1. NAME OF THE MEDICINAL PRODUCT

SARCLISA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate for solution for infusion contains 20 mg of isatuximab.

Each vial contains 100 mg of isatuximab in 5 mL of concentrate (100 mg/5mL).
Each vial contains 500 mg of isatuximab in 25 mL of concentrate (500 mg/25mL).

Isatuximab is an immunoglobulin G1 (IgG1) monoclonal antibody (mAb) produced from a mammalian cell line (Chinese Hamster Ovary, CHO).

Excipient with known effect
Each vial with 5 ml of concentrate for solution for infusion of isatuximab contains 1 mg of polysorbate 80.
Each vial with 25 ml of concentrate for solution for infusion of isatuximab contains 5 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Colourless to slightly yellow solution, essentially free of visible particulates (pH of 6.0; osmolality of 350 to 400 mOsm/kg).

Patient safety information card
The marketing of Sarclisa is subject to a risk management plan (RMP) including a 'Patient safety information card'. The Patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SARCLISA is indicated:
-in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
-in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see section 5.1).

4.2 Posology and method of administration

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

Premedication

Prevention of infusion reaction

Premedication should be used prior to SARCLISA infusion with the following medicinal products to reduce the risk and severity of infusion reactions:

- Dexamethasone 40 mg oral or intravenous (or 20 mg oral or intravenous for patients ≥75 years of age) when administered in combination with isatuximab and pomalidomide,

  Dexamethasone 20 mg (intravenous on the days of isatuximab and/or carfilzomib infusions, and oral on the other days): when administered in combination with isatuximab and carfilzomib.

- Acetaminophen 650 mg to 1000 mg oral (or equivalent).

- Diphenhydramine 25 mg to 50 mg intravenous or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (oral or intravenous) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide and before isatuximab and carfilzomib administration.

The recommended premedication agents should be administered 15-60 minutes prior to starting a SARCLISA infusion. Patients who do not experience an infusion reaction upon their first 4 administrations of SARCLISA may have their need for subsequent premedication reconsidered.

Management of neutropenia
The use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia. In the event of grade 4 neutropenia, SARCLISA administration should be delayed until neutrophil count improves to at least 1.0 x 10^9/L (see section 4.4).

Prevention of infection
Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) can be considered during treatment (see section 4.4).

Posology

The recommended dose of SARCLISA is 10 mg/kg body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone (Isa-Pd) , or in combination with carfilzomib and dexamethasone (Isa-Kd), according to the schedule in Table 1:

Table 1: SARCLISA dosing schedule in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone

Cycles	Dosing schedule
Cycle 1	Days 1, 8, 15 and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

For other medicinal products that are administered with SARCLISA, see section 5.1 and the respective current summary of product characteristics.

Missed dose
The administration schedule must be carefully followed. If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

Dose adjustments
No dose reduction of SARCLISA is recommended.

Administration adjustments should be made if patients experience infusion reactions (see "Method of administration" below).

For other medicinal products that are administered with SARCLISA, the respective current summary of product characteristics should be considered.

Special populations

Elderly
Based on population pharmacokinetic analysis, no dose adjustment is recommended in elderly patients.

Patients with renal impairment
Based on population pharmacokinetic analysis and on clinical safety, no dose adjustment is recommended in patients with mild to severe renal impairment (see section 5.2).

Patients with hepatic impairment
Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment. Data in patients with moderate and severe hepatic impairment are limited (see section 5.2), but there is no evidence to suggest that dose adjustment is required in these patients.

Paediatric population
The safety and efficacy of SARCLISA in children below 18 years of age have not been established.No data are available.

Method of administration
SARCLISA is for intravenous use. For instructions on dilution of the medicinal product before administration, see section 6.6.

Infusion rates
Following dilution, the SARCLISA infusion should be administered intravenously at the infusion rate presented in Table 2 below (see section 5.1). Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions (see section 4.8).

Table 2: Infusion rates of SARCLISA administration

	Dilution volume	Initial rate	Absence of infusion reaction	Rate increment	Maximum rate
First infusion	250 mL	25 mL/ hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/ hour
Second infusion	250 mL	50 mL/ hour	For 30 minutes	50 mL/ hour for 30 minutes then increase by 100 mL/ hour	200 mL/ hour
Subsequent infusions	250 mL	200 mL/ hour	____	____	200 mL/ hour

Administration adjustments should be made if patients experience infusion reactions (see section 4.4)

- In patients necessitating an intervention (Grade 2, moderate infusion reactions), a temporary interruption inthe infusion should be considered and additional symptomatic medicinal products can be administered. After symptom improvement to grade ≤1 (mild), SARCLISA infusion may be resumed athalf of the initial infusion rate under close monitoring and

supportive care, as needed. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2.

- If symptoms do not resolve rapidly or do not improve to Grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medicinal products, or require hospitalization or are life-threatening , treatment with SARCLISA should be permanently discontinued and additional supportive therapy should be administered, as needed.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Infusion reactions
Infusion reactions, mostly mild or moderate, have been observed in 38.2% of patients treated with SARCLISA in ICARIA-MM, and in 45.8% of patients treated with Isa-Kd in IKEMA (see section 4.8). In ICARIA-MM, all infusion reactions started during the first SARCLISA infusion and resolved on the same day in 98% of the infusions. The most common symptoms of an infusion reaction included dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension, dyspnoea, and bronchospasm. In IKEMA, the infusion reactions occurred on the infusion day in 99.2% of episodes. In patients treated with Isa-Kd, 94.4% of those experiencing an IR experienced it during the first cycle of treatment . All infusion reactions resolved . The most common symptoms of an infusion reaction included cough, dyspnoea, nasal congestion, vomiting and nausea. , The most common severe signs and symptomsincluded hypertension and dyspnoea (see section 4.8). However, serious infusion reactions including severe anaphylactic reactions have also been observed after SARCLISA administration (see section 4.8).

To decrease the risk and severity of infusion reactions, patients should be pre-medicated prior to SARCLISA infusion with acetaminophen, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment (see section 4.2). Vital signs should be frequently monitored during the entire SARCLISA infusion. When required, interrupt SARCLISA infusion and provide appropriate medical and supportive measures (seesection 4.2). In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medicinal products, require hospitalization or are life- threatening, permanently discontinue SARCLISA and institute appropriate management.

Neutropenia
In patients treated with Isa-Pd, neutropenia was reported as a laboratory abnormality in 96.1% of patients and as an adverse reaction (1) in 46.7% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 84.9% of patients and as an adverse reaction in 45.4% of patients. Neutropenic complications have been observed in 30.3% of patients, including 11.8% of febrile neutropenia and 25.0% of neutropenic infections. In patients treated with Isa-Kd, neutropenia was reported as a laboratory abnormality in 54.8% of patients and as an adverse reaction (1) in 4.5% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 19.2% of patients (with 17.5% Grade 3 and 1.7% Grade 4) and as an adverse reaction in 4.0% of patients. Neutropenic complications have been observed in 2.8% of patients, including 1.1% of febrile neutropenia and 1.7% of neutropenic infections (see section 4.8). Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. No dose reductions of SARCLISA are recommended. SARCLISA dose delays and the use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia (see section 4.2).

(1) Haematology laboratory values were recorded as adverse reactions only if they led to treatment discontinuation and/or dose modification and/or fulfilled a serious criterion.

