Product Monograph

Including Patient Medication Information

Pr SARCLISA ®

Isatuximab for injection

100 mg/5 mL concentrate for solution for infusion

500 mg/25 mL concentrate for solution for infusion

20 mg/mL isatuximab

Professed

Antineoplastic, monoclonal antibody

ATC code: L01FC02

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Recent Major Label Changes

Indications	2025-04
Geriatrics	2025-04
Dosing Considerations	2025-04
Recommended Dose and Dosage Adjustment	2025-01
Warnings And Precautions	2025-01
Geriatrics (≥ 65 years of age):	2025-04
Warnings And Precautions	2024-01

Table Of Contents

Sections or subsections that are not applicable at the time of authorization are not listed.

Part 1: Healthcare Professional Information

1 Indications

Sarclisa (isatuximab for injection) is indicated:

- in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant (ASCT).
- in combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of Sarclisa was assessed but not established in pediatric cancer patients (see 7 Warnings and Precautions, General); therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in efficacy were observed between older and younger patients. However, differences in safety were observed. (see 7 Warnings And Precautions, 7.1.4 Geriatrics and 10 Clinical Pharmacology, 10.3 Pharmacokinetics, *Geriatrics*).

2 Contraindications

Sarclisa is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition And Packaging.

4 Dosage And Administration

4.1 Dosing Considerations

- Sarclisa should be administered by a healthcare professional experienced in the treatment of cancer and with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions.
- Administer only as an intravenous infusion after dilution (see 4.3 Reconstitution).

Premedication
Premedication should be used prior to Sarclisa infusion with the following medications to reduce the risk and severity of infusion-related reactions (IRRs):

- Dexamethasone:

Treatment regimen	Dexamethasone dose	Additional information
Sarclisa in combination with pomalidomide and dexamethasone (Isa-Pd)	- Patients < 75 years: 40 mg PO or IV - Patients ≥ 75 years: 20 mg PO or IV	- The recommended dose of dexamethasone (PO or IV) corresponds to the total dose to be administered before infusion, as part of the premedication and of the backbone treatment; do not administer another dose. Administer dexamethasone before Sarclisa and pomalidomide and before Sarclisa and carfilzomib administration.
Sarclisa in combination with carfilzomib and dexamethasone (Isa-Kd)	- 20 mg: IV on the days of Sarclisa and/or carfilzomib infusions, and PO on Day 22 in cycle 2 and beyond, and PO on Day 23 in all cycles.	
Sarclisa in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd)	- Patients < 75 years: 20 mg; IV on the days of Sarclisa infusions, and PO on days 2, 4, 5, 9, 11, 12, 23, 25, 26, 30, 32, and 33 in cycles 1 to 4 and PO on day 8 and 22 in cycles 2 to 4 - Patients ≥ 75 years: 20 mg; IV on the days of Sarclisa infusions, and PO on days 4, 11, 25 and 32 in cycles 1 to 4 and PO on day 8 and 22 in cycles 2 to 4 for patients ≥75 years old.	

PO: oral; IV: intravenous

- Acetaminophen 650 mg to 1000 mg orally (or equivalent).
- H2 antagonists
- Diphenhydramine 25 mg to 50 mg IV or PO (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The intravenous route is preferred for at least the first 4 infusions.

The recommended premedication agents should be administered 15 to 60 minutes prior to starting a Sarclisa infusion.

Prophylaxis for Herpes Zoster Reactivation

Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) should be considered during treatment. (see 8 Adverse Reactions, 8.2 Clinical Trial Adverse Reactions, *Infections*).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of Sarclisa is 10 mg/kg body weight administered as an intravenous (IV) 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), according to schedules in Table 1 and Table 2.

Table 1: Sarclisa dosing schedule in combination with pomalidomide and dexamethasone (Isa-Pd) or in combination with carfilzomib and dexamethasone (Isa-Kd)

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

Each treatment cycle consists of a 28-day period.

Table 2: Sarclisa dosing schedule in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd)

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)

Treatment is repeated until disease progression or unacceptable toxicity.

Sarclisa is used in combination with pomalidomide and dexamethasone, in combination with carfilzomib and dexamethasone, or in combination with bortezomib, lenalidomide, and dexamethasone. For dosing instructions of other medicinal products that are administered with Sarclisa, see 14 Clinical Trials and the respective current Product Monographs (see 17 Supporting Product Monographs).

