

1.3.1

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

SARCLISA 20mg/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/5mL).

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

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

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.

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.
- in combination with bortezomib, lenalidomide, and dexamethasone, for the induction treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. This indication is approved based on minimal residual disease (MRD) negativity rate at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

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 1000 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 route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (oral or intravenous) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide, 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) can be considered during treatment (see section 4.4).

Posology

The recommended dose of SARCLISA is 10 mg/kg body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone (Isa-Pd) or in combination with carfilzomib and dexamethasone (Isa-Kd), or in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd).

SARCLISA dosing schedules are provided in Tables 1, 2, and 3:

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 cycles)	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 for patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT) (IMROZ)

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.

Table 3: SARCLISA dosing schedule in combination with bortezomib, lenalidomide, and dexamethasone for patients with NDMM who are eligible for ASCT (GMMG-HD7)

Cycles	Dosing schedule
<i>Induction treatment</i>	
Cycle 1 (42-day cycle)	Days 1, 8, 15, 22, and 29
Cycles 2 to 3 (42-day cycles)	Days 1, 15, and 29 (every 2 weeks)
Stop for intensification treatment (high dose chemotherapy and ASCT)	

Each treatment cycle consists of a 42-day period.

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 to severe renal impairment including end-stage renal disease (see section 5.2).

Patients with hepatic impairment

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

Paediatric population

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 4 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 4: 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 in IMROZ, 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. In patients treated with Isa-VRd during the induction period in GMMG-HD7, neutropenia was reported as a laboratory abnormality in 30.9% of patients and as an adverse reaction in 16.1% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 5.9% of patients (with 3.1% Grade 3 and 2.8% Grade 4) and as an adverse reaction in 16.1% of patients (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. The overall benefit of Isa-Pd remains favourable (see section 5.1). In ongoing IKEMA study, at a median follow-up time of 20.73 months, SPMs were reported in 13 patients (7.3%) treated with Isa-Kd and in 6 patients (4.9%) treated with Kd. SPMs were skin cancers in 9 patients (5.1%) treated with Isa-Kd and in 3 patients (2.5%) treated with Kd, and were solid tumours other than skin cancer in 5 patients (2.8%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd. One patient (0.6%) 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. In patients with SPM of skin cancer, 6 patients (27.3%) treated with Isa-VRd and no patient treated with VRd had a medical history of skin cancer. In patients with SPM of solid tumours other than skin cancer, 2 patients (11.8%) treated with Isa-VRd and 1 patient (14.3%) treated with VRd had a medical history of cancer. Six patients (6, 2.3%) treated with Isa-VRd (4 with solid tumour other than skin cancer, 1 with skin cancer, and 1 with haematological malignancy) and 3 patients (1.7%) treated with VRd group (1 with solid tumour other than skin cancer, 1 with skin cancer, and 1 with haematological malignancy) discontinued treatment due to SPM. 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 benefit of Isa-VRd remains favourable (see section 5.1). 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). 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 SARCLISA. Based on the half-life of isatuximab, it is anticipated that isatuximab mediated positive indirect Coombs test may persist for approximately 6 months after the last infusion.

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).

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 ($\geq 20\%$) 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 ($\geq 20\%$) 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 ($\geq 20\%$) 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.

In GMMG-HD7, during the induction period, the most frequent adverse reactions ($\geq 10\%$) are polyneuropathy (18.8%), neutropenia (16.1%), and infusion related reactions (12.4%). Serious adverse reactions occurred in 35.2% of patients receiving Isa-VRd. The most frequent serious adverse reactions are pneumonia (3.6%), pyrexia (3.3%), and diarrhoea (2.1%). Adverse reactions with a fatal outcome during treatment (Grade 5 TEAEs) were reported in 1.2% of patients treated with Isa-VRd (due to COVID-19, pneumonia influenza, septic shock, and haemorrhage intracranial, each reported in 0.3% of patients). Permanent discontinuation of treatment because of adverse reactions was reported in 3% 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 trials (see section 5.1) and post-market settings.

Table 5: 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	Skin cancer	Common	4.9%	1.6%
	Solid tumour (non-skin cancer)	Common	2.9%	1.6%

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N=244)	
			Any Grade	Grade ≥ 3
unspecified (incl cysts and polyps) ^c	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 6^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%

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N=177)	
			Any Grade	Grade ≥3
	Bronchitis	Very common	22.6%	2.3%
	Herpes zoster	Common	2.3%	0.6%
Vascular disorders	Hypertension	Very common	36.7%	20.3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) ^d	Skin cancers	Common	7.3%	1.7%
	Solid tumours (non-skin cancers)	Common	4.0 %	3.4%
Blood and lymphatic system disorders	Anaemia	Common	5.1%	4.5%
	Neutropenia	Common	4.5%	4.0%
	Thrombocytopenia	Common	2.8%	2.3%
	Lymphopenia	Not known	—	—
Immune system disorders	Anaphylactic reaction ^e	Uncommon	0.3%	0.3%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	27.7%	5.1%
	Cough	Very common	19.8%	0%
Gastrointestinal disorders	Diarrhoea	Very common	36.2%	2.8%
	Vomiting	Very common	15.3%	1.1%
General disorders and administration site conditions	Fatigue	Very common	28.2%	3.4%
Injury, poisoning and procedural complications	Infusion reaction ^c	Very common	45.8%	0.6%

^a Cut-off date of 07-Feb-2020. Median follow-up time=20.73 months.