Infection
A higher incidence of infections including grade ≥ 3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis**,** occurred with SARCLISA (see section 4.8). Patients receiving SARCLISA should be closely monitored for signs of infection and appropriate standard therapy instituted.
Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) according to treatment guidelines shouldbe considered during treatment (see sections 4.2 and 4.8).

Second primary malignancies
In ICARIA-MM, second primary malignancies (SPMs) were reported at a median follow-up time of 52.44 months in 10 patients (6.6%) treated with Isa-Pd and in 3 patients (2%) treated with Pd. SPM were skin cancer in 6 patients treated with Isa-Pd and in 3 patients treated with Pd, solid tumours other than skin cancer in 3 patients treated with Isa-Pd (one patient also had a skin cancer), and haematological malignancy (myelodysplastic syndrome) in 1 patient treated with Isa-Pd (see section 4.8). Patients continued treatment after resection of the new malignancy, except two patients treated with Isa-Pd. One patient developed metastatic melanoma and the other developed myelodysplastic syndrome. In IKEMA study, at a median follow-up time of 56.61 months, SPMs were reported in 18 patients (10.2%) treated with Isa-Kd and in 10 patients (8.2%) treated with Kd. SPMs were skin cancers in 13 patients (7.3%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd, were solid tumours other than skin cancer in 7 patients (4.0%) treated with Isa-Kd and in 6 patients (4.9%) treated with Kd, and heamatological malignancy (acute myeloid leukaemia) in 1 patient (0.8%) in the Kd group. For 1 patient (0.6%) in the Isa-Kd group, the aetiology of the SPM was unknown. Two patients (1.1%) in the Isa-Kd group and one patient (0.8%) in the Kd group had both skin cancer and solid tumours other than skin cancer (see section 4.8). Patients with skin cancer continued treatment after resection of the skin cancer. Solid tumours other than skin cancer were diagnosed within 3 months after treatment initiation in 3 patients (1.7%) treated with Isa-Kd and in 2 patients (1.6%) treated with Kd. The overall incidence of SPMs in all the SARCLISA-exposed patients is 4.3%. Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated.

Tumour lysis syndrome
Cases of tumour lysis syndrome (TLS) have been reported in patients who received isatuximab. Patients should be monitored closely and appropriate precautions taken.

Interference with serological testing (indirect antiglobulin test)
Isatuximab binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). This interference with the indirect Coombs test may persist for at least 6 months after the last infusion of SARCLISA. To avoid potential problems with RBC transfusion, patients being treated with SARCLISA should have blood type and screen tests performed prior to the first infusion. Phenotyping may be considered prior to starting SARCLISA treatment as per local practice.
If treatment with SARCLISA has already started, the blood bank should be informed. Patients should be monitored for theoretical risk of haemolysis. If an emergency transfusion is required, non- cross- matched ABO/Rh-compatible RBCs can be given as per local blood bank practices (see section 4.5).

Interference with determination of complete response
Isatuximab is an IgG kappa monoclonal antibody that could be detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5). This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein. Twenty-two patients in the Isa-Pd arm who met Very Good Partial Response (VGPR) criteria with only residual immunofixation-positivity were tested for interference. Serum samples from these patients were tested by mass spectrometry to separate isatuximab signal from the myeloma M-proteinsignal. In the Isa-Kd arm, out of the 27 patients identified with potential interference and tested by mass spectrometry at the sensitivity level of the immunofixation test (25 mg/dL), 15 non-Complete Response (non-CR) patients as per Independent Response Committee (IRC) showed no detectable residual myeloma M-protein. Among these 15 patients, 11 patients had plasma cell <5% in bone

marrow. This indicates that 11 additional patients out of the 179 Isa-Kd patients (6.1%) could have CR as best response leading to a potential CR rate of 45.8% (see section 4.5).

Elderly
Data are limited in the elderly population ≥ 85 years old (see section 4.2).

Excipient with known effect
This medicine contains 0.2 mg of polysorbate 80 in each mL of isatuximab concentrate for solution for infusion, which is equivalent to 0.1 mg/kg of body weight.
Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Isatuximab has no impact on the pharmacokinetics of pomalidomide or carfilzomib, or vice versa.

Interference with serological testing
Because CD38 protein is expressed on the surface of red blood cells, isatuximab, an anti-CD38 antibody, may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with isatuximab (see section 4.4). The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt isatuximab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Isatuximab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assaysused for monitoring disease monoclonal immunoglobulins (M-protein) , and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria (see section 4.4). In patients with persistent very good partial response, where isatuximab interference is suspected, consider using a validated isatuximab-specific IFE assay to distinguish isatuximab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Women of childbearing potential treated with isatuximab should use effective contraception during treatment and for 5 months after cessation of treatment.

Pregnancy
There are no available data on isatuximab use in pregnant women. Animal reproduction toxicity studies have not been conducted with isatuximab. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of isatuximab in pregnant women is not recommended.

Breast-feeding
It is unknown whether isatuximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; however, a risk to the breast-fed child cannot be excluded during this short period just after birth. For this specific period, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isatuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Afterwards, isatuximab could be used during breast-feeding if clinically needed.

Fertility
No human and animal data are available to determine potential effects of isatuximab on fertility in males and females (see section 5.3).

For other medicinal products that are administered with isatuximab, refer to the respective current summary of product characteristics.

4.7 Effects on ability to drive and use machines

SARCLISA has no or negligible influence on the ability to drive and use machines. Fatigue and dizziness have been reported in patients taking SARCLISA and this should be taken into account when driving or using machines. For other medicinal products that are administered with SARCLISA, refer to the respective current Prescribing information.

4.8 Undesirable effects

Summary of the safety profile
In ICARIA-MM, the most frequent adverse reactions (>20%) are neutropenia (46.7%), infusion reactions (38.2%), pneumonia (30.9%), upper respiratory tract infection (28.3%), diarrhoea (25.7%) 8 and bronchitis (23.7%). Serious adverse reactions occurred in 61.8% of patients receiving Isa-Pd. The most frequent serious adverse reactions are pneumonia (25.7%) and febrile neutropenia (6.6%). Permanent discontinuation of treatment because of adverse reactions was reported in 7.2% of patients treated with Isa-Pd. Adverse reactions with a fatal outcome during treatment were reported in 7.9% of patients treated with Isa-Pd (those occurring in more than 1% of patients were pneumonia occurring in 1.3% of patients and other infections occurring in 2.0% of patients).

In IKEMA, the most frequent adverse reactions (≥20%) are infusion reactions (45.8%), hypertension (36.7%), diarrhoea (36.2%), upper respiratory tract infection (36.2%), pneumonia (28.8%), fatigue (28.2%), dyspnoea (27.7%), insomnia (23.7%), bronchitis (22.6%), and back pain (22.0%). Serious adverse reactions occurred in 59.3% of patients receiving Isa-Kd. The most frequent serious adverse reaction is pneumonia (21.5%). Permanent discontinuation of treatment because of adverse reactions was reported in 8.5% of patients treated with Isa-Kd. Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients treated with Isa-Kd (those occurring in more than 1% of patients were pneumonia and cardiac failure both occurring in 1.1% of patients).

Tabulated list of adverse reactions
Adverse reactions are described using the NCI Common Toxicity Criteria, the COSTART and the MedDRA terms. 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); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

The adverse reactions were reported in clinical studies (see section 5.1) and post-market settings.

