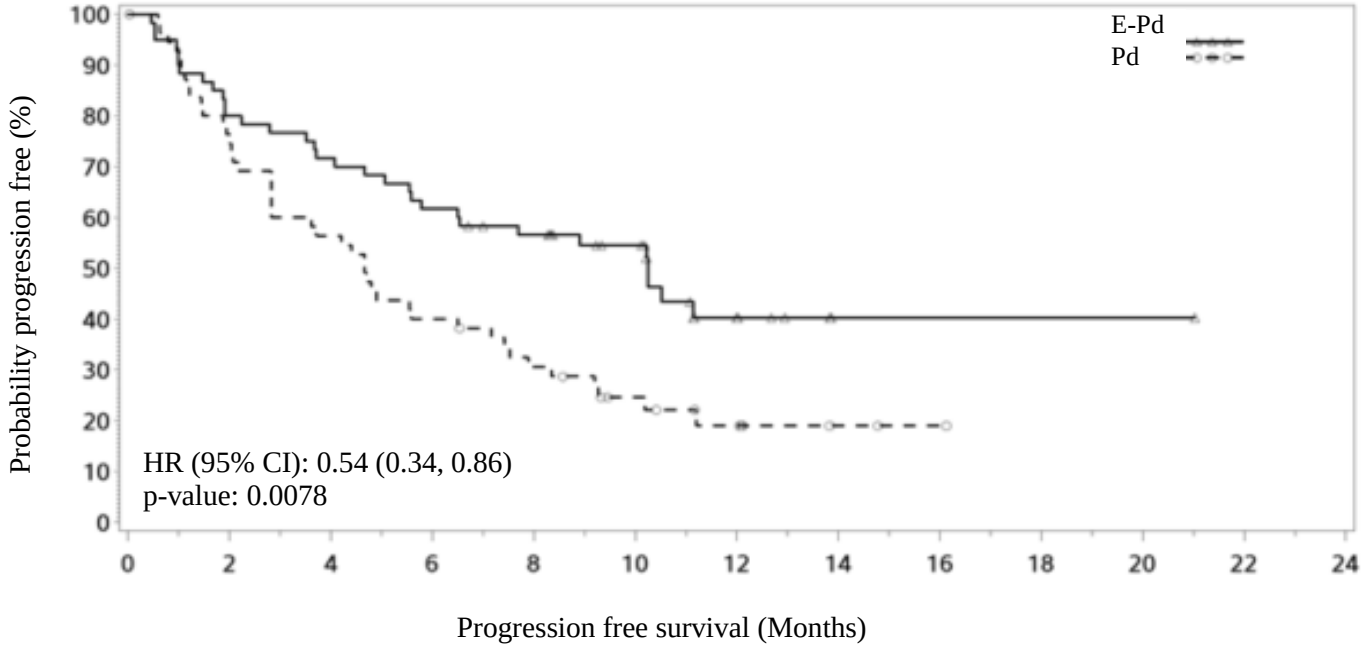
[c] p-value based on the Cochran-Mantel-Haenszel chi-square test stratified by stage of disease at study entry (International Staging System I-II vs III) and number of prior lines of therapy (2-3 vs ≥ 4) at randomization.

[d] Complete response (CR) + stringent complete response (sCR).

[e] Complete response rates in Empliciti group may be underestimated due to interference of elotuzumab monoclonal antibody with immunofixation assay and serum protein electrophoresis assay.

[f] IRC assessment was performed post-hoc.

Figure 3: CA204125 Progression free survival per investigator



Number of subjects at risk

E-Pd	60	48	43	37	32	25	7	1	1	1	1
Pd	57	42	31	22	16	10	6	2	1		

PFS ITT assessment per investigator was evaluated in several subgroups including age (< 65 versus ≥ 65), race, ISS stage, prior therapies, transplant, risk category, ECOG status, creatinine clearance, and cytogenic abnormalities. Regardless of the subgroup evaluated, PFS was generally consistent with that observed in the ITT population for the treatment groups. However, results should be taken with caution as assessment of consistency of effect within the different subgroups was hampered by the very limited number of patients included in the different subgroups.