Dosage Adjustment

Health Canada has not authorized an indication for pediatric use and Sarclisa should not be used in pediatrics outside of a clinical trial setting (see 1 INDICATIONS and 7 WARNINGS and PRECAUTIONS, General).

No dose adjustment is recommended in geriatric patients (≥ 65 years of age) (see 10 Clinical Pharmacology, 10.3 Pharmacokinetics, *Geriatrics*).

No dose adjustment is recommended in patients with mild hepatic impairment. Limited data are available in patients with moderate hepatic impairment, and no data are available in patients with severe hepatic impairment (see 10 Clinical Pharmacology, 10.3 Pharmacokinetics, *Hepatic Insufficiency*).

No dose adjustment is recommended in patients with renal impairment (see 10 Clinical Pharmacology, 10.3 Pharmacokinetics, *Renal Insufficiency*).

Temporary interruption or definitive discontinuation of Sarclisa treatment may be required for infusion-related reactions (IRRs) or neutropenia; no dose reduction of Sarclisa is recommended (Table 3).

Table 3 : Adjustments for Sarclisa treatment administration following IRRs or neutropenia

Adverse Reaction	NCI-CTCAE version 4.03 criteria definition	Administration adjustment
Infusion-related reactions (IRRs)	Mild (Grade 1): Infusion interruption or intervention not indicated	• Continue Sarclisa infusion per the judgment of the physician with close direct monitoring of the patient's clinical status. • Sarclisa infusion may be stopped at any time if deemed necessary.
	Moderate (Grade 2): Infusion interruption indicated but responsive promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	• Stop Sarclisa infusion. • Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) as needed. • If symptoms improve to Grade ≤1, restart Sarclisa infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. 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 4. • If symptoms do not resolve rapidly or do not improve to Grade ≤1 after interruption of Sarclisa infusion, persist or worsen despite appropriate medications, or require hospitalization or are life-threatening, treatment with Sarclisa should be permanently discontinued and additional supportive therapy should be administered, as needed.
	Severe (Grade 3) or life-threatening (Grade 4) Grade 3: prolonged symptoms (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: life-threatening consequences; urgent intervention indicated	• Stop Sarclisa infusion. • Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. • Discontinue Sarclisa treatment.

Table 3 : Adjustments for Sarclisa treatment administration following IRRs or neutropenia

Adverse Reaction	NCI-CTCAE version 4.03 criteria definition	Administration adjustment
Neutropenia	Grade 3/4	• Sarclisa administration should be delayed until neutrophil count improves to at least 1.0 x 10^9/L. • The use of colony-stimulating factors (e.g. G-CSF) should be considered, according to local guidelines (see 7 Warnings And Precautions).

NSAIDs: nonsteroidal anti-inflammatory drugs

For dosage adjustment information concerning medicinal products given in combination with Sarclisa, consult the corresponding Product Monographs (see 17 Supporting Product Monographs).

4.3 Reconstitution

The preparation of the infusion solution must be done under aseptic conditions.

- The dose (mg) of required Sarclisa concentrate should be calculated based on patient weight (measured prior to each cycle to have the administered dose adjusted accordingly, see 4 Dosage And Administration, 4.2 Recommended Dose and Dosage Adjustment). More than one Sarclisa concentrate 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.

- The appropriate volume of Sarclisa concentrate should be withdrawn from Sarclisa vial and diluted in an infusion bag with 250 mL of 0.9% sodium chloride or dextrose 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 mix the diluted solution by inverting the bag. Do not shake.

4.4 Administration

- The infusion solution must be administered by intravenous infusion using an IV tubing infusion set (in polyethylene [PE], polyvinyl chloride [PVC] with or without di (2-ethylhexyl) phthalate [DEHP], polybutadiene [PBD] or polyurethane [PU]) with an 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 Infusion Rates).

- Prepared Sarclisa infusion solution should be used within 48 hours when stored at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature.

- 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.

- On the days where both Sarclisa and carfilzomib are administered, administer dexamethasone first, followed by Sarclisa infusion, then followed by carfilzomib infusion.

Infusion Rates

Following dilution, the Sarclisa infusion should be administered intravenously at the infusion rates presented in Table 4 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion related reactions (IRRs) (see Dosage Adjustment, 7 Warnings And Precautions, and 8 Adverse Reactions).

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

4.5 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.