Table 3: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with pomalidomide and low-dose dexamethasone

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (%) (N=152)	
			Any Grade	Grade ≥3
Infections and infestations	Pneumonia [a b]	Very common	34.8%	27.9%
	Upper respiratory tractinfection	Very common	40.2%	3.3%
	Bronchitis	Very common	20.9%	3.7%

	Herpes zoster	Common	2.5%	0.4%
Neoplasms benign, malignant and unspecified (incl cystsand polyps)[c]	Skin cancer	Common	4.9%	1.6%
	Solid tumour (non-skin cancer)	Common	2.9%	1.6%
	Haematology malignancy	Uncommon	0.4%	0.4%
Blood and lymphatic system disorders	Neutropenia	Very common	52.5%	51.6%
	Thrombocytopenia	Very common	12.7%	11.9%
	Febrile neutropenia	Common	7.4%	7.4%
	Anaemia	Common	6.1%	4.5%
	Lymphopenia	Not known	-----	-----
Immune system disorders	Anaphylactic reaction[d]	Uncommon	0.3%	0.3%
Metabolism and nutrition disorders	Decreased appetite	Very common	11.5%	1.2%
Cardiac disorders	Atrial fibrillation	Common	5.7%	2.5%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	25.8%	5.7%
Gastrointestinal disorders	Diarrhoea	Very common	34.0%	2.5%
	Nausea	Very common	22.1%	0%
	Vomiting	Very common	14.8%	0.8%
Investigations	Weight decreased	Common	4.9%	0%
Injury, poisoning and procedural complications	Infusion reaction [b]	Very common	39.3%	2.0%

[a] The term pneumonia is a grouping of the following terms: atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, , pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal and pneumocystis jirovecii pneumonia.
[b] See "Description of selected adverse reactions".
[c] Based on second primary malignancies reported during study treatment period and during post-treatment period.
[d] Based on post-marketing adverse reactions.

Table 4: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with carfilzomib and dexamethasone[a]

System Organ Class Preferred Term	**Adverse reaction**	**Frequency**	**Incidence (N=177)**	
			Any Grade	**Grade ≥3**
Infections and	Pneumonia[b c]	Very common	28.8%	20.9%

infestations	Upper respiratory tract infection	Very common	36.2%	3.4%
	Bronchitis	Very common	22.6%	2.3%
	Herpes zoster	Common	2.3%	0.6%
Vascular disorders	Hypertension	Very common	36.7%	20.3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)[d]	Skin cancers	Common	7.3%	1.7%
	Solid tumours (non-skin cancers)	Common	4.0%	3.4%
Blood and lymphatic system disorders	Anaemia	Common	5.1%	4.5%
	Neutropenia	Common	4.5%	4.0%
	Thrombocytopenia	Common	2.8%	2.3%
	Lymphopenia	Not known	-----	-----
Immune system disorders	Anaphylactic reaction[e]	Uncommon	0.3%	0.3%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	27.7%	5.1%
	Cough	Very common	19.8%	0%
Gastrointestinal disorders	Diarrhoea	Very common	36.2%	2.8%
	Vomiting	Very common	15.3%	1.1%
General disorders and administration site conditions	Fatigue	Very common	28.2%	3.4%
Injury, poisoning and procedural complications	Infusion reaction[c]	Very common	45.8%	0.6%

[a] Cut-off date of 07-Feb-2020. Median follow-up time=20.73 months.
[b] The term pneumonia is a grouping of the following terms: atypical pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia influenza, pneumonia legionella, pneumonia streptococcal, pneumonia viral, and pulmonary sepsis.
[c] See "Description of selected adverse reactions".
[d] Cut-off date of 07-Feb-2023. Median follow-up time=56.61 months. Based on second primary malignancies reported during study treatment period and during post-treatment period.
[e] Based on post-marketing adverse reactions.

Description of selected adverse reactions

Infusion reactions
In ICARIA-MM, infusion reactions were reported in 58 patients (38.2%) treated with SARCLISA. All patients who experienced infusion reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2.0%) also having infusion reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion reactions were reported in 3.9%, Grade 2 in 31.6%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. All infusion reactions were reversible and resolved the same day in 98% of the infusions. Signs and symptoms of Grade 3 or 4 infusion reactionsincluded dyspnoea, hypertension and bronchospasm.
The incidence of infusion interruptions because of infusion reactions was 28.9%. The median time to infusion interruption was 55 minutes.
Discontinuations from treatment due to infusion reaction were reported in 2.6% of patients in Isa-Pd group.

In IKEMA, infusion reactions were reported in 81 patients (45.8%) treated with Isa-Kd. Grade 1 infusion reactions were reported in 13.6%, Grade 2 in 31.6%, and Grade 3 in 0.6% of the patients treated with Isa-Kd. All infusion reactions were reversible and resolved the same day in 73.8% of episodes in Isa-Kd patients and in more than 2 days in 2.5% of episodes in Isa-Kd patients. Signs and symptoms of Grade 3 infusion reactions included dyspnoea and hypertension. The incidence of patients with isatuximab infusion interruptions because of infusion reactions was 29.9%. The median time to isatuximab infusion interruption was 63 minutes. Isatuximab was discontinued in 0.6% of patients due to infusion reactions.(see sections 4.2 and 4.4).

Infections

In ICARIA-MM, the incidence of Grade 3 or higher infections was 42.8%. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 21.7% of patients in the Isa-Pd group compared to 16.1% in the Pd group,and Grade 4 in 3.3% of patients in the Isa-Pd group compared to 2.7% in the Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in the Isa-Pd group compared to 5.4% in the Pd group. Fatal infections were reported in 3.3%of patients in the Isa-Pd group and 4.0% in the Pd group. In IKEMA, the incidence of Grade 3 or higher infections was 38.4%. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 15.8% of patients in the Isa-Kd group compared to 10.7% in the Kd group, and Grade 4 in 3.4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.8% of patients in the Isa-Kd group compared to 4.9% in the Kd group. Fatal infections were reported in 2.3% of patients in the Isa-Kd group and 0.8% in the Kd group. (see section 4.4).

In relapsed and refractory multiple myeloma clinical studies,, herpes zoster was reported in 2.0% of patients. In ICARIA-MM, the incidence of herpes zoster was 4.6% in the Isa-Pd group compared to 0.7% in the Pd group, and in IKEMA, incidence was 2.3% in the Isa-Kd group compared to 1.6% in the Kd group.

Cardiac failure

In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure, and pulmonary oedema) was reported in 7.3% of patients with the Isa-Kd group (4.0% of Grade ≥3) and in 6.6% of patients with the Kd group (4.1% of Grade ≥3). Serious cardiac failure was observed in 4.0% of patients in the Isa-Kd group and in 3.3% of patients in the Kd group. Cardiac failure with a fatal outcome during treatment was reported in 1.1% of patients in the Isa-Kd group and not reported in the Kd group (see the current prescribing information for carfilzomib).