Overall survival (OS) was a key secondary study endpoint. The OS data from the exploratory analysis were not mature at the data cut-off (29 November 2018) with a minimum follow up of 18.3 months. A total of 40 (67%) patients were alive in the E-Pd arm and 29 (51%) in the Pd arm. Median OS was not reached for E-Pd treatment group. The hazard ratio and 95% CI were 0.54 (0.30, 0.96).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of elotuzumab was studied in patients with multiple myeloma. Elotuzumab exhibits nonlinear PK with decrease in clearance with increase in dose from 0.5-20 mg/kg.

Absorption
Elotuzumab is dosed via intravenous route and therefore is immediately and completely bioavailable.

Distribution
The geometric mean volume of distribution of elotuzumab at the recommended dosing regimen in combination with lenalidomide/dexamethasone or pomalidomide/dexamethasone at steady state is 5.7 L (CV: 23%) and 5.6 L (CV: 21%) respectively.

Biotransformation
The metabolic pathway of elotuzumab has not been characterized. As an IgG monoclonal antibody, elotuzumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination
The geometric mean total clearance of elotuzumab at 10 mg/kg (in combination with lenalidomide and dexamethasone) at steady state is 0.194 L/day (CV: 62.9%). Upon discontinuation of elotuzumab in combination with lenalidomide and dexamethasone or in combination with pomalidomide and dexamethasone, concentrations of elotuzumab will decrease to approximately 3% (approximately 97% washout as estimated by 5 half-lives) of the population predicted steady-state maximal serum concentration by 3 months.

Special populations
Based on a population PK analysis using data from 440 patients, the clearance of elotuzumab increased with increasing body weight supporting a weight-based dose. Population PK analysis suggested that the following factors had no clinically important effect on the clearance of elotuzumab: age, gender, race, baseline LDH, albumin, renal impairment, mild hepatic impairment, and coadministration with lenalidomide/dexamethasone or pomalidomide/dexamethasone.
Target-mediated clearance of elotuzumab increased with higher serum M-protein concentrations.

Renal impairment
An open-label study (CA204007) evaluated the pharmacokinetics of elotuzumab in combination with lenalidomide and dexamethasone in patients with multiple myeloma with varying degrees of renal impairment (classified using the CrCl values). The effect of renal impairment on the pharmacokinetics of elotuzumab was evaluated in patients with normal renal function (CrCl > 90 mL/min; N = 8), severe renal impairment not requiring dialysis (CrCl <30 mL/min; N = 9), or end-stage renal disease requiring dialysis (CrCl < 30 mL/min; N = 9). No clinically important differences in the pharmacokinetics of elotuzumab were found between patients with severe renal impairment (with and without dialysis) and patients with normal renal function (see section 4.2).

Hepatic impairment
Empliciti is an IgG1 monoclonal antibody, which is principally cleared by catabolism. Thus, hepatic functional impairment is not likely to alter its clearance. The effect of hepatic impairment on the clearance of Empliciti was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] ≤ the upper limit of normal [ULN] and AST > ULN or TB < 1 to 1.5 × ULN and any AST; N = 33). No clinically important differences in the clearance of Empliciti were found between patients with mild hepatic impairment and patients with normal hepatic function. Elotuzumab has not been studied in patients with moderate (TB > 1.5 to 3 × ULN and any AST) or severe hepatic impairment (TB > 3 × ULN and any AST) (see section 4.2).

5.3 Preclinical safety data

Elotuzumab only recognizes human SLAMF7 protein. Because elotuzumab does not recognize non-human forms of SLAMF7 protein, *in vivo* safety data from animal studies are irrelevant. In the same line, no carcinogenicity data are available for elotuzumab in animals, nor were fertility and embryo-foetal toxicity studies performed. Non-clinical safety information primarily consists of limited *in vitro* human cell/tissue studies where no safety findings were identified.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate (as dihydrate)
Polysorbate 80
Citric acid monohydrate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

After reconstitution and dilution
The reconstituted solution should be transferred from the vial into the infusion bag immediately.

Chemical and physical in use stability of the reconstituted and diluted solution has been demonstrated for 24 hours at 2°C - 8°C and protected from light.

