ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SARCLISA 20 mg/mL concentrate for solution for infusion

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

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).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SARCLISA 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.
- 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).
- in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

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.
  Dexamethasone 20 mg (intravenous on the days of isatuximab infusion, and oral on the other days): when administered in combination with isatuximab, bortezomib, and lenalidomide.
- Acetaminophen 650 mg to 1 000 mg oral (or equivalent).
- H2 antagonists (ranitidine 50 mg IV or equivalent [e.g., cimetidine]), or oral proton pump inhibitors (e.g., omeprazole, esomeprazole).
- Diphenhydramine 25 mg to 50 mg intravenous or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The intravenous use 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, before isatuximab and carfilzomib, and before isatuximab, bortezomib, and lenalidomide 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 3 or grade 4 neutropenia or febrile neutropenia and/or neutropenic infection, SARCLISA administration should be delayed or omitted until recovery (see section 4.4).

Prevention of infection

Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) according to treatment guidelines should 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), or in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd).

SARCLISA dosing schedules are provided in Tables 1 and 2:

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

Cycles	Dosing schedule
Cycle 1 (28-day cycle)	Days 1, 8, 15 and 22 (weekly)
Cycle 2 and beyond (28-day cycle)	Days 1, 15 (every 2 weeks)

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

Table 2: SARCLISA dosing schedule in combination with bortezomib, lenalidomide, and dexamethasone

Cycles	Dosing schedule
Cycle 1 (42-day cycle)	Days 1, 8, 15, 22, and 29
Cycles 2 to 4 (42-day cycles)	Days 1, 15, and 29 (every 2 weeks)
Cycles 5 to 17 (28-day cycles)	Days 1 and 15 (every 2 weeks)
Cycles 18 and beyond (28-day cycles)	Days 1 (every 4 weeks)

Each treatment cycle consists of a 42-day period from cycle 1 to 4, and of a 28-day period from cycle 5. 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), or in case of Grade 3 or 4 neutropenia, or febrile neutropenia and/or neutropenic infection (see "Management of neutropenia" above).

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 data, no dose adjustment is recommended in patients with mild (GFR ≥ 60 - < 90 mL/min/1.73m^2) to severe (GFR < 30 mL/min/1.73m^2) renal impairment including end-stage renal disease (GFR < 15 mL/min/1.73m^2) (see section 5.2).

Patients with hepatic impairment

Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment ([total bilirubin > 1 to 1.5 times upper limit of normal (ULN) or aspartate amino transferase (AST) > ULN). Data in patients with moderate (total bilirubin > 1.5 to 3 times ULN and any AST) and severe (total bilirubin > 3 times ULN and any AST) 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

Outside its authorised indications, SARCLISA has been studied in children aged 28 days to less than 18 years of age with relapsed or refractory acute lymphoblastic or myeloid leukaemia but efficacy has not been established. Currently available data are described in sections 4.8, 5.1, and 5.2.

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 3 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 3: 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 in the infusion should be considered and additional symptomatic medicinal products can be administered. After symptom improvement to grade ≤ 1 (mild), SARCLISA infusion may be resumed at half 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 3.
- 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.
- In case of Grade≥ 3 hypersensitivity reactions or infusion reactions, SARCLISA treatment should be permanently discontinued.

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

Infusion reactions

Infusion reactions, mostly mild or moderate, have been observed in 38.2 % of patients treated with SARCLISA in ICARIA-MM, in 45.8 % of patients treated with Isa-Kd in IKEMA, and in 24.0% of patients treated with Isa-VRd in IMROZ (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 symptoms included hypertension and dyspnoea. In IMROZ, the IRs started on the infusion day in all patients, mostly during the first SARCLISA infusion, and resolved the same day in 97.3% of patients. All IRs resolved. The most common symptoms of an IR included dyspnoea and chills. The most common severe sign and symptom was hypertension (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 (see section 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. In patients treated with Isa-VRd, neutropenia was reported as a laboratory abnormality in 87.5% of patients and as an adverse reaction in 30% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 54.4% of patients (with 35.7% Grade 3 and 18.6% Grade 4) and as an adverse reaction in 30% of patients. Neutropenic complications have been observed in 12.5% of patients, including 2.3% of febrile neutropenia and 10.6% of neutropenic infection (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 should be 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 haematological 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. In IMROZ study, at a median follow-up time of 59.73 months, SPMs were reported in 42 patients (16.0%) treated with Isa-VRd (0.041 events per patient-year) and in 16 patients (8.8%) treated with VRd (0.026 events per patient-year). SPMs were skin cancers in 22 patients (8.4%) treated with Isa-VRd and in 7 patients (3.9%) treated with VRd, were solid tumours other than skin cancer in 17 patients (6.5%) treated with Isa-VRd and in 7 patients (3.9%) treated with VRd, and haematological malignancy in 3 patients (1.1%) treated with Isa-VRd and in 2 patients (1.1%) treated with VRd. Patients with SPM of skin cancer continued treatment after resection of the skin cancer, except one patient in each treatment group. SPMs with fatal outcome were reported in 6 patients (2.3%) treated with Isa-VRd (neuroendocrine carcinoma of the skin, malignant melanoma, squamous cell carcinoma of skin, squamous cell carcinoma of lung, colorectal cancer, and rectal adenocarcinoma) and in 2 patients (1.1%) treated with VRd (metastases to peritoneum and adenocarcinoma of colon). The overall incidence of SPMs in all the SARCLISA-exposed patients is 6.0 %. 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-protein signal. 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 bortezomib, or lenalidomide, 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) assays used 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 summary of product characteristics.

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 %) 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).

In IMROZ, the most frequent adverse reactions (≥20%) are diarrhoea (54.8%), peripheral sensory neuropathy (54.4%), pneumonia (39.9%), cataract (38.0%), constipation (35.7%), fatigue (34.6%), upper respiratory tract infections (34.2%), oedema peripheral (32.7%), neutropenia (30.0% as an adverse reaction), infusion reaction (23.6%), insomnia (22.4%), Covid-19 (22.4%), back pain (22.1%), bronchitis (22.1%). and asthenia (21.7%), Serious adverse reactions occurred in 70.7% of patients receiving Isa-VRd. The most frequent serious adverse reaction was pneumonia (29.7%, including Covid-19 pneumonia). Adverse reactions with a fatal outcome during treatment (Grade 5 TEAEs) were reported in 11% of patients with Isa-VRd including Grade 5 infectious TEAEs occurring in 6.5% of patients. Permanent discontinuation of treatment because of adverse reactions was reported in 22.8% of patients treated with Isa-VRd.