5 Overdose

There has been no experience of overdosage of isatuximab in clinical studies. Doses of intravenous Sarclisa up to 20 mg/kg have been administered in clinical studies. In the event of overdose, closely monitor patients for signs and symptoms of adverse reactions and initiate appropriate symptomatic and supportive treatment (see 7 Warnings And Precautions, 8 Adverse Reactions).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre. or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition And Packaging

To help ensure the traceability of biologic products, health professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 5: Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) Infusion	Concentrate for solution for infusion • 100 mg/5 mL (6 mL single use vial); Pack size of one or three single-use vials • 500 mg/25 mL (30 mL single use vial); Pack size of one single-use vial Each mL of Sarclisa concentrate contains 20 mg of isatuximab.	Histidine, Histidine hydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injection

7 Warnings And Precautions

General

The safety and efficacy of Sarclisa was assessed, but not established, in a single-arm study in 67 pediatric patients aged 1.4 years to < 17 years with relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL), B-cell acute lymphoblastic leukemia (B-ALL), or acute myeloid leukemia (AML), irrespective of CD38 status. Pediatric patients should not receive Sarclisa outside of a clinical trial setting.

Sarclisa is administered in combination with other medications; therefore, the contraindications, warnings and precautions and distribution restriction applicable for use with those medications also apply to Sarclisa combination therapy. The Product Monographs of all medications used in combination with Sarclisa should be consulted before starting the therapy (see 17 Supporting Product Monographs).

Carcinogenesis and Genotoxicity

Second Primary Malignancies

The incidence of second primary malignancies (SPMs) is increased in patients treated with Sarclisa-containing regimens. In clinical trials (IMROZ, ICARIA-MM and IKEMA), in patients treated with Sarclisa (N=592), second primary malignancies occurred in 71 patients (12%).

The most common (≥1%) second primary malignancies in ICARIA-MM, IKEMA, and IMROZ (N=592) included skin cancers (7% with Sarclisa-containing regimens and 3.1% with comparative regimens) and solid tumors other than skin cancer (4.6% with Sarclisa-containing regimens and 2.9% with comparative regimens). Patients with non-melanoma skin cancer continued treatment after resection of the skin

cancer, except 2 patients on the Isa-VRd arm and 1 patient on the VRd arm of the IMROZ study (see 8 Adverse Reactions).

Healthcare professionals should carefully monitor patients for the development of second primary malignancies and initiate treatment as necessary.

Driving and Operating Machinery

Fatigue and dizziness have been reported in patients taking Sarclisa. Patients should avoid driving or using machines until these events resolve.

Endocrine and Metabolism

Tumour Lysis Syndrome

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

Hematologic

Neutropenia

In clinical trials (ICARIA-MM, IKEMA, and IMROZ), in patients treated with Sarclisa (N=592), neutropenia based on laboratory values was reported in 81%, with grade 3 or 4 reported in 52%. Neutropenic infections occurred in 12% of patients, with grade 3 or 4 in 4.9%, and febrile neutropenia in 4% (see 8 Adverse Reactions).

Monitor complete blood cell counts at baseline and periodically during treatment. Antibacterial, and antiviral prophylaxis (such as herpes zoster prophylaxis) can be considered during treatment. Monitor patients with neutropenia for signs of infection. No dose reductions of Sarclisa are recommended. Sarclisa dose delays, modification of pomalidomide and dexamethasone treatment and the use of G-CSF may be required to allow improvement of neutrophil count (see 4 Dosage And Administration, 4.2 Recommended Dose and Dosage Adjustment).

Immune

Infusion-Related Reactions (IRRs)

In clinical trials (ICARIA-MM, IKEMA, and IMROZ), in patients treated with Sarclisa (N=592), infusion-related reactions occurred in 206 patients (35%). Among these 206 patients, 92% experienced infusion-related reactions during the first infusion and 12% after the first cycle. The most common symptoms (≥5%) of an infusion-related reaction included dyspnea and cough. Grade 1 infusion-related reactions were reported in 6% of patients, grade 2 in 28%, and grade 3 or 4 in 1.2%. Anaphylactic reactions occurred in less than 1% of patients. The total incidence of Sarclisa infusion interruptions was less than 1% and the incidence of patients with at least one Sarclisa infusion interruption due to infusion-related reactions was 26%. The median time to first Sarclisa infusion interruption was 61 minutes (range 4 to 240 minutes). Sarclisa was discontinued in 1% of patients due to infusion-related reactions (see 8 Adverse Reactions).