Haematology laboratory values

Table 5: Haematology laboratory abnormalities in patients receiving isatuximab combined with pomalidomide and dexamethasone–versus pomalidomide and dexamethasone(ICARIA-MM)

Laboratory parameter	**SARCLISA + Pomalidomide + Dexamethasone n(%) (N=152)**			**Pomalidomide + Dexamethasone n(%) (N=147)**		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Anemia	151 (99.3)	48 (31.6)	0	145 (98.6)	41 (27.9)	0
Neutropenia	146 (96.1)	37 (24.3)	92 (60.5)	137 (93.2)	57 (38.8)	46 (31.3)
Lymphopenia	140 (92.1)	64 (42.1)	19 (12.5)	137 (93.2)	52 (35.4)	12 (8.2)
Thrombocytopenia	127 (83.6)	22 (14.5)	25 (16.4)	118 (80.3)	14 (9.5)	22 (15.0)

The denominator used for the percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

Table 6: Haematology laboratory abnormalities in patients receiving isatuximab combined with carfilzomib and dexamethasone versus carfilzomib and dexamethasone (IKEMA)

Laboratory parameter	SARCLISA + Carfilzomib + Dexamethasone (N=177)			Carfilzomib + Dexamethasone (N=122)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Anaemia	99.4%	22.0%	0%	99.2%	19.7%	0%
Neutropenia	54.8%	17.5%	1.7%	43.4%	6.6%	0.8%
Lymphopenia	94.4%	52.0%	16.9%	95.1%	43.4%	13.9%
Thrombocytopenia	94.4%	18.6%	11.3%	87.7%	15.6%	8.2%

The denominator used for the percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

Immunogenicity
Across 9 clinical studies in relapsed or refractory multiple myeloma (RRMM) with isatuximab single agent and combination therapies including ICARIA-MM and IKEMA (N=1023), the incidence of treatment emergent anti-drug antibodies (ADA)s was 2%. No effect of ADAs was observed on pharmacokinetics, safety or efficacy of isatuximab.

Additional adverse reactions in clinical trials
Very common: Covid-19, cataract

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

Signs and symptoms
There has been no experience of overdose of isatuximab in clinical studies. Doses of intravenous isatuximab up to20 mg/kg have been administered in clinical studies.

Management
There is no known specific antidote for SARCLISA overdose. In the event of overdose, monitor the patients for signs or symptoms of adverse reactions and take all appropriate measures immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FC02.

Mechanism of action
Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 receptor. CD38 is a transmembrane glycoprotein that is highly expressed on multiple myeloma cells.

In vitro, isatuximab acts through IgG Fc-dependent mechanisms including: antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Furthermore, isatuximab can also trigger tumor cell death by induction of apoptosis via an Fc-independent mechanism.

In vitro, isatuximab blocks the enzymatic activity of CD38 which catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR), a calcium mobilizing agent. Isatuximab inhibits the cADPR production from extracellular nicotinamide adenine dinucleotide (NAD) in multiple myeloma

cells.

In vitro, isatuximab can activate NK cells in the absence of CD38 positive target tumour cells. *In vivo, a* decrease in absolute counts of total $CD16^+$ and $CD56^+$ NK cells, $CD19^+$ B-cells, $CD4^+$ T-cells and T_{REG} ($CD3^+$, $CD4^+$, $CD25^+$, $CD127^-$) was observed in peripheral blood of patients treated with isatuximab monotherapy.

In multiple myeloma patients, SARCLISA monotherapy induced clonal expansion of the T-cell receptor repertoire indicating an adaptive immune response.

The combination of isatuximab and pomalidomide *in vitro* enhances cell lysis of CD38 expressing multiple myeloma cells by effector cells (ADCC), and by direct tumour cell killing compared to that of isatuximab alone. *In vivo* animal experiments using a human multiple myeloma xenograft model in mice demonstrated that the combination of isatuximab and pomalidomide results in enhanced antitumour activity compared to the activity of isatuximab or pomalidomide alone.

Clinical efficacy and safety

ICARIA-MM (EFC14335)

The efficacy and safety of SARCLISA in combination with pomalidomide and dexamethasone were evaluated in ICARIA-MM (EFC14335), a multicenter, multinational, randomised, open-label, 2-arm, phase III study in patients with relapsed and/or refractory multiple myeloma. Patients had received at least two prior therapies including lenalidomide and a proteasomeinhibitor with disease progression on or within 60 days after the end of the previous therapy. Patientswith primary refractory disease were excluded.

A total of 307 patients were randomised in a 1:1 ratio to receive either SARCLISA in combination with pomalidomide and dexamethasone (Isa-Pd, 154 patients) or pomalidomide and dexamethasone (Pd,153 patients). Treatment was administered in bothgroups in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA 10 mg/kg was administered as an I.V. infusion weekly in the first cycle and every two weeks thereafter.
Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Dexamethasone (oral/intravenous) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15 and 22 for each 28-day cycle.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups, with some minor imbalances. The median patient age was 67 years (range 36-86), 19.9% of patients were ≥75 years. ECOG PS was 0 in 35.7% of patients in the isatuximab arm and 45.1% in the comparator arm, 1 in 53.9% in the isatuximab arm and 44.4% in the comparator arm, and 2 in 10.4% in the isatuximab arm and 10.5% in the comparator arm, 10.4% of patients in the isatuximab arm versus 10.5% in the comparator arm entered the study with a history of COPD or asthma, and 38.6% versus 33.3% of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) were included in the isatuximab arm versus the comparator arm , respectively. The International Staging System (ISS) stage at study entry was I in 37.5% (41.6% in the isatuximab arm and 33.3% in the comparator arm), II in 35.5% (34.4% in the isatuximab arm and 36.6% in the comparator arm) and III in 25.1% (22.1% in the isatuximab arm and 28.1% in the comparator arm) of patients. Overall, 19.5% of patients (15.6% in the isatuximab arm and 23.5% in the comparator arm) had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14) and t(14;16) were present in 12.1% (9.1% in the isatuximab arm and 15.0% in the comparator arm), 8.5% (7.8% in the isatuximab arm and 9.2% in the comparator arm) and 1.6% (0.6% in the isatuximab arm and 2.6% in the comparator arm) of patients, respectively.

The median number of prior lines of therapy was 3 (range 2-11). All patients received a prior proteasome inhibitor, all patients received prior lenalidomide, and 56.4% of patients received prior stem cell transplantation. The majority of patients (92.5%) were refractory to lenalidomide, 75.9% to a proteasome inhibitor, and 72.6% to both an immunomodulatory and a proteasome inhibitor, and 59% of patients were refractory to lenalidomide at last line of therapy.

The median duration of treatment was 41.0 weeks for the Isa-Pd group compared to 24.0 weeks for the Pd group.

Progression free survival (PFS) was the primary efficacy endpoint of ICARIA-MM. The improvement in PFS represented a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-Pd .