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); frequency 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 4: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with pomalidomide and dexamethasone

System Organ Class Preferred Term	**Adverse reaction**	**Frequency**	**Incidence (N = 244)**	
			Any Grade	**Grade ≥ 3**
Infections and infestations	Pneumonia[a b]	Very common	34.8 %	27.9 %
	Upper respiratory tract infection	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 cysts and 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 5[a]: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with carfilzomib and dexamethasone

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N = 177)	
			Any Grade	Grade ≥ 3
Infections and infestations	Pneumonia[b c]	Very common	28.8 %	20.9 %
	Upper respiratory tract infection	Very common	36.2 %	3.4 %
	Bronchitis	Very common	22.6 %	2.3 %
	Herpes zoster	Common	2.3 %	0.6 %
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 %
Vascular disorders	Hypertension	Very common	36.7 %	20.3 %
Respiratory, thoracic	Dyspnoea	Very common	27.7 %	5.1 %

and mediastinal disorders	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.

Table 6: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone

System Organ Class Preferred Term	**Adverse reaction**	**Frequency**	**Incidence (N=336)**	
			Any Grade	**Grade ≥3**
Infections and infestations	Pneumonia[a]	Very common	34.2%	24.1%
	Bronchitis	Very common	22.6%	3.0%
	Covid-19	Very common	19.9%	1.2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer	Common	8.0%	2.7%
	Solid tumour (non-skin cancer)	Common	5.7%	3.6%
	Haematology malignancy	Uncommon	0.9%	0.3%
Blood and lymphatic system disorders	Neutropenia	Very common	28.0%	27.1%
	Thrombocytopenia	Very common	13.4%	10.7%
	Anaemia	Common	6.3%	2.7%
	Lymphopenia	Not known	———	———
Immune system disorders	Anaphylactic reaction	Uncommon	0.3%	0.3%
Eye disorders	Cataract	Very common	36.0%	13.1%
Gastrointestinal disorders	Diarrhoea	Very common	56.8%	8.3%
	Vomiting	Common	9.5%	0.3%
General disorders and administration site conditions	Fatigue	Very common	32.7%	6.5%
Injury, poisoning and procedural	Infusion reaction	Very common	27.4%	0.6%

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N=336)	
			Any Grade	Grade ≥3
complications				

[a] The term pneumonia is a grouping of the following terms: Atypical pneumonia, Bronchopulmonary aspergillosis, Covid-19 pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia klebsiella, Pneumonia legionella, , Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia viral, Pulmonary sepsis, Tuberculosis.

MedDRA 26.0

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 reactions included 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.
In IMROZ, infusion reactions were reported in 63 patients (24.0%) treated with Isa-VRd. Grade 1 IRs were reported in 1.9%, Grade 2 in 21.3%, Grade 3 in 0.4%, and Grade 4 in 0.4% of the patients treated with Isa-VRd. The IRs started on the infusion day in all patients, mostly during the first SARCLISA infusion, and resolved the same day in 97.3% of patients. All IRs resolved. Signs and symptoms of Grade 3 or 4 IRs included hypertension, bronchospasm, and hypoxia. The incidence of patients with isatuximab infusion interruptions because of infusion reactions was 20.9%. The median time to isatuximab infusion interruption was 66.0 minutes. Isatuximab was discontinued in 0.8% 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. In IMROZ, the incidence of Grade 3 or higher infections was 44.9% in the Isa-VRd group and 38.1% in the VRd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 25.1% of patients in the Isa-VRd group compared to 15.5% in the VRd group, Grade 4 in 2.3% of patients in the Isa-VRd group compared to 3.9% in the VRd group. Grade 5 pneumonia, based on preferred term, occurred in 1.5% of patients in the Isa-VRd group compared to 1.1% in the VRd group. Discontinuations from treatment due to infection were reported in 8.4% of patients in the Isa-VRd group compared to 9.4% in the VRd group. Fatal infections were reported in 6.5% of patients in the Isa-VRd group and 4.4% in the VRd 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. In newly diagnosed multiple myeloma clinical trials, herpes zoster was reported in 3.3% of patients. In IMROZ, the incidence of herpes zoster was 5.7% in the Isa-VRd group compared to 5.5% in the VRd 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 7: 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**
Anaemia	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 8: 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

Laboratory parameter	SARCLISA + Carfilzomib + Dexamethasone % (N = 177)			Carfilzomib + Dexamethasone % (N = 122)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
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.

Table 9: Haematology laboratory abnormalities in patients receiving isatuximab combined with bortezomib, lenalidomide, and dexamethasone versus bortezomib, lenalidomide, and dexamethasone (IMROZ and TCD13983)

Laboratory parameter	SARCLISA + Bortezomib + Lenalidomide + Dexamethasone (N=336)			Bortezomib + Lenalidomide + Dexamethasone (N=181)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anaemia	99.1%	15.8%	0%	97.8%	16.0%	0%
Lymphopenia	96.1%	45.5%	18.5%	92.3%	37.6%	15.5%
Thrombocytopenia	94.6%	16.7%	14.6%	84.5%	19.3%	8.3%
Neutropenia	86.9%	35.4%	17.3%	80.1%	28.2%	8.8%

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.
CTCAE version: 4.03.

Elderly patients

Of the total number of patients in clinical studies of SARCLISA, 42.7% (763 patients) were less than 65, 43.2% (772 patients) were 65-74, and 14.1% (252 patients) were 75 or older. Differences in safety were observed between older versus younger age groups. Grade ≥3 TEAEs were reported in 64.6% of patients less than 65, 79.7% of patients 65-74 and 76.2% of patients 75 or older, Grade 5 TEAEs were reported in 5.5% of patients less than 65, 7.5% of patients 65-74, and 12.3% of patients 75 or older. Serious TEAEs were reported in 46.7% of patients less than 65, 58.8% of patients 65-74, and 60.7% of patients 75 or older. TEAEs leading to definitive treatment discontinuation were reported in 6% of patients less than 65, 14% of patients 65-74, and 15.5% of patients 75 or older.
In IMROZ study, no Grade 5 TEAEs were reported in patients less than 65, they were reported in 10.7% of patients 65-74, and in 13.2% of patients 75 or older.

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 (ADAs) was <2%. No effect of ADAs was observed on pharmacokinetics, safety or efficacy of isatuximab. Across 3 clinical studies in newly diagnosed multiple myeloma (NDMM) with isatuximab in combination therapy with bortezomib, lenalidomide, and dexamethasone, including IMROZ, ADA incidence ranged from 8.7% to 21.6%. In IMROZ, out of the 263 patients with NDMM treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone, 253 were evaluable for the presence of ADA, 22 patients (8.7%) tested positive for treatment-emergent ADAs, with 21 patients considered to have a transient ADA response and 1 considered to have an indeterminate ADA response. Among these 22 ADA-positive patients, 13 had neutralizing antibodies (incidence of neutralizing antibodies: 5.1%). In IMROZ, a trend to lower exposure was observed in ADA-positive patients. In patients with ADA-positive status to isatuximab no meaningful impact of ADAs on efficacy of isatuximab was observed. No conclusions can be drawn on safety due to the small subgroup of ADA positive patients.