Sarclisa may cause serious infusion reactions including anaphylactic reactions. Signs and symptoms of anaphylactic reactions included bronchospasm, dyspnea, angioedema, and swelling (see 8 Adverse Reactions).

To decrease the risk and severity of IRRs, patients should be pre-medicated prior to Sarclisa infusion with acetaminophen, H2 antagonists, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment on the day of Sarclisa infusion (see 4 Dosage And Administration, 4.1 Dosing Considerations, Premedication). Vital signs should be frequently monitored during the entire Sarclisa infusion. In the event of an IRR in which infusion interruption or intervention (Grade 2) is indicated, interrupt Sarclisa infusion and provide appropriate medical and supportive measures (see 4 Dosage And Administration, 4.2 Recommended Dose and Dosage Adjustment). If symptoms improve to Grade ≤1, restart Sarclisa infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. 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 4. In case symptoms do not improve to Grade ≤1 after interruption of Sarclisa infusion, persist or worsen despite appropriate medications, require hospitalization or are life-threatening (Grade 3 or 4), permanently discontinue Sarclisa and institute appropriate management (see 4 Dosage And Administration, 4.2 Recommended Dose and Dosage Adjustment).

Monitoring and Laboratory Tests

Interference with Response Assessment

Sarclisa is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE) assays used for the clinical monitoring of endogenous myeloma (M)-protein (see 9 Drug Interactions, 9.7 Drug-Laboratory Test Interactions). This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa-expressing myeloma protein. In patients with persistent very good partial response (VGPR), consider other methods to evaluate the depth of response (see 9 Drug Interactions).

Interference with Serological Testing *(indirect antiglobulin test)*

Sarclisa binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). ABO/RhD typing was not affected by Sarclisa treatment. To avoid potential problems with RBC transfusion, patients being treated with Sarclisa should have blood type and screen tests performed prior to the first Sarclisa 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 that the patient is receiving Sarclisa and Sarclisa interference with blood compatibility testing can be resolved using dithiothreitol (DTT)-treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices (see 9 Drug Interactions, 9.7 Drug-Laboratory Test Interactions).

Reproductive Health

- **Fertility**

No human and animal data are available to determine potential effects of Sarclisa on fertility in males and females (see 16 Non-Clinical Toxicology).

7.1 Special Populations

7.1.1 Pregnancy

There are no available data on Sarclisa use in pregnant women. Animal reproduction toxicity studies have not been conducted with Sarclisa. Sarclisa is an immunoglobulin G1 (IgG1) monoclonal antibody

which is known to cross the placenta. Based on its mechanism of action and findings in CD38-knockout mice, exposure to isatuximab may cause fetal harm, e.g., immune cell depletion, neurological deficits, decreased bone density and metabolic disorders. The use of Sarclisa in pregnant women is not recommended. Women of childbearing potential treated with Sarclisa should use effective contraception during treatment and for at least 5 months after cessation of Sarclisa treatment.

Sarclisa in combination with pomalidomide is contraindicated in pregnant women and women at risk of becoming pregnant, as pomalidomide is contraindicated in these populations. Refer to pomalidomide and dexamethasone Product Monographs for requirements regarding contraception and for additional details (see 17 Supporting Product Monographs).

7.1.2 Breast-feeding

There are no available data on the presence of Sarclisa in human milk, milk production, or the effects on the breastfed infant. Human IgG antibody is known to be present in human milk. However, the effect of exposure to isatuximab via gastrointestinal tract is unclear in breastfed infants. As there is a potential for serious adverse reactions in breastfed infants, the use of Sarclisa in breastfeeding women is not recommended.

Sarclisa in combination with pomalidomide is contraindicated in breast-feeding women, as pomalidomide is contraindicated in this population. Refer to pomalidomide and dexamethasone Product Monographs for additional details (see 17 Supporting Product Monographs).

7.1.3 Pediatrics (< 18 years of age):

Sarclisa should not be used in pediatrics outside of a clinical trial setting (see 7 WARNINGS and PRECAUTIONS, General above).