Efficacy results are presented in Table 7 and Kaplan-Meier curves for PFS and OS are provided in Figures 1 and 2:

Table 7 : Efficacy of SARCLISA in combination with pomalidomide and dexamethasone versus pomalidomide and dexamethasone in the treatment of multiplemyeloma (intent-to-treat analysis)

Endpoint	**SARCLISA + pomalidomide + dexamethasone N =154**	**Pomalidomide + dexamethasone N = 153**
Progression-Free Survival[a b]		
Median (months) [95% CI]	11.53 [8.936-13.897]	6.47 [4.468-8.279]
Hazard ratio[c] [95% CI]	0.596 [0.436-0.814]	
p-value (stratified log-rank test)[c]	0.0010	
Overall Response Rate[d] Responders (sCR+CR+VGPR+PR) n(%) [95% CI][e]	93 (60.4) [0.5220-0.6817]	54 (35.3) [0.2775-0.4342]
Odds ratio vs comparator [95% exact CI]	2.795 [1.715-4.562]	
p-value (stratified Cochran-Mantel-Haenszel)[c]	<0.0001	
Stringent Complete Response (sCR) + Complete Response (CR) n(%)	7 (4.5)	3 (2.0)
Very Good Partial Response (VGPR) n(%)	42 (27.3)	10 (6.5)
Partial Response (PR) n(%)	44 (28.6)	41 (26.8)
VGPR or better n(%) [95% CI][e]	49 (31.8) [0.2455-0.3980]	13 (8.5) [0.0460-0.1409]
Odds ratio vs comparator [95% exact CI]	5.026 [2.514-10.586]	
p-value (stratified Cochran-Mantel Haenszel)[c]	<0.0001	
Duration of Response[f] * Median in months [95% CI][g]	13.27 [10.612-NR]	11.07 [8.542-NR]

[a] PFS results were assessed by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria.
[b] Patients without progressive disease or death before the analysis cut-off or the date of initiation of further anti-myeloma treatment were censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever came first.
[c] Stratified on age (<75 years versus ≥75 years) and number of previous lines of therapy (2 or 3 versus >3) according to IRT.
[d] sCR, CR, VGPR and PR were evaluated by the IRC using the IMWG response criteria.
[e] Estimated using Clopper-Pearson method.
[f] The duration of response was determined for patients who achieved a response of ≥PR (93 patients in the isatuximab arm and 54 patients in the comparator arm). Kaplan-Meier estimates of duration of response.
[g] CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley.
*Cut-off date of 11-Oct-2018. Median follow-up time=11.60 months. HR<1 favours Isa-Pd arm.
NR: not reached

In patients with high-risk cytogenetics (central laboratory assessment), median PFS was 7.49 (95% CI: 2.628 to NC) in the Isa-Pd group and 3.745 (95% CI: 2.793 to 7.885) in the Pd group (HR=0.655; 95% CI: 0.334 to 1.283). PFS improvements in the Isa-Pd group were also observed in patients ≥75 years (HR=0.479; 95% CI: 0.242 to 0.946), with ISS stage III at study entry (HR=0.635; 95% CI: 0.363 to 1.110), with baseline creatinine clearance < 60 ml/min/1.73 m² (HR=0.502; 95% CI: 0.297 to 0.847), with > 3 prior lines of therapy (HR=0.590; 95%CI: 0.356 to 0.977), in patients refractory to prior therapy with lenalidomide (HR=0.593; 95% CI: 0.431 to 0.816) or proteasome inhibitor (HR=0.578; 95% CI: 0.405 to 0.824) and in those refractory to lenalidomide at the last line before to the study entry (HR= 0.601; 95%CI: 0.436 to 0.828).
Insufficient data is available to conclude on the efficacy of Isa-Pd in patients previously treated with daratumumab (1 patient in the isatuximab arm and no patient in the comparator arm).

The median time to first response in responders was 35 days in the Isa-Pd group versus 58 days in the Pd group. At a median follow-up time of 52.44 months, final median overall survival was 24.57 months in the Isa-Pd group and 17.71 months in the Pd group (HR=0.776; 95% CI: 0.594 to 1.015).

Figure 1: Kaplan-Meier Curves of PFS – ITT population – ICARIA-MM (assessment by the IRC)

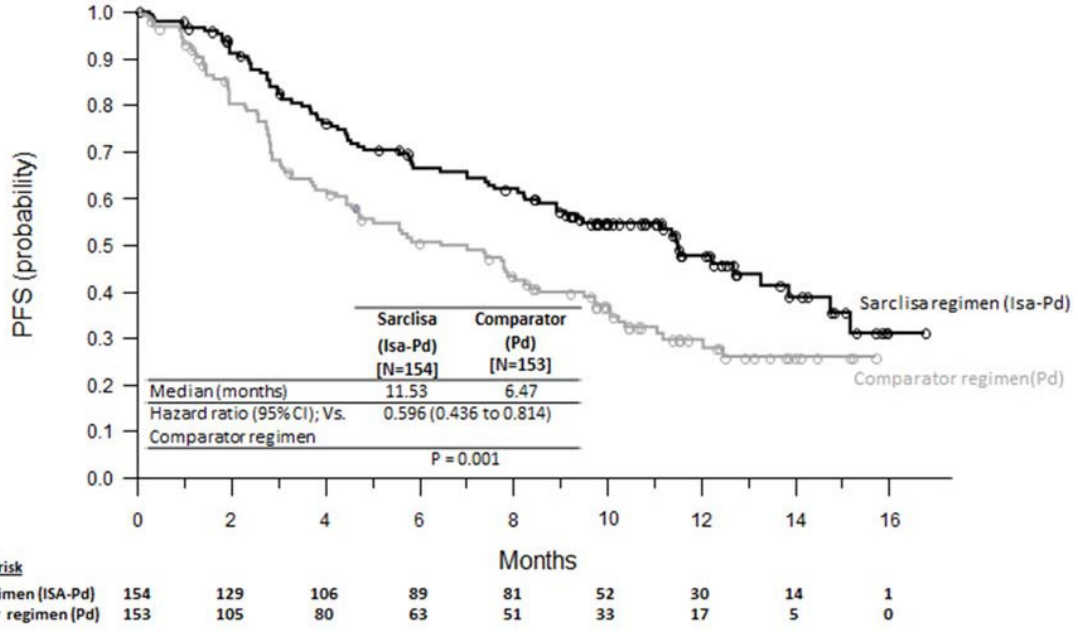
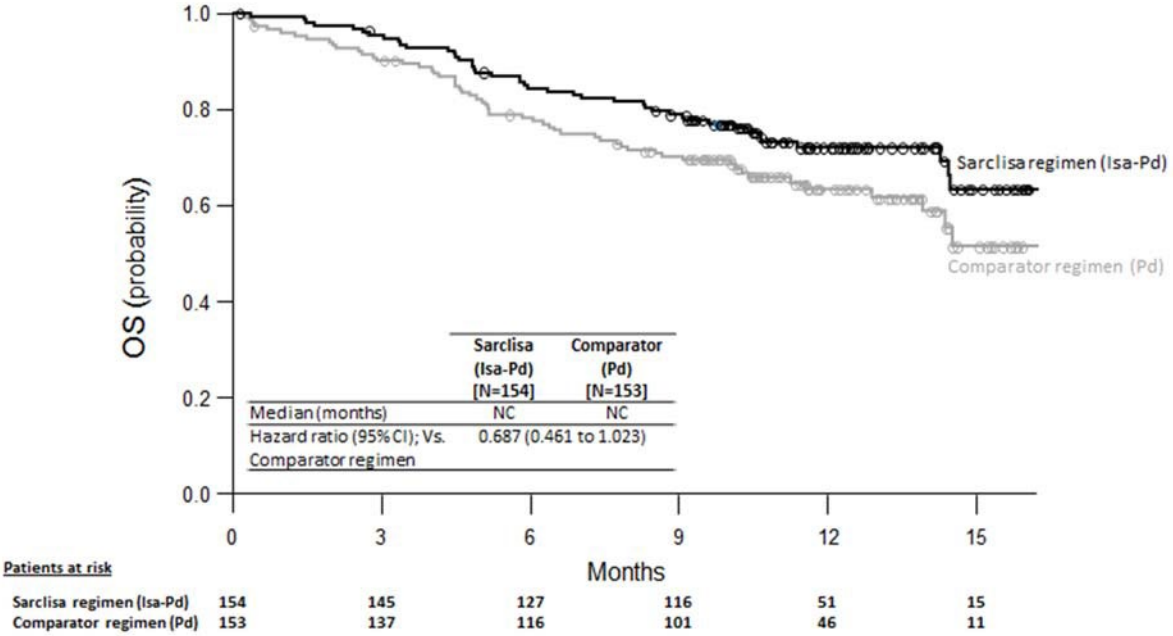


Figure 2: Kaplan-Meier Curves of OS – ITT population – ICARIA-MM



Cutoff date = 07 February 2023

In the ICARIA-MM (EFC14335) study, a weight-based volume was used for isatuximab infusion. The fixed volume infusion method as described in section 4.2 was evaluated in study TCD14079 Part B and pharmacokinetics simulations confirmed minimal differences between the pharmacokinetics following injection applying a volume based on patient weight and a fixed volume of 250 mL (see section 5.2). In study TCD14079 part B, there were no new safety signals or differences in efficacy and safety as compared to ICARIA-MM .