Paediatric population

In a phase 2 single-arm study conducted in 67 paediatric patients with relapsed or refractory acute lymphoblastic leukaemia or acute myeloid leukaemia, all evaluable for safety, Grade ≥ 3 TEAEs was reported in 79.1 % of patients. The most common Grade ≥ 3 TEAEs occurring in > 10% of patients included febrile neutropenia (41.8 %), septic shock (11.9 %), and stomatitis (10.4 %). The addition of SARCLISA to standard chemotherapies did not modify the expected safety profile observed with standard chemotherapies in this paediatric population and was consistent with isatuximab safety profile for adults with multiple myeloma in ICARIA and IKEMA studies (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms

There has been no experience of overdose of isatuximab in clinical studies. Doses of intravenous isatuximab up to 20 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 tumour cell death by induction of apoptosis via an Fc-independent mechanism.

In vitro, isatuximab blocks the enzymatic activity of CD38 which catalyses 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

Relapsed and/or refractory multiple myeloma

ICARIA-MM (EFC14335)

The efficacy and safety of SARCLISA in combination with pomalidomide and dexamethasone were evaluated in ICARIA-MM (EFC14335), a multicentre, 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 proteasome inhibitor with disease progression on or within 60 days after the end of the previous therapy. Patients with 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 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. 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 10 and Kaplan-Meier curves for PFS and OS are provided in Figures 1 and 2:

Table 10: Efficacy of SARCLISA in combination with pomalidomide and dexamethasone versus pomalidomide and dexamethasone in the treatment of multiple myeloma (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)

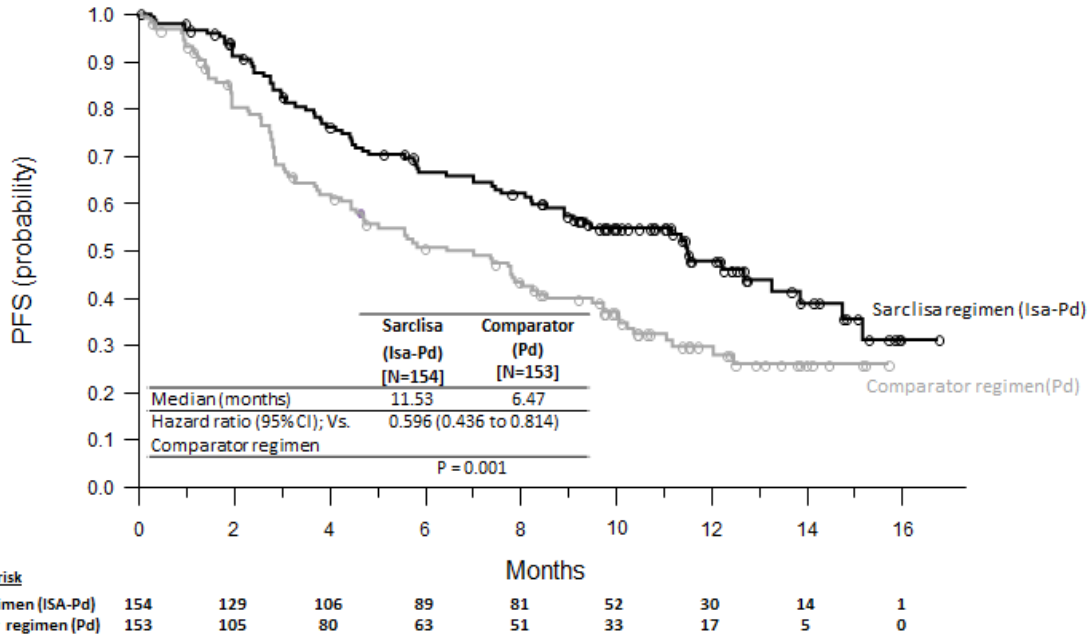
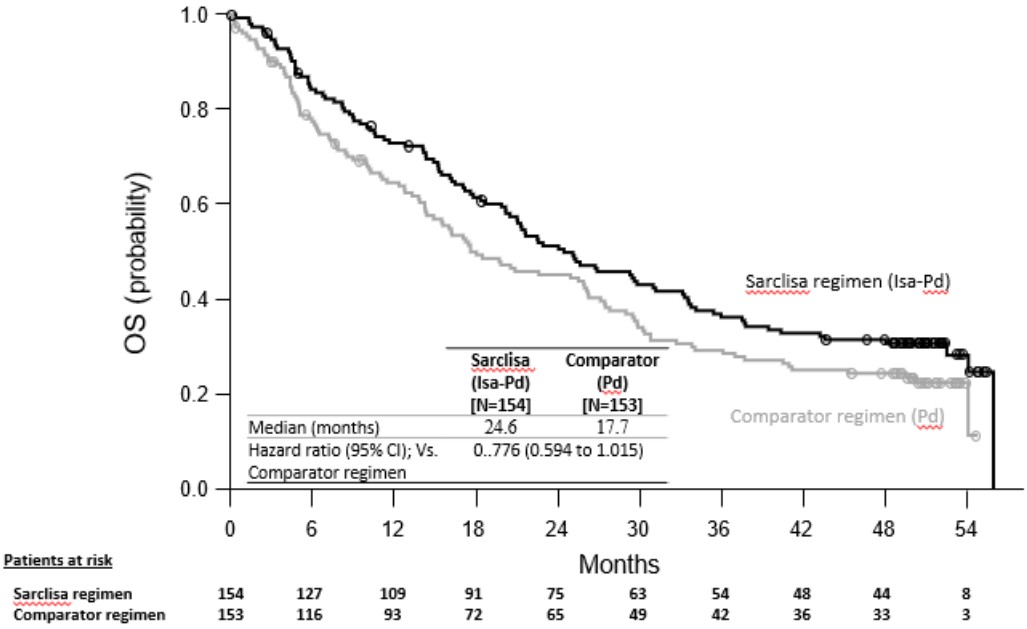


Figure 2: Kaplan-Meier Curves of OS – ITT population – ICARIA-MM



Cut-off 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 Isa-Kd 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 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 11 and Kaplan-Meier curves for PFS and OS are provided in the Figures 3 and 4:

Table 11: 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) [95 % CI]	NR [NR -NR]	19.15 [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) [95 % CI][d]	86.6 % [0.8071-0.9122]	82.9 % [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) [95 % CI][d]	72.6 % [0.6547-0.7901]	56.1 % [0.4687 -0.6503]
p-value (stratified Cochran-Mantel-Haenszel)[b e]	0.0021	
CR[f] [95 % CI][d]	39.7 % [0.3244-0.4723]	27.6 % [0.1996 to 0.3643]