^b The term pneumonia is a grouping of the following terms: atypical pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia influenza, pneumonia legionella, pneumonia streptococcal, pneumonia viral, and pulmonary sepsis.

^c See “Description of selected adverse reactions”.

^d Cut-off date of 07-Feb-2023. Median follow-up time=56.61 months. Based on second primary malignancies reported during study treatment period and during post-treatment period.

^e Based on post-marketing adverse reactions.

Table 7: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (IMROZ)

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N=336)	
			Any Grade	Grade ≥3
Infections and	Pneumonia ^a	Very common	34.2%	24.1%

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N=336)	
			Any Grade	Grade ≥ 3
infestations	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 complications	Infusion reaction	Very common	27.4%	0.6%

^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

Table 8: Adverse reactions reported during induction period in patients with multiple myeloma treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (GMMG-HD7)

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N=330)	
			Any Grade	Grade ≥ 3
Infections and infestations	Pneumonia ^{a b}	Common	5.5%	4.8%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Solid tumours (non-skin cancers)	Uncommon	0.3%	0.3%
Blood and lymphatic system disorders	Neutropenia	Very common	16.1%	16.1%
	Anaemia	Common	3.6%	3.6%

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (N=330)	
			Any Grade	Grade ≥3
	Thrombocytopenia	Common	4.5%	4.5%
	Lymphopenia	Common	3.3%	3.3%
Immune system disorders	Anaphylactic reaction	Uncommon	0.3%	0.3%
Injury, poisoning and procedural complications	Infusion reaction ^b	Very common	12.7%	0.9%

^a The term pneumonia is a grouping of the following terms: Pneumonia, Pneumonia influenza, Atypical pneumonia, Pneumonia fungal.

^b See “Description of selected adverse reactions”.

Description of selected adverse reactions

Infusion reactions

In ICARIA-MM, infusion reactions were reported in 58 patients (38.2%) treated with SARCLISA. All patients who experienced infusion reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2.0%) also having infusion reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion reactions were reported in 3.9%, Grade 2 in 31.6%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. All infusion reactions were reversible and resolved the same day in 98% of the infusions. Signs and symptoms of Grade 3 or 4 infusion 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.

In GMMG-HD7, during the induction period, infusion reactions were reported in 42 patients (12.7%) treated with Isa-VRd. Grade 1 infusion reactions were not collected in the study. Grade 2 infusion reactions were reported in 11.8%, Grade 3 in 0.6%, and Grade 4 in 0.3% of the patients treated with Isa-VRd. All infusion reactions resolved. The incidence of patients with isatuximab infusion interruptions because of infusion reactions was 7.6%. Isatuximab was discontinued in 0.3 % of patients due to infusion reactions (see section 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 (0.174 versus 0.171 event rate per patient year, respectively). 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 trials, 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. In GMMG-HD7, during the induction period, the incidence of herpes zoster was 0.9% in the Isa-VRd group compared to 0.3% 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 9: 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 10: Haematology laboratory abnormalities in patients receiving isatuximab combined with carfilzomib and dexamethasone versus carfilzomib and dexamethasone (IKEMA)

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

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

Table 11: 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.

Table 12: Haematology laboratory abnormalities in patients receiving isatuximab combined with bortezomib, lenalidomide, and dexamethasone versus bortezomib, lenalidomide, and dexamethasone during induction period (GMMG-HD7)

Laboratory parameter	SARCLISA + Bortezomib + Lenalidomide + Dexamethasone (N=330)			Bortezomib + Lenalidomide + Dexamethasone (N=328)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Anaemia	80.0%	1.6%	0%	79.7%	0.9%	0%
Neutropenia	30.9%	3.1%	2.8%	22.9	2.5%	1.9%
Lymphopenia	54.4%	15.6%	2.2%	67.4%	18.7%	5.1%
Thrombocytopenia	21.6%	0.6%	0.9%	20.3%	0.3%	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.

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 64.7% of patients less than 65, 79.7% of patients 65-74 and 76.6% of patients 75 or older. Grade 5 TEAEs were reported in 5.6% 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, 59.3% of patients 65-74, and 61.1% of patients 75 or older. TEAEs leading to definitive treatment discontinuation were reported in 6.4% of

patients less than 65, 14.4% of patients 65-74, and 15.9% 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 (5.9%) had neutralizing antibodies. In IMROZ, a trend to lower exposure was observed in ADA-positive patients, which was considered not clinically relevant since, in patients with ADA-positive status to isatuximab including those with neutralizing antibodies, no meaningful impact of ADAs on safety or efficacy of isatuximab was observed.