IKEMA (EFC15246)

The efficacy and safety of SARCLISA in combination with carfilzomib and dexamethasone were evaluated in IKEMA (EFC15246), a multicentre, multinational, randomized, open-label, 2-arm, phase III study in patients with relapsed and/or refractory multiple myeloma. Patients had received one to three prior therapies. Patients with primary refractory disease, who had previously been treated with carfilzomib, or who were refractory to previous anti-CD38 monoclonal antibody treatment were excluded.
A total of 302 patients were randomized in a 3:2 ratio to receive either SARCLISA in combination with carfilzomib and dexamethasone (Isa-Kd, 179 patients) or carfilzomib and dexamethasone (Kd, 123 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA 10 mg/kg was administered as an I.V. infusion weekly in the first cycle and every two weeks thereafter. Carfilzomib was administered as an I.V. infusion at the dose of 20 mg/m² on days 1 and 2; 56 mg/m² on days 8, 9, 15 and 16 of cycle 1; and at the dose of 56 mg/m² on days 1, 2, 8, 9, 15 and 16 for subsequent cycles of each 28-day cycle. Dexamethasone (IV on the days of isatuximab and/ or carfilzomib infusions, and PO on the other days) 20 mg was given on days 1, 2, 8, 9, 15, 16, 22 and 23 for each 28-day cycle.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 64 years (range 33-90), 8.9% of patients were ≥75 years. ECOG PS was 0 in 53.1% of patients in the Isa-Kd group and 59.3% in the Kd group, 1 in 40.8% in the IsaKd group and 36.6% in the Kd group, and 2 in 5.6% in the Isa-Kd group and 4.1% in the Kd group, and 3 in 0.6% in the Isa-Kd group and 0% in the Kd group. The proportion of patients with renal impairment (eGFR<60 mL/min/1.73 m^2) was 24.0% in the Isa-Kd group versus 14.6% in the Kd group. The International Staging System (ISS) stage at study entry was I in 53.0%, II in 31.1%, and III

in 15.2% of patients. The Revised-ISS (R-ISS) stage at study entry was I in 25.8%, II in 59.6%, and III in 7.9% of patients. Overall, 24.2% of patients had high -risk chromosomal abnormalities at study 17 entry; del(17p), t(4;14), t(14;16) were present in 11.3%, 13.9% and 2.0% of patients, respectively. In addition, gain(1q21) was present in 42.1% of patients.

The median number of prior lines of therapy was 2 (range 1-4) with 44.4% of patients who received 1 prior line of therapy. Overall, 89.7% of patients received prior proteasome inhibitors, 78.1% received prior immunomodulators (including 43.4% who received prior lenalidomide), and 61.3 % received prior stem cell transplantation. Overall, 33.1% of patients were refractory to prior proteasome inhibitors, 45.0% were refractory to prior immunomodulators (including 32.8% refractory to lenalidomide), and 20.5% were refractory to both a proteasome inhibitor and an immunomodulator.

The median duration of treatment was 80.0 weeks for the Isa-Kd group compared to 61.4 weeks for the Kd group.

Progression-free survival (PFS) was the primary efficacy endpoint of IKEMA. With a median follow up time of 20.73 months, the primary analysis of PFS showed a statistically significant improvement in PFS represented by a 46.9% reduction in the risk of disease progression or death in patients treated with Isa-Kd compared to patients treated with Kd.
Efficacy results are presented in Table 8 and Kaplan-Meier curves for PFS and OS are provided in the Figures3 and 4:

Table 8: Efficacy of SARCLISA in combination with carfilzomib and dexamethasone versus carfilzomib and dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Endpoint	SARCLISA + carfilzomib + dexamethasone N =179	Carfilzomib + dexamethasone N = 123
Progression-Free Survival[a]		
Median (months)	NR	19.15
[95% CI]	[NR -NR]	[15.77-NR]
Hazard ratio[b] [99% CI]	0.531 [0.318-0.889]	
p-value (Stratified Log-Rank test)[b]	0.0013	
Overall Response Rate[c]		
Responders (sCR+CR+VGPR+PR)	86.6%	82.9%
[95% CI][d]	[0.8071-0.9122]	[0.7509-0.8911]
p-value (stratified Cochran-Mantel-Haenszel)[b]	0.3859	
Complete Response (CR)	39.7%	27.6%
Very Good Partial Response (VGPR)	33.0%	28.5%
Partial Response (PR)	14.0%	26.8%
VGPR or better (sCR+CR+VGPR)	72.6%	56.1%
[95% CI][d]	[0.6547-0.7901]	[0.4687 -0.6503]
p-value (stratified Cochran-Mantel-Haenszel)[b e]	0.0021	
CR[f]	39.7%	27.6%
[95% CI][d]	[0.3244-0.4723]	[0.1996 to 0.3643]
Minimal Residual Disease negative rate[g]	29.6%	13.0%
[95% CI][d]	[0.2303-0.3688]	[0.0762-0.2026]
p-value (stratified Cochran-Mantel-Haenszel)[b e]	0.0008	

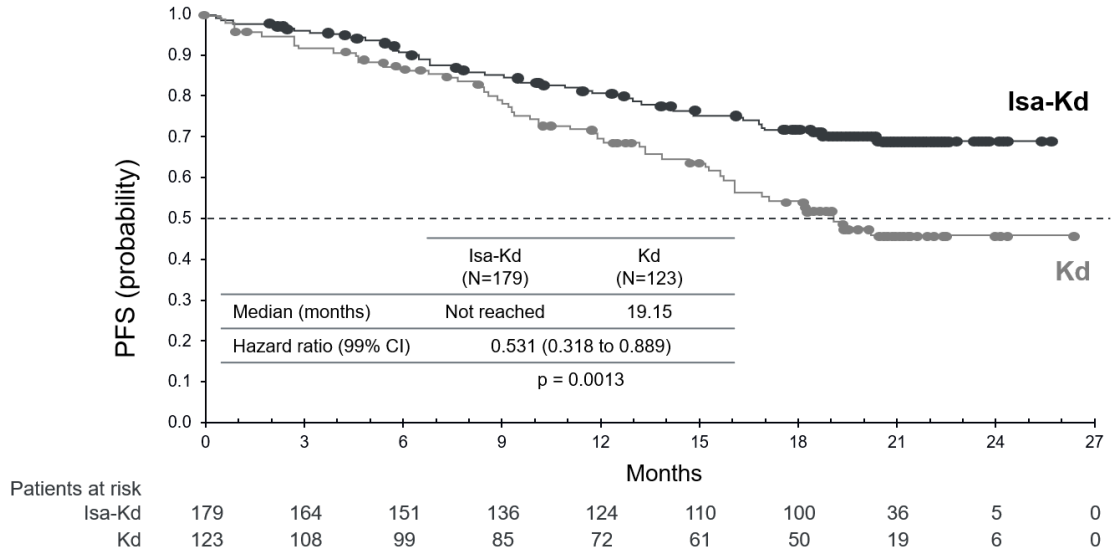
Endpoint	SARCLISA + carfilzomib + dexamethasone N =179	Carfilzomib + dexamethasone N = 123
Duration of Response[h] *****(PR or better)		
Median in months [95% CI][i]	NR [NR-NR]	NR [14.752-NR]
Hazard ratio[b] [95% CI]	0.425 [0.269-0.672]	