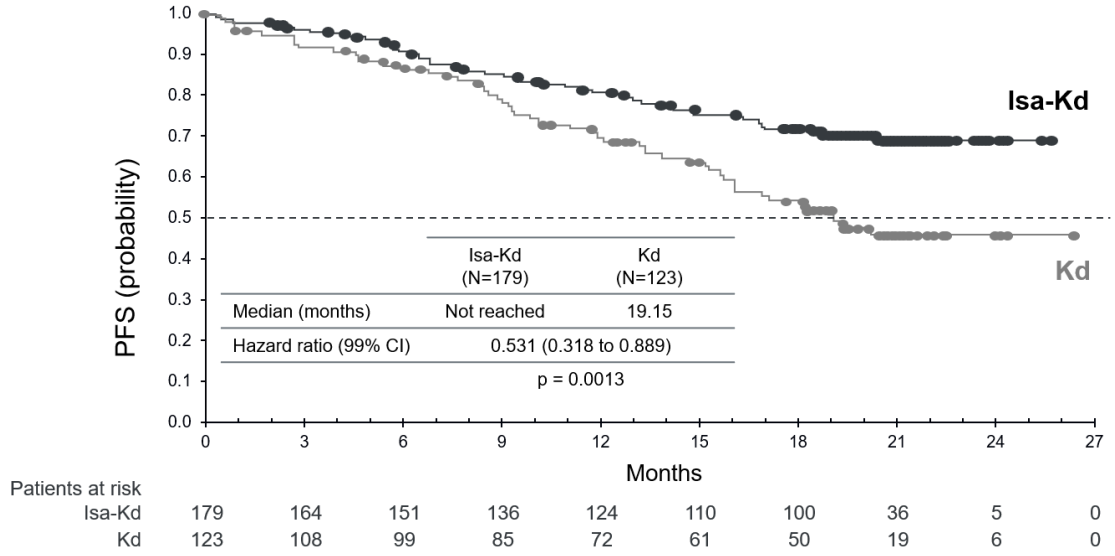
Endpoint	SARCLISA + carfilzomib + dexamethasone N = 179	Carfilzomib + dexamethasone N = 123
Minimal Residual Disease negative rate[g]	29.6 %	13.0 %
[95 % CI][d]	[0.2303-0.3688]	[0.0762-0.2026]
p-value (stratified Cochran-Mantel-Haenszel)[b e]	0.0008	
Duration of Response[h] *(PR or better)		
Median in 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).

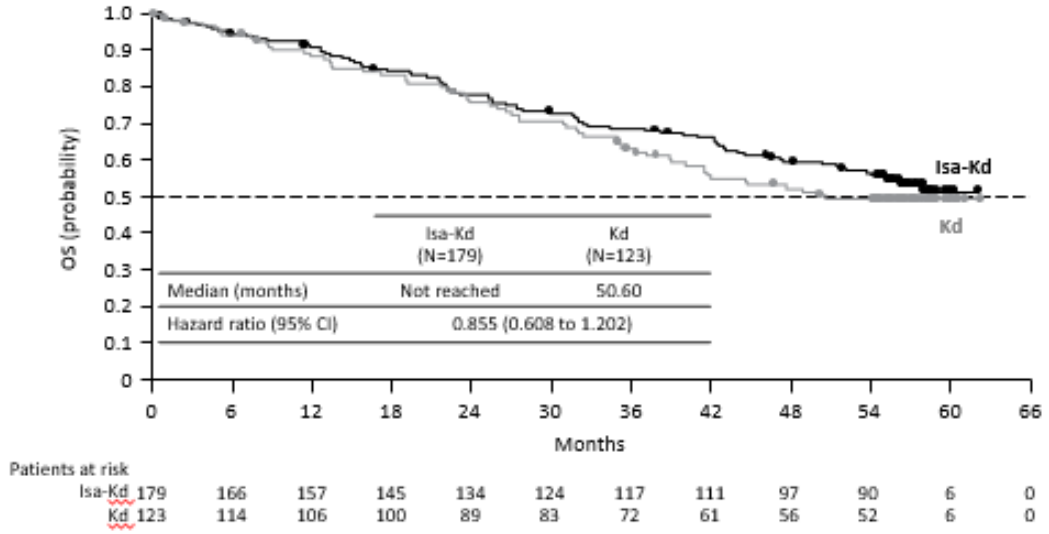
The median time to first response was 1.08 months in the Isa-Kd group and 1.12 months in the Kd group. The median time to next anti-myeloma treatment was 43.99 months in the Isa-Kd group and 25.00 months in the Kd group (HR = 0.583; 95 % CI: 0.429 to 0.792).

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



Cut-off 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).

Newly diagnosed multiple myeloma

IMROZ (EFC12522)

The efficacy and safety of SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone were evaluated in IMROZ (EFC12522), a multicentre, international, randomized, open-label, 2-arm, phase III study in patients with newly diagnosed multiple myeloma (NDMM) who are not eligible for stem cell transplantation. Patients over the age of 80 years were excluded, as well as patients with comorbidities that do not allow transplant procedures in patients with NDMM, based on investigator's medical assessment (e.g., lung or coronary heart disease).

A total of 446 patients were randomized in a 3:2 ratio to receive either SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd, 265 patients) or bortezomib, lenalidomide, and dexamethasone (VRd, 181 patients) administered in both groups during 4 cycles of 42-day for the induction period. After completion of cycle 4, patients entered the continuous treatment period starting from cycle 5, 28-day cycles administered up to disease progression or unacceptable toxicity. During the continuous treatment period, patients of the Isa-VRd group received SARCLISA in combination with lenalidomide, and dexamethasone (Isa-Rd), and patients in the VRd group received lenalidomide, and dexamethasone (Rd).

During the induction period (cycle 1 to 4, 42-day cycles), SARCLISA 10 mg/kg was administered as an I.V. infusion on day 1, 8, 15, 22, and 29, in the first cycle and on day 1, 15, and 29, from cycle 2 to 4. Bortezomib was administered subcutaneously at the dose of 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32 of each cycle. Lenalidomide was administered per os at the dose of 25 mg/day from day 1 to 14 and from day 22 to 35 of each cycle. Dexamethasone (I.V. on the days of isatuximab infusions, and PO on the other days) 20 mg/day was given on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 of each cycle, and administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32 of each cycle for patients ≥75 years old.