Across 9 clinical studies in multiple myeloma (MM) with isatuximab single agent and combination therapies including ICARIA-MM and IKEMA (N=1018), the incidence of treatment emergent ADAs was 1.9%. No effect of ADAs was observed on pharmacokinetics, safety or efficacy of isatuximab.

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

To report any side effect(s):

• Saudi Arabia:
- The National Pharmacovigilance and Drug Safety Centre (NPC)
• SFDA call center : 19999
• E-mail: npc.drug@sfda.gov.sa
• Website: https://ade.sfda.gov.sa/
• Sanofi- Pharmacovigilance: KSA_Pharmacovigilance@sanofi.com

4.9 Overdose

Signs and symptoms

There has been no experience of overdosage 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 12 and Kaplan-Meier curves for PFS and OS are provided in Figures 1 and 2:

Table 13: 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) ^e	<0.0001	

Endpoint	SARCLISA + pomalidomide + dexamethasone N =154	Pomalidomide + dexamethasone N = 153
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] ^c	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)

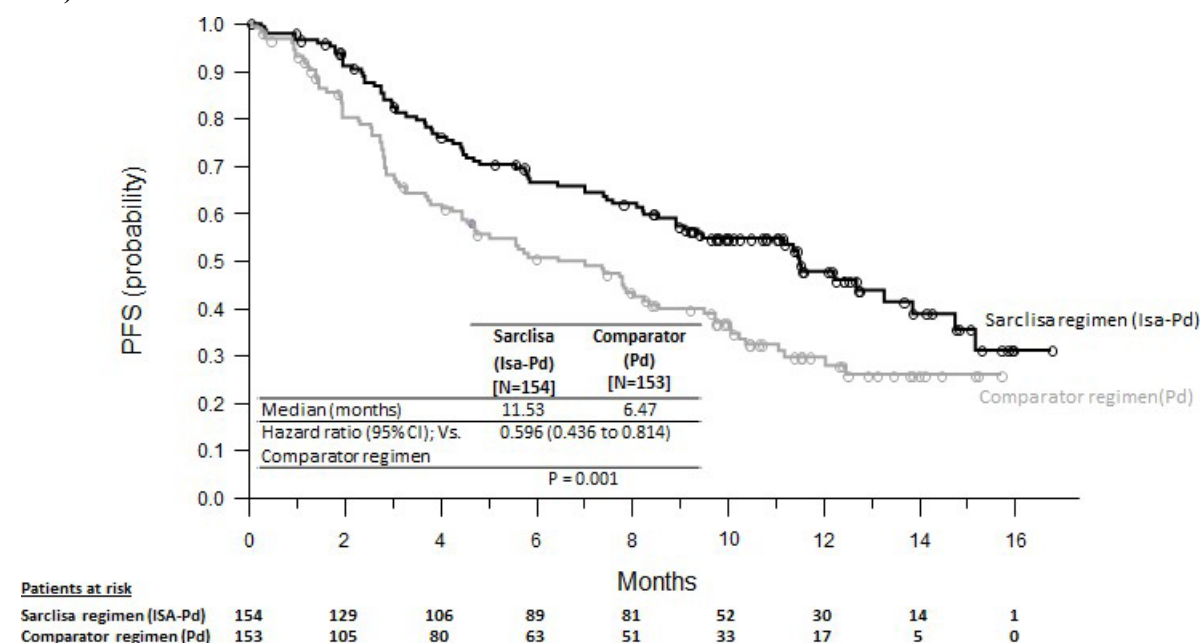
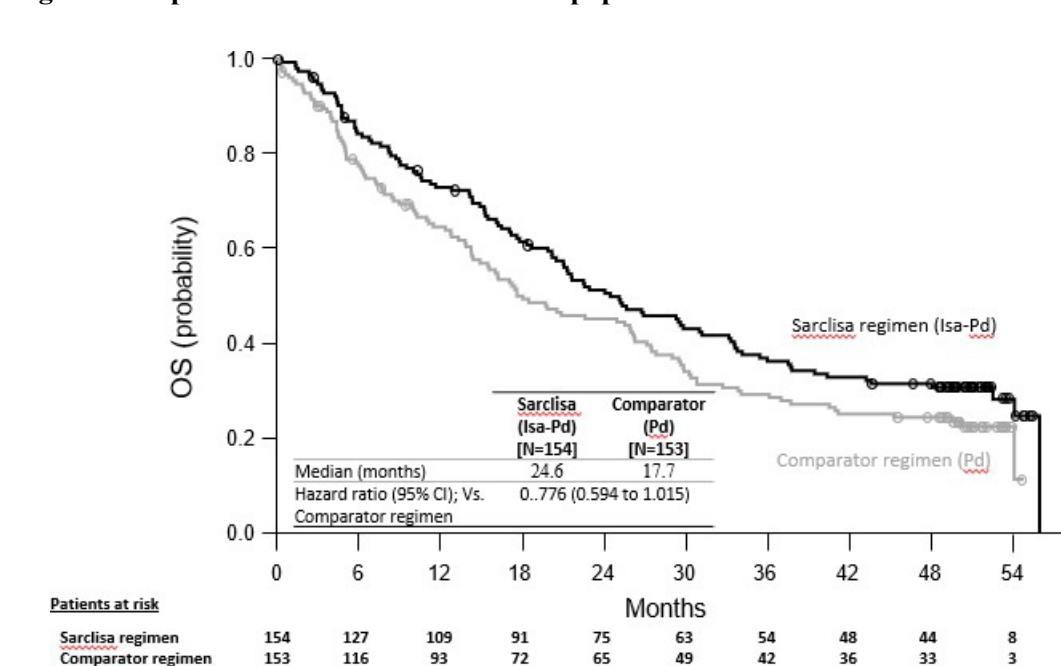