[a] PFS results were assessed by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria.
[b] Stratified on number of previous lines of therapy (1 versus >1) and R-ISS (I or II versus III versus not classified) according to IRT.
[c] sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria.
[d] Estimated using Clopper-Pearson method.
[e] Nominal p-value.
[f] CR to be tested with final analysis.
[g] Based on a sensitivity level of 10^{-5} by NGS in ITT population.
[h] Based on Responders in the ITT population. Kaplan-Meier estimates of duration of response.
[i] CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley.
* Cut-off date of 7 February 2020. Median follow-up time=20.73 months. HR<1 favours Isa-Kd arm.
NR: not reached.

PFS improvements in the Isa-Kd group were observed in patients with high -risk cytogenetics (central laboratory assessment, HR = 0.724; 95% CI: 0.361 to 1.451), with gain (1q21) chromosomal abnormality (HR=0.569; 95% CI: 0.330 to 0.981), ≥65 years (HR =0.429; 95% CI: 0.248 to 0.742), with baseline eGFR (MDRD) < 60 mL/min/1.73 m² (HR =0.273; 95% CI: 0.113 to 0.660), with >1 prior line of therapy (HR =0.479; 95% CI: 0.294 to 0.778), with ISS stage III at study entry (HR=0.650; 95% CI: 0.295 to 1.434), and in patients refractory to prior therapy with lenalidomide (HR=0.598; 95% CI: 0.339 to 1.055).
In the sensitivity analysis without censoring for further anti-myeloma therapy, the median PFS was not reached (NR) in the Isa-Kd group versus 19.0 months (95% CI: 15.38 to NR) in the Kd group (HR=0.572; 99% CI: 0.354 to 0.925, p=0.0025).
Insufficient data is available to conclude on the efficacy of Isa-Kd in patients previously treated with daratumumab (1 patient in the isatuximab arm and no patient in the comparator arm).

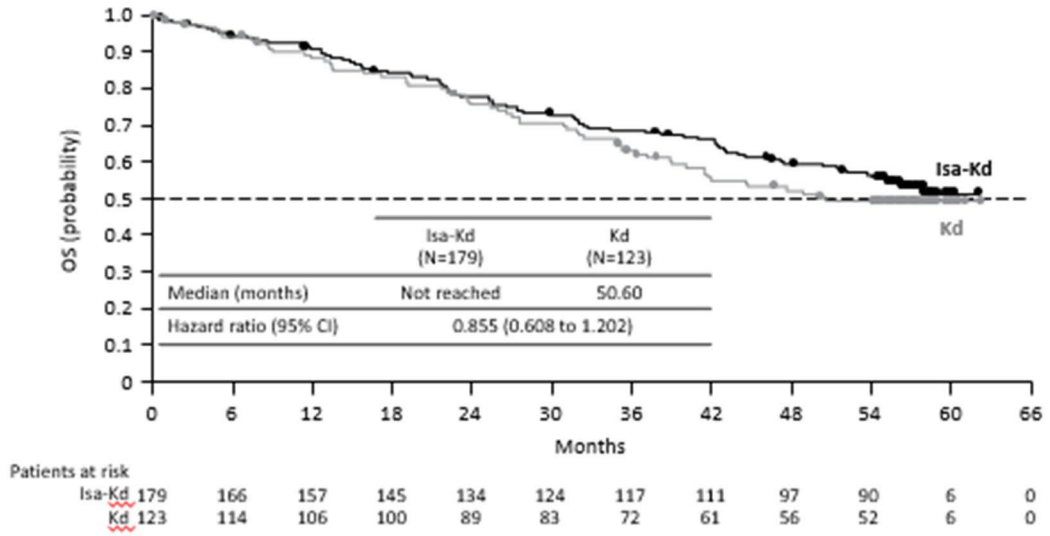
The median time to first response was 1.08 months in the Isa-Kd group and 1.12 months in the Kd group. The median time to next anti-myeloma treatment was 43.99months in the Isa-Kd group and 25.00 months in the Kd group (HR=0.583; 95% CI: 0.429 to 0.792).

Figure 3 – Kaplan-Meier Curves of PFS – ITT population – IKEMA (assessment by the IRC)



Cutoff date = 07 February 2020.

Figure 4: Kaplan-Meier Curves of OS – ITT population – IKEMA



Cut-off date = 07 February 2023

Among patients with eGFR (MDRD) <50 mL/min/1.73 m^2 at baseline, complete renal response (≥60 mL/min/1.73 m^2 at ≥1 postbaseline assessment) was observed for 52.0% (13/25) of patients in the Isa-Kd group and 30.8% (4/13) in the Kd group. Sustained complete renal response (≥60 days) occurred in 32.0% (8/25) of patients in the Isa-Kd group and in 7.7% (1/13) in the Kd group. In the 4 patients in the Isa-Kd group and the 3 patients in the Kd group with severe renal impairment at baseline (eGFR (MDRD) >15 to <30 mL/min/1.73 m^2), minimal renal response (≥30 to <60 mL/min/1.73 m^2 at ≥1 postbaseline assessment) was observed for 100% of patients in the Isa-Kd group and 33.3% of patients in the Kd group.

At a median follow-up time of 43.96 months, final PFS analysis showed a median PFS of 35.65 months for Isa-Kd group compared to 19.15 months for Kd group, with a hazard ratio of 0.576 (95.4% CI: 0.418 to 0.792). Final complete response, determined using a validated isatuximab-specific IFE assay (Sebia Hydrashift) (see section 4.5), was 44.1% in Isa-Kd group compared to 28.5% in Kd group, with odds ratio 2.094 (95% CI: 1.259 to 3.482, descriptive p=0.0021). In 26.3% of patients in Isa-Kd group, both MRD negativity and CR were met compared to 12.2% in Kd group, with odds ratio 2.571 (95% CI: 1.354 to

4.882, descriptive p=0.0015).
At a median follow-up time of 56.61 months, median overall survival was not reached in the Isa-Kd group (95% CI: 52.172 to NR) and was 50.60 months in Kd group (95% CI: 38.932 to NR) (HR=0.855; 95% CI: 0.608 to 1.202).

5.2 Pharmacokinetic properties

The pharmacokinetics of isatuximab were assessed in 476 patients with multiple myeloma treated with isatuximab intravenous infusion as a single agent or in combination with pomalidomide and dexamethasone, at doses ranging from 1 to 20 mg/kg, administered either once weekly; every 2 weeks; or every 2 weeks for 8 weeks followed by every 4 weeks; or every week for 4 weeks followed by every 2 weeks.