During the continuous treatment period (from cycle 5, 28-day cycles), SARCLISA 10 mg/kg was administered as an I.V. infusion on day 1 and 15 from cycle 5 to 17, and on day 1 from cycle 18. Lenalidomide was administered per os at the dose of 25 mg/day from day 1 to 21 of each cycle. Dexamethasone (I.V. on the days of isatuximab infusions, and PO on the other days) 20 mg/day was given on days 1, 8, 15, and 22 of each cycle.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 72 years (range 60-80), 26% of patients were ≥75 years. ECOG PS was 0 in 46.4% of patients in the Isa-VRd group and 43.6% in the VRd group, 1 in 42.3% in the Isa-VRd group and 45.9% in the VRd group, and 2 in 10.9% in the Isa-VRd group and 10.5% in the VRd group,and 3 in 0.4% in the Isa-VRd group and 0% in the VRd group. The proportion of patients with renal impairment (eGFR<60 mL/min/1.73m^2) was 24.9% in the Isa-VRd group versus 34.3% in the VRd group. The Revised International Staging System (R-ISS) stage at study entry was I in 24.9%, II in 61.5%, and III in 10.2% of patients. Overall, 15.1% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14), and t(14;16) were present in 5.7%, 7.9% and 1.9% of patients, respectively. In addition, 1q21+ was present in 35.8% of patients.

The median duration of treatment was 53.2 months for the Isa-VRd group compared to 31.3 months for the VRd group.

Progression-free survival (PFS) was the primary efficacy endpoint of IMROZ. With a median follow-up time of 59.73 months, the pre-planned second interim analysis of PFS showed a statistically significant improvement in PFS representing a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-VRd compared to patients treated with VRd.

Efficacy results are presented in Table 12 and Kaplan-Meier curves for PFS are provided in Figure 5:

Table 12*: Efficacy of SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone versus bortezomib, lenalidomide, and dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Endpoint	SARCLISA + bortezomib + lenalidomide + dexamethasone N =265	Bortezomib + lenalidomide + dexamethasone N = 181
Progression-Free Survival [a]		
Median (months)	NR	54.34
[95% CI]	[NR-NR]	[45.21-NR]
Hazard ratio [b] [98.5% CI]	0.596 [0.406-0.876]	
p-value (Stratified Log-Rank test)[b]	0.0009	
CR or better (sCR and CR)	74.7%	64.1%
[95% CI][c]	[0.6904-0.7984]	[0.5664-0.7107]
p-value (Stratified Log-Rank test)[b]	0.0160	
Minimal Residual Disease negativity[d] and CR	55.5%	40.9%
[95% CI][c]	[0.4927-0.6155]	[0.3365-0.4842]
p-value (stratified Cochran-Mantel-Haenszel)[b]	0.0026	
Overall Response Rate[e]	91.3%	92.3%
Responders (sCR+CR+VGPR+PR)	[0.8726-0.9442]	[0.8736-0.9571]
[95% CI][c]		
Stringent Complete Response (sCR)	10.9%	5.5%
Complete Response (CR)	63.8%	58.6%
Very Good Partial Response (VGPR)	14.3%	18.8%
Partial Response (PR)	2.3%	9.4%

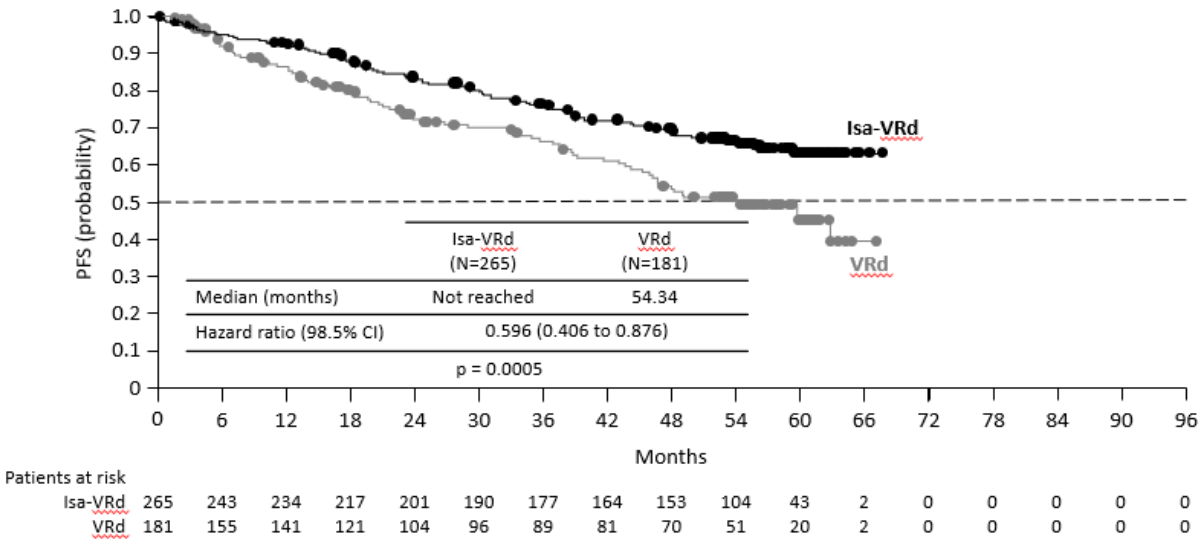
[a] PFS results were assessed by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria.
[b] Stratified by age (<70 years vs ≥70 years) and Revised International Staging System (R-ISS) stage (I or II vs. III or not classified) according to IRT
[c] Estimated using Clopper-Pearson method.

[d] Based on a sensitivity level of 10^{-5} by NGS in ITT population.
[e] sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria. Results should be interpreted descriptively.
* Cut-off date of 26 September 2023. Median follow-up time=59.73 months.
NR: not reached

PFS improvement in the Isa-VRd group was confirmed by the sensitivity analyses sand was observed across most subgroups of patients, including patients with 1q21+ chromosomal abnormality (HR=0.407; 95% CI: 0.253 to 0.653), ≥70 years (HR=0.671; 95% CI: 0.463 to 0.972), with baseline eGFR (MDRD) < 60 mL/min/1.73 m² (HR=0.63; 95% CI: 0.371 to 1.068), and with ECOG PS>1 (HR=0.606; 95% CI: (0.246 to 1.493).