Figure 2: Kaplan-Meier Curves of OS – ITT population – ICARIA-MM



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 m²) 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 14 and Kaplan-Meier curves for PFS and OS are provided in the Figures 3 and 4:

Table 14: Efficacy of SARCLISA in combination with carfilzomib and dexamethasone versus carfilzomib and dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

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

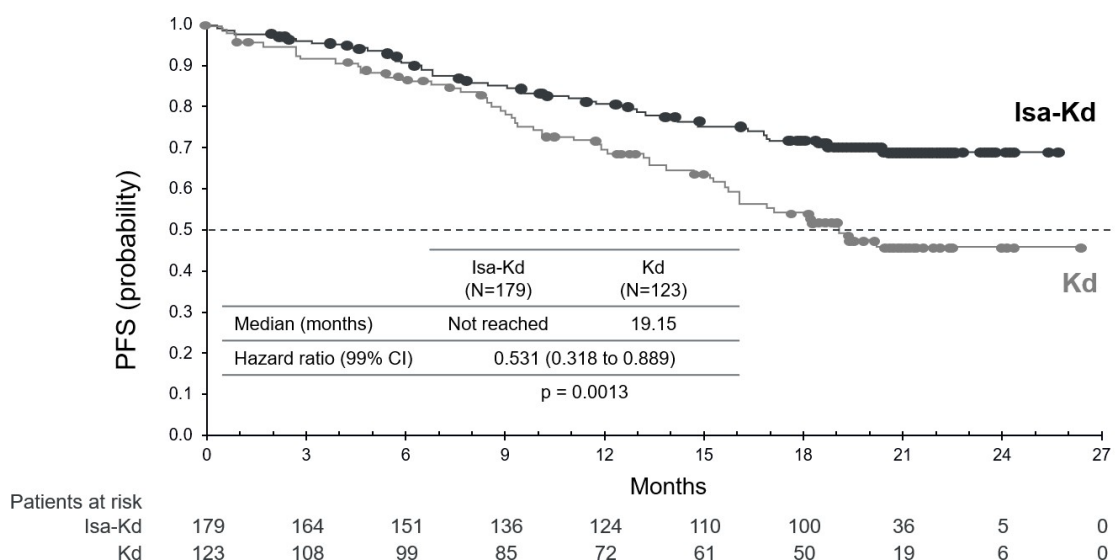
PFS improvements in the Isa-Kd group were observed in patients with high -risk cytogenetics (central laboratory assessment, HR = 0.724; 95% CI: 0.361 to 1.451), with gain (1q21) chromosomal abnormality (HR=0.569; 95% CI: 0.330 to 0.981), ≥ 65 years (HR =0.429; 95% CI: 0.248 to 0.742), with baseline eGFR (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).

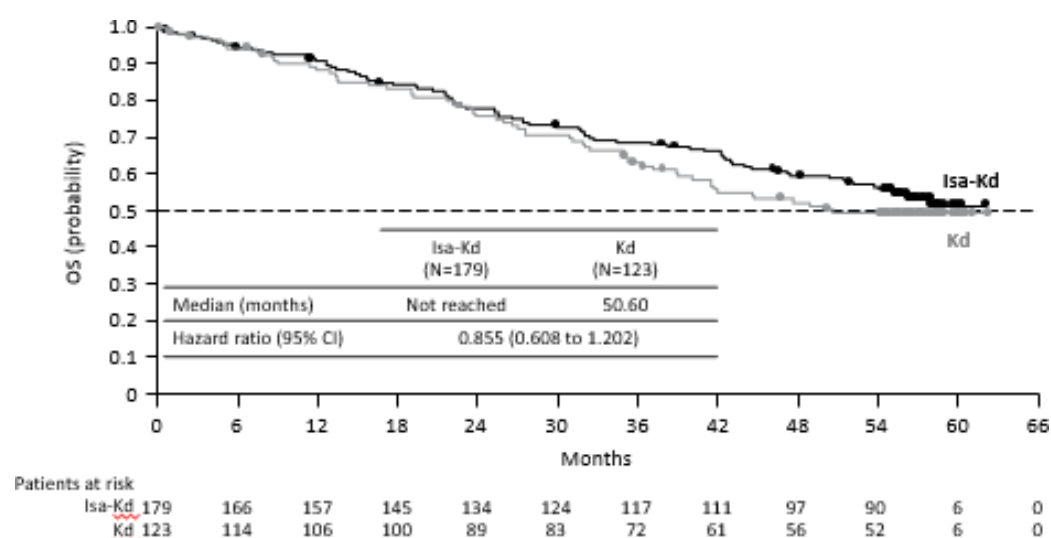
The median time to first response was 1.08 months in the Isa-Kd group and 1.12 months in the Kd group. The median time to next anti-myeloma treatment was 43.99 months in the Isa-Kd group and 25.00 months in the Kd group (HR=0.583; 95% CI: 0.429 to 0.792).