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C protected from light. Do not freeze the reconstituted or diluted solution. The solution for infusion may be stored for a maximum of 8 hours of the total 24 hours at 20°C − 25°C and room light. This 8-hour period should be inclusive of the product administration period.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze or shake.
Store in the original package in order to protect from light.

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml Type I glass vial, closed with a grey butyl stopper and sealed with aluminium crimp seal with a polypropylene flip off button, containing either 300 mg or 400 mg elotuzumab. The flip-off seal button colour is ivory for the 300 mg presentation and blue for the 400 mg presentation.
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Calculating the dose
Calculate the dose (mg) and determine the number of vials needed for the dose (10 mg/kg or 20 mg/kg) based on patient weight. More than one vial of Empliciti may be needed to give the total dose for the patient.

- The total elotuzumab dose in mg equals the patient's weight in kg multiplied by the elotuzumab dose (10 or 20 mg/kg, see section 4.2).

Reconstitution of vials
Aseptically reconstitute each Empliciti vial with a syringe of adequate size and an 18 gauge or smaller needle as shown in Table 12. A slight back pressure may be experienced during administration of the water for injections, which is considered normal.

Table 12: Reconstitution instructions

Strength	**Amount of water for injections, required for reconstitution**	**Final volume of reconstituted Empliciti in the vial (including volume displaced by the solid cake)**	**Post-reconstitution concentration**
300 mg vial	13.0 mL	13.6 mL	25 mg/mL
400 mg vial	17.0 mL	17.6 mL	25 mg/mL

Hold the vial upright and swirl the solution by rotating the vial to dissolve the lyophilised cake. Then invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Avoid vigorous agitation, DO NOT SHAKE. The lyophilised powder should dissolve in less than 10 minutes.

After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes. The reconstituted solution is colourless to slightly yellow, and clear to very opalescent. Empliciti should be inspected visually for particulate matter and discolouration prior to administration. Discard the solution if any particulate matter or discolouration is observed.

Preparation of the solution for infusion
The reconstituted solution should be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection to obtain a final infusion concentration range between 1 mg/mL and 6 mg/mL. The volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection should be adjusted so as to not exceed 5 mL/kg of patient weight at any given dose of Empliciti.

Calculate the volume (mL) of diluent (either sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection) needed to make up the solution for infusion for the patient.

Withdraw the necessary volume for the calculated dose from each vial, up to a maximum of 16 mL from 400 mg vial and 12 mL from 300 mg vial. Each vial contains a slight overfill to ensure sufficient extractable volume.

Transfer the withdrawn volumes of all vials needed according to the calculated dose for this patient into one single infusion bag made of polyvinyl chloride or polyolefin containing the calculated volume of diluent. Gently mix the infusion by manual rotation. Do not shake.

Empliciti is for single use only. Discard any unused portion left in the vial.

Administration
The entire Empliciti infusion should be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2-1.2 µm) using an automated infusion pump.

Empliciti infusion is compatible with:

- PVC and polyolefin containers
- PVC infusion sets
- polyethersulfone and nylon in-line filters with pore sizes of 0.2 μm to 1.2 μm.

Empliciti should be initiated at an infusion rate of 0.5 mL/min for 10 mg/kg dose and 3 mL/min for 20 mg/kg dose. If well tolerated, the infusion rate may be increased stepwise as described in Tables 3 and 4 (see section 4.2 Method of administration). The maximum infusion rate should not exceed 5 mL/min.

The Empliciti infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C − 8°C protected from light. Do not freeze the reconstituted or diluted solution. The solution for infusion may be stored for a maximum of 8 hours of the total 24 hours at 20°C − 25°C and room light. This 8-hour period should be inclusive of the product administration period.

Disposal

Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MANUFACTURER

Bristol-Myers Squibb Holdings Pharma, Ltd., Liability Company, Manati, Puerto Rico, U.S.A.

LICENSE HOLDER

Bristol-Myers Squibb Israel Ltd. 18 Aharon Bart St., Kiryat Arye, Petah-Tikva 4951448, Israel

REGISTRATION NUMBER

Empliciti 300 mg — 157-13-34688-00

Empliciti 400 mg — 157-14-34685-00