NGS MRD negativity (10^{-5} sensitivity threshold) was reached in 58.1% of patients in the Isa-VRd group with a median time to first NGS MRD negativity of 196.5 days (range: 87-1834). In the VRd group, NGS MRD negativity (10^{-5} sensitivity threshold) was reached in 43.6% of patients with a median time to first NGS MRD negativity of 197.0 days (range: 107-1512).
Sustained NGS MRD negativity rate for at least 12 months occurred in 46.8% of patients in the Isa-VRd group and in 24.3% in the VRd group.
The median time to progression was not reached in the Isa-VRd group and was 59.70 months (95% CI: 48.164 to NR) in the VRd group (HR=0.414; 95% CI: 0.286 to 0.598). The median duration of response was not reached in the Isa-VRd group and was 58.25 months (95% CI: 44.583 to NR) in the VRd group. The median time to first response was 1.51 months in the Isa-VRd group and 1.48 months in the VRd group. In the Isa-VRd group, 52.1% of patients discontinued the study treatment, 14.3% due to disease progression. In the VRd group, 75.7% of patients discontinued the study treatment. 37% due to disease progression. The median time to next anti-myeloma treatment was not reached in the Isa-VRd group and was 63.57 months in the VRd group (HR=0.376; 95% CI: 0.265 to 0.534). Median overall survival was not reached for either treatment group. Based on the descriptive analysis of overall survival data, 26% of patients in the Isa-VRd group and 32.6% of patients in the VRd group had died (HR=0.776; 99.97% CI: 0.407 to 1.48).

Figure 5 – Kaplan-Meier Curves of PFS – ITT population – IMROZ (assessment by the IRC)



Cutoff date = 26-September-2023.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with SARCLISA in one or more subsets of the paediatric population in the treatment of malignant neoplasms of the haematopoietic and lymphoid tissue. See section 4.2 for information on paediatric use.

A phase 2, single-arm, study in 67 paediatric patients was conducted in 3 separate disease cohorts. Fifty-nine patients with relapsed or refractory T-acute lymphoblastic leukaemia (T-ALL, 11 patients), B-acute lymphoblastic leukemia (B-ALL, 25 patients), and acute myeloid leukaemia (AML, 23 patients) were evaluable for efficacy. For patients with T-ALL and B-ALL, the treatment consisted of one induction cycle and one consolidation cycle. For patients with AML, the treatment consisted of up to two induction cycles. The median age was 8 years (range 17 months to 17 years). Patients were treated with SARCLISA in combination with standard chemotherapies (e.g., antimetabolites, anthracyclines, and alkylating agents). At interim analysis, complete response rate (the primary efficacy endpoint, defined as complete response, CR, or complete response with incomplete peripheral recovery, CRi), did not meet the pre-specified statistical threshold in the 3 cohorts with 52.0 % of B-ALL patients, 45.5 % of T-ALL patients, and 60.9 % of AML patients reaching complete response (CR+CRi). The study was stopped after the prespecified interim analysis.

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 from a 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 patient weight 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. In IMROZ, clinical trial performed in newly diagnosed multiple myeloma patients treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone, the mean (CV%) predicted maximum plasma concentration C_{max} and AUC_{2weeks} at steady state were 494 µg/mL (25.5%) and 119,000 µg.h/mL (31.8%), respectively. Exposure parameters were consistent in IMROZ and TCD13983 studies.

A trend toward lower exposure was observed in ADA-positive patients in NDMM patients from IMROZ, with a geometric mean ratio (ADA-positives versus ADA-negatives) of 0.82 and 0.70 for cumulative AUC over the first 4 weeks of treatment (AUC4W) and C_{trough} at 4 weeks (CT4W), respectively. However, as ADA kinetics was transient with an onset time primarily at the beginning of isatuximab treatment (ie during the first month of isatuximab treatment), the mean linear CL at steady state between ADA-positive and ADA-negative patients remained comparable.

The pharmacokinetics of isatuximab and pomalidomide, or of isatuximab and carfilzomib, or of isatuximab and bortezomib and lenalidomide 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.
A Pharmacokinetics analysis on 22 patients with End-Stage Renal Disease (ESRD) including patients on dialysis (eGFR< 15 mL/min/1.73 m²) showed no clinically meaningful effects of ESRD on isatuximab pharmacokinetics compared to those of normal, mild, or moderate renal function.

Paediatric population

In the paediatric patient population (from 17 months to 17 years old), after the first isatuximab administration, among the 3 cohorts, the mean Cmax ranged from 322 to 433 µg/mL, mean AUC1week from 28 592 to 31 703 µg.h/mL, and after repeated isatuximab administrations over 3 weeks, cumulative mean AUC ranged from 130 862 to 148 397 µg.h/mL. Pharmacokinetics data reported in paediatric population with AML and ALL were consistent with those from adults with ALL and MM at the same isatuximab dose.

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
Histidine hydrochloride monohydrate
Histidine
Polysorbate 80 (E433)
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

3 years

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 (15°C - 25°C).

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 discoloured.
- 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 glucose 5 % 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, polybutadiene (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 Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1435/001
EU/1/20/1435/002
EU/1/20/1435/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 May 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

Sanofi Chimie,
9, quai Jules Guesde, BP35
94403 Vitry-sur-Seine cedex, France

Lonza Biologics, Inc.
101 International Drive
Portsmouth, NH 03801, USA

Name and address of the manufacturer responsible for batch release

Sanofi-Aventis Deutschland GmbH
Industriepark Hoechst Brueningstrasse 50
65926 Frankfurt am Main
Germany

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of SARCLISA® in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at:

- increasing the awareness about the risk of interference for blood typing (minor antigen) (positive indirect Coombs test) and its possible adverse clinical consequences for the patient;
- providing guidance on how to manage it and;
- at re-inforcing the communication between healthcare professionals (HCPs) and patients and share reliable and prompt information.

The MAH shall ensure that in each Member State where SARCLISA® is marketed, all HCPs who are expected to prescribe/dispense SARCLISA® and blood banks/transfusion centers are provided with the following educational package to be disseminated through professional bodies:

- Healthcare professionals and blood banks educational material
- Patient card (for HCPs prescribing/dispensing SARCLISA)

1. HCPS AND BLOOD BANKS EDUCATIONAL MATERIAL

The HCPs and blood banks educational material includes the following elements:

- The summary of product characteristics (SmPC)
- The HCPs and blood banks brochure
- Patient card

1.1 Healthcare professionals and Blood Banks brochure

The HCPs and Blood Banks brochure will contain the following key information:

Relevant information of the safety concern "Interference for blood typing (minor antigen) (positive indirect Coombs' test)":

- Isatuximab bound to red blood cells (RBCs) may mask the detection of antibodies to minor antigens in the patient's serum
- The determination of a patient's ABO and Rh blood type are not impacted

Details on how to minimize the safety concern addressed by the additional risk minimization measures through appropriate measures:

- All patients should be blood typed and screened prior to start treatment with isatuximab. Phenotyping may be considered prior to starting isatuximab treatment as per local practice.