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 m² at baseline, complete renal response (≥60 mL/min/1.73 m² 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 m²), minimal renal response (≥30 to <60 mL/min/1.73 m² 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/1.73m²) 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 15 and Kaplan-Meier curves for PFS are provided in Figure 5:

Table 15* – 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	

Endpoint	SARCLISA + bortezomib + lenalidomide + dexamethasone N =265	Bortezomib + lenalidomide + dexamethasone N = 181
CR or better (sCR and CR) [95% CI] ^c p-value (Stratified Log-Rank test) ^b	74.7% [0.6904-0.7984]	64.1% [0.5664-0.7107]
	0.0160	
Minimal Residual Disease negativity^d and CR [95% CI] ^c p-value (stratified Cochran-Mantel- Haenszel) ^b	55.5% [0.4927-0.6155]	40.9% [0.3365-0.4842]
	0.0026	
Overall Response Rate^c Responders (sCR+CR+VGPR+PR) [95% CI] ^c	91.3% [0.8726-0.9442]	92.3% [0.8736-0.9571]
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 and 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).

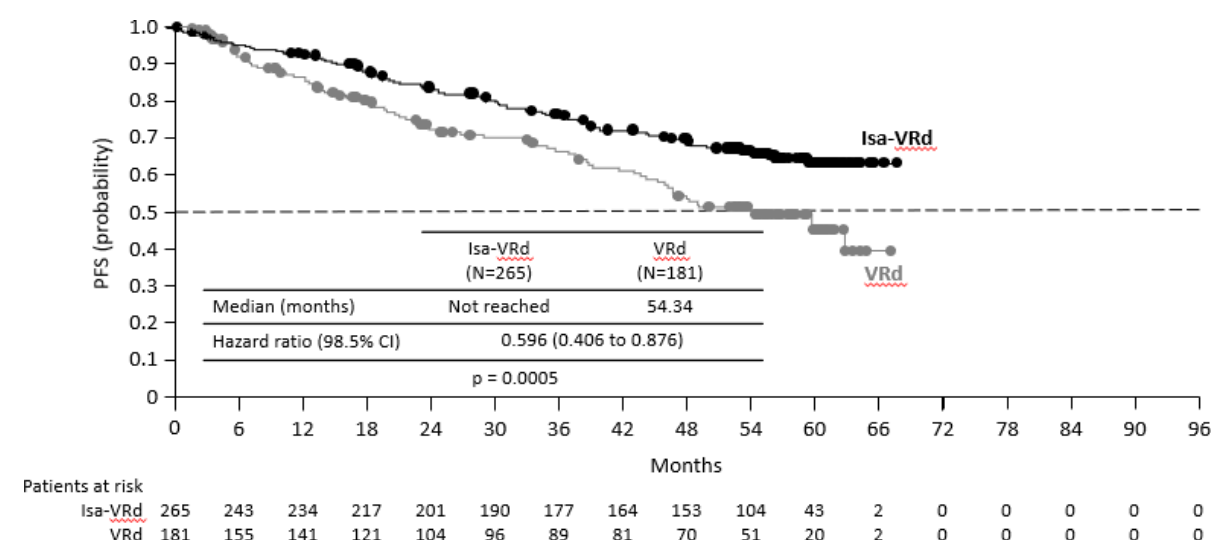
NGS MRD negativity (10⁻⁵ sensitivity threshold) was reached in 58.1% of patients in the Isa-VRd group with a median time to first NGS MRD negativity of 196.5 days (range: 87-1834). In the VRd group, NGS MRD negativity (10⁻⁵ sensitivity threshold) was reached in 43.6% of patients with a median time to 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.