Isatuximab displays nonlinear pharmacokinetics with target-mediated drug disposition due to its binding to CD38 receptor.
Isatuximab exposure (area under the plasma concentration-time curve over the dosing interval AUC) increases in a greater than dose proportional manner from 1 to 20 mg/kg following every 2 weeks schedule, while no deviation to the dose proportionality is observed between 5 and 20 mg/kg following every week for 4 weeks followed by every 2 weeks schedule. This is due to the high contribution of nonlinear target-mediated clearance to the total clearance at doses below 5 mg/kg, which becomes negligible at higher doses. After isatuximab 10 mg/kg administration every week for 4 weeks followed by every 2 weeks, the median time to reach steady state was 18 weeks with a 3.1-fold accumulation. In ICARIA-MM, clinical study performed in relapsed and/or refractory multiple myeloma patients treated with isatuximab in combination with pomalidomide and dexamethasone, the mean (CV%) predicted maximum plasma concentration C_{max} and AUC at steady state were 351 µg/mL (36.0%) and 72,600 µg.h/mL (51.7%), respectively. Although the change froma weight-based volume administration method for isatuximab infusion to the fixed volume infusion method resulted in changes in the t_{max}, the change had a limited impact on pharmacokinetics exposure with comparable simulated C_{max} at steady state (283 µg/mL vs 284 µg/mL) and C_{trough} at 4 weeks (119 µg/mL vs 119 µg/mL) for a patient with median weight (76 kg). Also for other patientweight groups, C_{max} and C_{trough} were comparable. In IKEMA, clinical study performed in relapsed and/or refractory multiple myeloma patients treated with isatuximab in combination with carfilzomib and dexamethasone, the mean (CV%) predicted maximum plasma concentration C_{max} and AUC at steady state were 637 µg/mL (30.9%) and 152,000 µg.h/mL (37.8%), respectively.

The pharmacokinetics of isatuximab and pomalidomide, or of isatuximab and carfilzomib, were not influenced by their co-administration.

Distribution
The estimated total volume of distribution of isatuximab is 8.75 L.

Metabolism
As a large protein, isatuximab is expected to be metabolized by non-saturable proteolytic catabolism processes.

Elimination
Isatuximab is eliminated by two parallel pathways, a nonlinear target-mediated pathway predominating at low concentrations, and a nonspecific linear pathway predominating at higher concentrations. In the therapeutic plasma concentrations range, the linear pathway is predominant and decreases over time by 50% to a steady state value of 9.55 mL/h (0.229 L/day). This is associated with a terminal half-life of 28 days.

Specific populations

Age
The population pharmacokinetic analyses of 476 patients aged 36 to 85 years showed comparable exposure to isatuximab in patients <75 years old (n=406) versus ≥ 75 years old (n=70).

Gender
The population pharmacokinetic analysis with 207 female (43.5%) and 269 male (56.5%) patients showed no clinically meaningful effect of gender on isatuximab pharmacokinetics.

Race
The population pharmacokinetic analysis with 377 Caucasian (79%), 25 Asian (5%), 18 Black (4%), and 33 other race (7%) patients showed no clinically meaningful effect of race on isatuximab pharmacokinetics.

Weight
Based on a population pharmacokinetics analysis using data from 476 patients, the clearance of isatuximab increased with increasing body weight, supporting the body-weight based dosing.

Hepatic impairment
No formal studies of isatuximab in patients with hepatic impairment have been conducted. Out of the 476 patients of the population pharmacokinetic analyses, 65 patients presented with mild hepatic impairment [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate amino transferase (AST) > ULN] and 1 patient had moderate hepatic impairment (total bilirubin> 1.5 to 3 times ULN and any AST). Mild hepatic impairment had no clinically meaningful effect on the pharmacokinetics of isatuximab. The effect of moderate (total bilirubin >1.5 times to 3 times ULN and any AST) and severe hepatic impairment (total bilirubin >3 times ULN and any AST) on isatuximab pharmacokinetics is unknown. However, since isatuximab is a monoclonal antibody, it is not expected to be cleared via hepatic-enzyme mediated metabolism and as such, variation in hepatic function is not expected to affect the elimination of isatuximab (see section 4.2).

Renal impairment
No formal studies of isatuximab in patients with renal impairment have been conducted. The population pharmacokinetic analyses on 476 patients included 192 patients with mild renal impairment (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (e-GFR) <90 mL/min/1.73 m^2), 163 patients with moderate renal impairment (30 mL/min/1.73 m^2≤ e-GFR < 60 mL/min/1.73 m^2) and 12 patients with severe renal impairment (e-GFR <30 mL/min/1.73 m^2). Analyses suggested no clinically meaningful effect of mild to severe renal impairment on isatuximab pharmacokinetics compared to normal renal function.

Paediatric population
Isatuximab was not evaluated in patients under 18 years of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, albeit the species selected is not pharmacologically responsive and therefore the relevance for humans is not known. Genotoxicity, carcinogenic potential and toxicity to reproduction and development studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L-Histidine hydrochloride monohydrate
L-Histidine
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened Vial
The expiry date of the product is indicated on the packaging materials.

After dilution
Chemical and physical in-use stability of SARCLISA infusion solution has been demonstrated for 48 hours at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
No protection from light is required for storage in the infusion bag.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

5 ml concentrate containing 100 mg of isatuximab in a 6 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stopper. The vials are crimped with an aluminium seal with a grey flip-off button. The fill volume has been established to ensure removal of 5 mL (i.e. 5.4 mL). Pack size of one or three vials.

25 ml concentrate containing 500 mg of isatuximab in a 30 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stopper. The vials are crimped with an aluminium seal with a blue flip-off button. The fill volume has been established to ensure removal of 25 mL (i.e. 26 mL). Pack size of one vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation for the intravenous administration
The preparation of the infusion solution must be done under aseptic conditions.

- The dose (mg) of SARCLISA concentrate should be calculated based on patient weight (measured prior to each cycle to have the administered dose adjusted accordingly, see section 4.2). More than one vial may be necessary to obtain the required dose for the patient.
- Vials of SARCLISA concentrate should be visually inspected before dilution to ensure they do not contain any particles and are not discolored.
- Do not shake vials.
- The volume of diluent equal to the required volume of SARCLISA concentrate should be removed from a 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 5% solution diluent bag.
- The appropriate volume of SARCLISA concentrate should be withdrawn from the SARCLISA vial and diluted in the 250 mL infusion bag with sodium chloride 9 mg/mL

(0.9%) solution for injection or glucose5% solution.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di (2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

Administration
- The infusion solution must be administered by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybudadiene (PBD) or polyurethane (PU)) with a 0.22 micron in-line filter (polyethersulfone (PES), polysulfone or nylon).
- The infusion solution should be administered for a period of time that will depend on the infusion rate (see section 4.2).
- No protection from light is required for the prepared infusion bag in a standard artificial light environment.
- Do not infuse SARCLISA solution concomitantly in the same intravenous line with other agents.

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Israel Ltd, Greenwork Park, P.O box 47, Yakum

8. MANUFACTURER

Sanofi-Aventis Deutschland GmbH, INDUSTRIEPARK HOCHST, D-65926
Frankfurt am Main, Germany.

9. License number 168-30-36603-00

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