- There is currently no available information with regards to how long the interference with the indirect Coombs test may persist after the last infusion of isatuximab. Based on the half-life of isatuximab, isatuximab mediated positive indirect Coombs test may persist for at least6 months after the last isatuximab infusion therefore the HCP should advise the patient to carry the patient card until at least 6 months after the treatment has ended.
- 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.
- In case of urgent need for transfusion, non-cross matched ABO/Rh compatible RBC units can be administered as per local bank practices.
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the risk of interference with indirect antiglobulin tests.
- Emphasize the need to consult the SmPC.
- Instruct the HCP regarding the need to give the patient card to the patients and to advise them to consult the Package Leaflet (PL).

1.2 Patient card

The patient card will contain the following brief and concise information regarding the risk of "Interference for blood typing (minor antigen) (positive indirect Coombs' test)" both for patients and HCPs consulted by the patient:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using SARCLISA (isatuximab), and that this treatment is associated with the important identified risk of interference for blood typing (minor antigen) (positive indirect Coombs' test), which may persist for at least 6 months after the last isatuximab infusion
- A clear reference that the patient should continue to carry this card until at least 6 months after the treatment has ended.
- Contact details of the prescriber and the patient.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

SARCLISA 20 mg/mL concentrate for solution for infusion
isatuximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: sucrose, histidine hydrochloride monohydrate, histidine, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial, 100 mg/5 mL
3 vials, 100 mg/5 mL
1 vial, 500 mg/25 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
For single-use only
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1435/001
EU/1/20/1435/002
EU/1/20/1435/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SARCLISA 20 mg/mL concentrate for solution for infusion
isatuximab
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/5 mL
500 mg/25 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Sarclisa 20 mg/mL concentrate for solution for infusion
isatuximab

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

What is in this leaflet

1. What Sarclisa is and what it is used for

What Sarclisa is
Sarclisa is a cancer medicine that contains the active substance isatuximab. It belongs to a group of medicines called "monoclonal antibodies".
Monoclonal antibodies, such as Sarclisa, are proteins that have been designed to recognise and attach themselves to a target substance. In the case of Sarclisa, the target is a substance called CD38 that is found on cells of multiple myeloma, a cancer of the bone marrow. By attaching to multiple myeloma cells, the medicine helps the natural defences of your body (immune system) identify and destroy them.

What is Sarclisa used for
Sarclisa is used to treat multiple myeloma.
It is used together with two other medicines in patients who have received treatments for multiple myeloma before:
- pomalidomide and dexamethasone or
- carfilzomib and dexamethasone.

It is used together with three other medicines in patients with a newly diagnosed multiple myeloma:
- bortezomib, lenalidomide, and dexamethasone.

If you have any questions on how Sarclisa works or about your treatment with Sarclisa, ask your doctor.

2. What you need to know before you use Sarclisa

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

Warnings and precautions
Talk to your doctor or nurse before using Sarclisa and follow all instructions carefully.

Infusion reactions
Tell your doctor or nurse immediately if you have signs of infusion reactions during or after the infusion of Sarclisa - see in section 4 "Possible side effects" for the list of signs of 'Infusion reactions'.
- Before starting a Sarclisa infusion, you may be given medicines to reduce infusion reactions (see section 3 "How Sarclisa is given").
- Infusion reactions can happen during the Sarclisa infusion or after the infusion and may be serious. These reactions are reversible. The hospital staff will monitor you closely during treatment.

If you get an infusion reaction, your doctor or nurse may give you additional medicines to treat your symptoms and prevent complications. They may also temporarily stop, slow down, or completely stop the Sarclisa infusion.

Fever and low number of white blood cells
Tell your doctor or nurse immediately if you develop fever, as it may be a sign of infection. Sarclisa can lower the number of white blood cells - which are important for fighting infections.

Your doctor or nurse will check your blood cell counts during treatment with Sarclisa. Your doctor may prescribe an antibiotic or antiviral medicine (for example, for herpes zoster [shingles]) to help prevent infection, or a medicine to help increase your white blood cell counts during treatment with Sarclisa.

Heart problems
Talk to your doctor or nurse before using Sarclisa in combination with carfilzomib and dexamethasone if you have heart problems, or if you have ever taken a medicine for your heart. Contact your doctor or nurse immediately if you experience any difficulty breathing, cough, or leg swelling.

Risk of new cancers
New cancers have occurred in patients during treatment with Sarclisa when given with pomalidomide and dexamethasone, or with carfilzomib and dexamethasone, or with bortezomib, lenalidomide, and dexamethasone. Your doctor or nurse will monitor you for new cancers during treatment.

Tumour lysis syndrome
A fast breakdown of cancer cells (tumour lysis syndrome) may occur. Symptoms may include irregular heartbeat, seizures (fits), confusion, muscle cramps, or decrease in urine output. Contact your doctor immediately if you experience any of these symptoms.

Blood transfusion
If you need a blood transfusion, you will have a blood test first to match your blood type.

Tell the person doing the blood test that you are being treated with Sarclisa. This is because it may affect the results of this blood test for at least 6 months after your final dose of Sarclisa.

Children and adolescents
Sarclisa is not recommended for use in children and adolescents aged under 18 years. This is because the effectiveness of Sarclisa has not been established in paediatric patients.

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

Tell your doctor or nurse before having Sarclisa if you have ever taken a medicine for your heart.

Sarclisa is used together with two or three other medicines when treating multiple myeloma:
- pomalidomide and dexamethasone or
- carfilzomib and dexamethasone or
- bortezomib, lenalidomide, and dexamethasone.

For information on the other medicines used with Sarclisa, see their package leaflets.

Pregnancy

Ask your doctor, pharmacist or nurse for advice before using Sarclisa.
Use of Sarclisa is not recommended during pregnancy. If you are pregnant or planning to become pregnant, talk to your doctor about using Sarclisa.

For information on pregnancy and other medicines that are taken with Sarclisa, please look at the package leaflet for these other medicines.

Breast-feeding

Ask your doctor, pharmacist or nurse for advice before using Sarclisa.
- This is because Sarclisa may pass into breast milk. It is not known how it could affect the baby.
- You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby.

Contraception

Women who are using Sarclisa and are able to become pregnant must use an effective method of contraception. Talk to your doctor about the method of contraception that you must use during this time. Use contraception during treatment - and for 5 months after the last dose of Sarclisa.

Driving and using machines
Sarclisa is unlikely to affect your ability to drive or use machines. However, Sarclisa is used with other medicines that may affect your ability to drive or use machines. Please look at the package leaflet from the other medicines you take with Sarclisa.

Sarclisa contains polysorbate 80
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. Tell your doctor if you have any known allergies.

3. How Sarclisa is given

How much Sarclisa is given
The amount of Sarclisa you will be given is based on how much you weigh. The recommended dose is 10 mg of Sarclisa per kilogram of your body weight.

How Sarclisa is given
Your doctor or nurse will give you Sarclisa as a drip into a vein (intravenous infusion).