TCD13983

In a multicenter, open label, non-comparative dose escalation, 2-part, Phase Ib/II study (TCD13983), SARCLISA 10 mg/kg was administered intravenously in combination with 2 bortezomib-based regimens: cyclophosphamide, bortezomib, and dexamethasone (Isa-VCd) and lenalidomide, bortezomib, and dexamethasone (Isa-VRd) in adult patients with newly diagnosed multiple myeloma (NDMM) noneligible for transplantation (Isa-VCd and Isa-VRd Part A and B) or no intent for immediate transplantation (Isa-VRd Part B). In TCD13983, treatment regimen and schedule of administration, patient population and characteristics were similar to IMROZ. In TCD13983 Part A, 27 and 26 patients were evaluable for safety and efficacy, respectively, and 46 and 45 in Part B, respectively.

Isa-VRd efficacy and safety results from TCD13983 Part A and B are described below.

At a median follow-up time of 35.83 and 25.26 months respectively, the primary endpoint of CR and better (sCR/CR) rate was 50% and 60% in part A and part B respectively (response adjusted using isatuximab-specific IFE assay (Sebia Hydrashift), MRD negativity rate (10^{-5} sensitivity threshold) by combining NGF and NGS methods was 46.2% and 53.3% in part A and B, respectively. MRD negativity rate in adjusted sCR/CR patients (10^{-5} sensitivity threshold) by combining NGF and NGS methods was 30.8% and 44.4% in Part A and B, respectively. At a median follow up time of 37.90 and 26.18 months respectively, median PFS was not reached for both part A and B. The ORR was 100% and 97.8% in part A and B, respectively. At a median follow up time of 35.83 and 25.26 months respectively, the median time to first response was 1.41 months for both part A and B, and the median

duration of response was not reached in both parts A and B. At a median follow-up time of 37.90 months and 26.18 months respectively, 3.7% and 8.7% of patients died in in part A and B, respectively.

Grade ≥ 3 TEAEs were reported in 88.9% of patients in part A and in 73.9% in part B, and serious TEAEs in 55.6% in part A and 52.2% in part B. Permanent discontinuation of treatment due to TEAEs was reported in 22.2% of patients in part A and in 17.4% in part B. The safety profile of Isa-VRd in part A and B of TCD13983 was manageable, with no new safety concerns identified compared to IMROZ (see section 4.8). TCD13983 Efficacy and safety results were consistent with IMROZ results.

GMMG-HD7 (IIT 15403)

The efficacy and safety of SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone were evaluated in GMMG-HD7, a prospective, randomized, open-label, 2-arm, phase III study performed by the German-Speaking Myeloma Multicenter Group (GMMG), in patients with newly diagnosed multiple myeloma who are eligible for stem cell transplantation. The study was conducted in 2 Parts; Part 1 includes induction and intensification treatments, and Part 2 is the maintenance treatment (ongoing phase). The results from Part 1 are described.

A total of 662 patients were randomized in a 1:1 ratio to receive either SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd, 331 patients) or bortezomib, lenalidomide, and dexamethasone (VRd, 331 patients), administered in both groups during 3 cycles (cycles 1 to 3) of 42 days each for the induction treatment. After cycle 3, patients were given a standard intensification treatment including ASCT. ASCT was repeated 2-3 months after initial ASCT in patients with no CR or in high-risk patients. In Part 2, prior to the start of the maintenance treatment, patients were randomized again in a 1:1 ratio to receive either SARCLISA in combination with lenalidomide or lenalidomide alone. Maintenance treatment is administered with 28-day cycles for a maximum of 3 years until disease progression or unacceptable toxicity, whichever occurred first. In both treatment arms, patients received dexamethasone for the first maintenance cycle only.

During the induction period, SARCLISA 10 mg/kg was administered as an IV infusion on days 1, 8, 15, 22, and 29, in cycle 1, and on days 1, 15, and 29, from cycles 2 to 3. 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 orally at the dose of 25 mg/day from days 1 to 14 and from days 22 to 35 of each cycle. Dexamethasone (IV on the days of SARCLISA infusions, and orally 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.

During the maintenance period, SARCLISA 10 mg/kg was administered as an IV infusion on days 1, 8, 15 and 22 in cycle 4, followed by days 1 and 15 in cycles 5 and 6, and on day 1 from cycle 7 onwards (the 3-year maintenance period). Lenalidomide was administered orally at the dose of 10 mg/day (increased to 15mg/day after the first 3 cycles if the patient tolerated treatment) continuously for all cycles. Dexamethasone (IV on the days of SARCLISA infusions, and orally on the other days) 20 mg/day was given on days 1, 8, 15, and 22 for the first maintenance cycle.

Overall, demographic and disease characteristics at baseline were similar between the treatment groups (Isa-VRd versus VRd). The median patient age was 59.5 years (range 26-70), 23.9% of patients were ≥ 65 years. The proportion of patients with renal impairment (eGFR <60 mL/min/1.73m²) was 19.7% in the Isa-VRd group versus 17.7% in the VRd group. The International Staging System (ISS) stage at study entry was I in 41.4%, II in 36.9%, and III in 21.8% of patients. The Revised International Staging System (R-ISS) stage at study entry was I in 26.6%, II in 61%, and III in 8% of patients. Overall, 18.7% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14), and t(14;16) were present in 8.9%, 10.1% and 2.6% of patients, respectively. In addition, 1q21+ was present in 32.9% of patients.

The median duration of induction treatment was 18 weeks for the Isa-VRd and VRd groups. The median duration of Part 1 (induction and intensification treatments) was 45.4 weeks for the Isa-VRd group and 45.1 weeks for the VRd group.

Minimal residual disease (MRD) negativity rate after induction treatment was the primary efficacy endpoint of GMMG-HD7. Results showed a clinically significant improvement in MRD negativity rate (NGF at 10⁻⁵ sensitivity level), representing a 14.8% increase in the Isa-VRd group compared to the VRd group after induction treatment.

Progression-free survival (PFS) from the 1st randomization regardless of the 2nd randomization was the key secondary efficacy endpoint of GMMG-HD7. With a median follow-up time of 49.31 months, the primary analysis of PFS showed a statistically significant improvement in PFS represented by a 29.9% reduction in the risk of disease progression or death in patients treated with Isa-VRd compared to patients treated with VRd after induction treatment.

Efficacy results are presented in Table 16 and Kaplan-Meier curves for PFS are provided in Figure 5

Table 16: 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) (GMMG-HD7)

Endpoint	SARCLISA + bortezomib + lenalidomide + dexamethasone (N=331)	Bortezomib + lenalidomide + dexamethasone (N=331)
Minimal Residual Disease negativity rate at the end of induction^a	50.5%	35.6%
[95% CI] ^b	[0.4493 - 0.5597]	[0.3049 - 0.4107]
Odds ratio [95% CI] ^c	1.838 [1.346 - 2.511]	
p-value (Logistic Regression test) ^c	0.0001	
Progression-Free Survival from 1st randomization regardless of 2nd randomization		
Median (months)	NR	NR
[95% CI]	[NR – NR]	[NR – NR]
Hazard ratio [95% CI]	0.701 [0.516 - 0.953]	
p-value ^d (stratified Log-Rank test) ^c	0.0227	
Overall Response Rates at the end of induction		
Responders (CR+nCR ^f +VGPR+PR)	93.4%	90.9%
[95% CI] ^b	[0.9011 - 0.9579]	[0.8731 - 0.9380]

Endpoint	SARCLISA + bortezomib + lenalidomide + dexamethasone (N=331)	Bortezomib + lenalidomide + dexamethasone (N=331)
Complete Response (CR)	24.8%	22.1%
Near Complete Response (nCR)	18.1%	16%
Very Good Partial Response (VGPR)	36.9%	26%
Partial Response (PR)	13.6%	26.9%
Complete response (CR) rate at end of induction	24.8%	22.1%
[95% CI] ^b	[0.2022 - 0.2979]	[0.1770 - 0.2691]
Odds ratio [95% CI] ^c	1.164 [0.8105 - 1.6704]	
Minimal Residual Disease negativity rate and CR at end of induction^a	18.7%	14.5%
[95% CI] ^b	[0.1467 - 0.2336]	[0.1089 - 0.1876]
Odds ratio [95% CI] ^c	1.360 [0.899 - 2.057]	
Minimal Residual Disease negativity rate at end of intensification^a	68.9%	49.2%
[95% CI] ^b	[0.6359 - 0.7383]	[0.4374 - 0.5477]
Odds ratio [95% CI] ^c	2.281 [1.661 - 3.133]	
Minimal Residual Disease negativity rate and CR at end of intensification^a	40.5%	26.6%
[95% CI] ^b	[0.3515 - 0.4599]	[0.2190 - 0.3169]
Odds ratio [95% CI] ^c	1.878 [1.353 - 2.607]	

^a Based on a sensitivity level of 10^{-5} by NGF in induction ITT population.

^b Estimated using Clopper-Pearson method.

^c Logistic regression including the randomization factor R-ISS (I or II vs III vs not classified) according to IRT