How often Sarclisa is given
When Sarclisa is used with two other medicines, either pomalidomide and dexamethasone or carfilzomib and dexamethasone, the treatment cycles last 28 days (4 weeks).
- In cycle 1: Sarclisa is given once a week on days 1, 8, 15 and 22
- In cycle 2 and beyond: Sarclisa is given every 2 weeks - on days 1 and 15.

When Sarclisa is used with three other medicines, bortezomib, lenalidomide, and dexamethasone, the treatment cycles last 42 days (6 weeks) from cycle 1 to 4 and lasts 28 days (4 weeks) from cycle 5 and onwards.
- In cycle 1: Sarclisa is given on days 1, 8, 15, 22, and 29,
- From cycle 2 to 4: Sarclisa is given every 2 weeks - on days 1, 15, and 29,
- From cycle 5 to 17: Sarclisa is given every 2 weeks - on days 1 and 15,
- From cycle 18 and onwards: Sarclisa is given every 4 weeks - on day 1.

Your doctor will continue to treat you with Sarclisa as long as you benefit from it and the side effects are acceptable.

Medicines given before Sarclisa
You will be given the following medicines before infusion of Sarclisa. This is to help reduce your chances of getting infusion reactions:
- medicines to reduce allergic reactions (antihistamine)
- medicines to reduce inflammation (corticosteroids)
- medicine to reduce pain and fever

If you miss a dose of Sarclisa
It is very important that you go to all your appointments to make sure you receive your treatment at the right time for it to work properly. If you miss any appointments, call your doctor or nurse as soon as possible to reschedule the appointment.

Your doctor or nurse will decide how your treatment should be continued.

If you are given more Sarclisa than you should
Sarclisa will be given to you by your doctor or nurse. If you are accidentally given too much (an overdose), your doctor will treat and monitor your side effects.

If you stop using Sarclisa
Do not stop your treatment with Sarclisa unless you have discussed that with your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

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

Your doctor will discuss the side effects of Sarclisa with you and will explain the possible risks and benefits of your treatment with Sarclisa.

The hospital staff will monitor your condition closely during treatment. Tell them immediately if you notice any of the effects below.

Infusion reactions - Very common (may affect more than 1 in 10 people):
Tell your doctor or nurse immediately if you feel unwell during or after the infusion of Sarclisa.

Severe signs of infusion reaction include:
- high blood pressure (hypertension)
- feeling short of breath
- serious allergic reaction (anaphylactic reaction affecting up to 1 in 100 people) with breathing difficulty and swelling of the face, mouth, throat, lips or tongue.

The most common signs of infusion reaction include:
- feeling short of breath
- cough
- chills
- nausea

You may also have other side effects during the infusion. Your doctor or nurse may decide to temporarily stop, slow down, or completely stop the Sarclisa infusion. They may also give you additional medicines to treat your symptoms and prevent complications.

Tell your doctor or nurse immediately if you feel unwell during or after the infusion of Sarclisa.

Other side effects
Talk to your doctor, pharmacist or nurse immediately if you have any of the side effects listed below:

Very common (may affect more than 1 in 10 people):
- lower number of some white blood cells (neutrophils) which are important in fighting infection
- lower number of blood platelets (thrombocytopenia) - tell your doctor or nurse if you have any unusual bruising or bleeding.
- infection of the lungs (pneumonia)
- infection of the airways (such as nose, sinuses or throat)
- diarrhoea
- bronchitis
- feeling short of breath
- nausea
- vomiting
- high blood pressure (hypertension)
- cough
- tiredness (fatigue)
- decreased appetite
- covid-19
- clouding of your eye (cataract)

Common (may affect up to1 in 10 people):
- heart problems, which may present as difficulty breathing, cough, or leg swelling when Sarclisa is given with carfilzomib and dexamethasone
- fever with a severe decrease in some white blood cells (febrile neutropenia) (see section 2 "What you need to know before you use Sarclisa" for further details)
- lower number of red blood cells (anaemia)
- weight loss
- irregular heart beat (atrial fibrillation)
- herpes zoster (shingles)

Frequency not known (cannot be estimated from the available data):
- lower number of some white blood cells (lymphocytes) which are important in fighting infection

If any of the above apply to you, or you are not sure, talk to your doctor, pharmacist or nurse immediately.

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

5. How to store Sarclisa

Sarclisa will be stored at the hospital or clinic.

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

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

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

Medicines should not be disposed of via wastewater. Your doctor, pharmacist or nurse will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What Sarclisa contains
- The active substance of Sarclisa is isatuximab.
- One mL of concentrate contains 20 mg of isatuximab.
- Each vial of concentrate contains either 100 mg of isatuximab in 5 mL of concentrate or 500 mg of isatuximab in 25 mL of concentrate.
- The other ingredients (excipients) are sucrose, histidine hydrochloride monohydrate, histidine, polysorbate 80, and water for injections (see sections 2 and 4.4).

What Sarclisa looks like and contents of the pack
Sarclisa is a concentrate for solution for infusion. It is a colourless to slightly yellow liquid, essentially free of visible particles.

Pack size:
100 mg of isatuximab in 5 mL of concentrate (100 mg/5 mL): Each carton contains 1 or 3 vials.
500 mg of isatuximab in 25 mL of concentrate (500 mg/25 mL): Each carton contains 1 vial.
Not all pack sizes may be marketed.

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This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:
SARCLISA vials are for single-use only. The infusion solution must be prepared under aseptic conditions, and administered by a healthcare professional in an environment where resuscitation facilities are available.

Preparation and administration of SARCLISA

- Calculate the dose (mg) of required SARCLISA concentrate, and determine the number of vials needed for the 10 mg/kg dose, based on the patient weight. More than one vial may be needed.
- Visually check the SARCLISA concentrate before dilution to ensure it does not contain any particles and is not discoloured.
- Remove the volume of diluent equal to the required volume of SARCLISA concentrate from a 250 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection or glucose 5 % solution diluent bag.
- Withdraw the appropriate volume of SARCLISA concentrate from the SARCLISA vial and dilute it in the 250 mL infusion bag with sodium chloride 9 mg/mL (0.9 %) solution for injection or glucose 5 % 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 invert the bag to homogenize the diluted solution. Do not shake.
- Administer the infusion solution intravenously using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene (PBD) or polyurethane (PU)) with a 0.22 micron in-line filter (polyethersulfone (PES), polysulfone or nylon).
- Administer the infusion solution for a period of time that will depend on the infusion rate (see EU-SmPC section 4.2 “Posology and method of administration”).
- Use the prepared SARCLISA infusion solution immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user and should normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
- 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.

Discard all unused portions of solution. All materials that have been utilised for dilution and administration should be disposed of according to standard procedures.