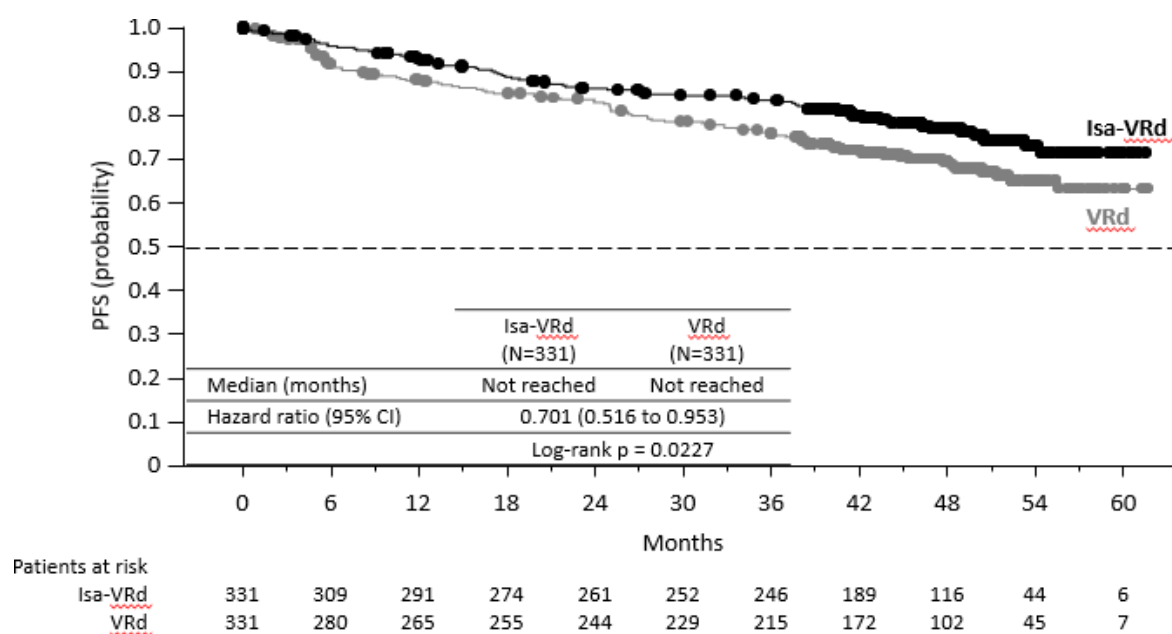
^d Two-sided significance level is 0.028

^e Stratified on R-ISS (I or II vs III vs Not classified) according to IRT.

^f nCR: Subcategory of VGPR defined as absence of serum and urine M-Protein on standard electrophoresis and/or standard 24h urinary measurement with a positive immunofixation status in serum and/or urine or both serum and urine immunofixation negative in absence of bone marrow aspirate.

Among patients who achieved a complete response (CR), the median time to first CR during Part 1 was 173 days in the Isa-VRd group versus 159.5 days in the VRd group. With a median follow-up time of 49.31 months, 14.8% patients in the Isa-VRd arm and 12.7% patients in the VRd arm had died.

Figure 5 – Kaplan-Meier Curves of PFS – ITT population – GMMG-HD7



Cut-off date = 31 January 2024

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30 and EORTC-QLQ-MY20. Data were analysed at four time points to assess health-related quality of life (HRQoL) during the induction and intensification phases: at baseline, after Cycle 3, after last ASCT, and at end of treatment (EOT). The EOT time point corresponds to patients who discontinued treatment during the induction or intensification phases and completed the questionnaire at the EOT visit. Only 24/331 (7.3%) and 15/331 (4.5%) patients in the VRd and Isa-VRd groups, respectively, discontinued the induction or intensification treatment and completed the PRO questionnaires at EOT. There was a notable reduction in pain observed after Cycle 3 in the Isa-VRd arm (mean change from baseline: -15.00), which was sustained after last ASCT (mean change from baseline: -17.34). Overall, a trend towards improvement in GHS/QoL was observed in patients treated with Isa-VRd after Cycle 3 (mean change from baseline: +5.90) and after last ASCT (mean change from baseline: +13.80). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

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 trial 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 trial 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. Following administration of isatuximab in combination with bortezomib, lenalidomide, and dexamethasone at the recommended dose and schedule, the mean (CV%) predicted C_{max} and AUC of isatuximab at steady state were 604 µg/mL (21.9%) and 155,000 µg.h/mL (23.9%), respectively. A trend toward lower exposure was observed in ADA-positive patients in NDMM clinical studies with 23%-29% decrease in cumulative AUC over the first 4 or 6 weeks of treatment (Cycle 1) in ADA-positive patients compared to ADA-negative patients. However, as ADA response was transient with an onset time primarily at the beginning of isatuximab treatment, the exposure 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) $> \text{ULN}$] 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 ($60 \text{ mL/min/1.73 m}^2 \leq \text{estimated glomerular filtration rate (e-GFR)} < 90 \text{ mL/min/1.73 m}^2$), 163 patients with moderate renal impairment ($30 \text{ mL/min/1.73 m}^2 \leq \text{e-GFR} < 60 \text{ mL/min/1.73 m}^2$) and 12 patients with severe renal impairment ($\text{e-GFR} < 30 \text{ mL/min/1.73 m}^2$). 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 ($\text{eGFR} < 15 \text{ mL/min/1.73 m}^2$) 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 C_{max} ranged from 322 to 433 $\mu\text{g/mL}$, mean $\text{AUC}_{1\text{week}}$ from 28592 to 31703 $\mu\text{g.h/mL}$, and after repeated isatuximab administrations over 3 weeks, cumulative mean AUC ranged from 130862 to 148397 $\mu\text{g.h/mL}$. 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
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-Aventis Groupe
54 rue La Boétie 75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

Sarclisa 100mg/5ml: 2403210642
Sarclisa 500mg/25ml: 2403210643

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2021

10. DATE OF REVISION OF THE TEXT

April 2026