7.1.4 Geriatrics (≥ 65 years of age):

Of the total number of patients in clinical studies of Sarclisa, 57.3% (1024 patients) were 65 and over, while 14.1% (252 patients) were 75 and over. No overall differences in efficacy were observed between younger (< 65 years of age) and older patients. Differences in safety were observed between patients 65 and over and younger patients. Grade ≥3 TEAEs was reported in 64.6%, of patients less than 65 and in 78.8% of patients 65 and above, Grade 5 TEAEs was reported in 5.5% of patients less than 65 and in 8.7% of patients 65 and above; serious TEAEs were reported in 46.7% of patients less than 65 and in 59.3% of patients 65 and above, TEAEs leading to definitive treatment discontinuation were reported in 6.0% of patients less than 65 and in 14.4% of patients 65 and over. In IMROZ in patients with newly diagnosed multiple myeloma not eligible for transplant, 28.3% of patients were 75 years and over. Grade 5 TEAEs were reported in 13.2% of patients in the Sarclisa arm and 3.5% of patients in the control treatment arm.

8 Adverse Reactions

8.1 Adverse Reaction Overview

Combination therapy with Sarclisa, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) in newly diagnosed multiple myeloma (IMROZ study)

The safety data described in this section are based on IMROZ, a randomized, open-label clinical trial in patients with newly diagnosed multiple myeloma. In IMROZ, Sarclisa 10 mg/kg was administered in

combination with bortezomib, lenalidomide, and dexamethasone (see 14 Clinical Trials). For adverse reaction evaluation, Sarclisa combined with bortezomib, lenalidomide, and dexamethasone (Isa-VRd) was compared with bortezomib, lenalidomide, and dexamethasone (VRd).

In IMROZ, the most frequent adverse reactions (in ≥20% of Isa-VRd patients) were diarrhea (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%), edema peripheral (32.7%), neutropenia (30.0%), 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 and in 67.4% of patients receiving VRd. The most frequent serious adverse reaction (in > 5% of Isa-VRd patients) was pneumonia (29.7% with Isa-VRd vs 21.0% with VRd, including Covid-19 pneumonia). Adverse reactions with a fatal outcome during treatment (Grade 5 TEAEs) were reported in 11% of patients with Isa-VRd and in 5.5% of patients treated with VRd (those occurring in more than 1% of patients, based on preferred terms, were Covid-19 pneumonia occurring in 3.0% of patients in the Isa-VRd group, and pneumonia occurring in 1.5% of patients in the Isa-VRd group and in 1.1% of patients in the VRd group). Permanent discontinuation of treatment because of adverse reactions was reported in 22.8% of patients treated with Isa-VRd and in 26% of patients treated with VRd (those occurring in more than 1% of patients, based on preferred terms, were Covid-19 pneumonia occurring in 3.0% of patients in the Isa-VRd group and in 0.6% in the VRd group, pneumonia. occurring in 2.3% of patients in the Isa-VRd group and in 2.2% in the VRd group, and sudden death occurring in 1.5% of patients in the Isa-VRd group).

Combination therapy with Sarclisa, pomalidomide and low-dose dexamethasone (Isa-Pd) in relapsed and/or refractory multiple myeloma (ICARIA-MM study)

The safety data described in this section are based on ICARIA-MM, a randomized, open-label clinical trial in patients with multiple myeloma. In ICARIA-MM, patients received Sarclisa10 mg/kg in combination with pomalidomide and dexamethasone (Isa-Pd) or pomalidomide and dexamethasone (Pd) (see 14 Clinical Trials).

The most frequent treatment-emergent adverse events (TEAEs, in >20% of Isa-Pd patients) were neutropenia, infusion reactions, pneumonia, upper respiratory tract infection, diarrhea and bronchitis.

The overall incidence of serious TEAEs was 61.8% in the Isa-Pd group and 53.7% in the Pd group. Serious TEAEs (≥2%) with at least a 2% higher incidence in the Isa-Pd group versus the Pd group included infections (39.5% vs. 30.9 %), febrile neutropenia (6.6% vs. 2.0%), neutropenia (3.3% vs. 1.3%) and infusion-related reactions (3.9% vs. 0 %). Fatal adverse events (AEs) were reported in 11.2% of patients in the Isa-Pd group and 11.4% in the Pd group. Fatal AEs reported in > 1% of patients in the Isa-Pd group were pneumonia and other infections (3.3%) (see 8.2 Clinical Trial Adverse Reactions).

Permanent discontinuation of treatment because of TEAEs was reported in 11 patients (7.2%) treated with Isa-Pd and in 19 patients (12.8%) treated with Pd. The most common TEAEs leading to treatment discontinuation in the Isa-Pd group were infections (2.6%).

Sarclisa dose reduction was not permitted in ICARIA-MM. In the Isa-Pd group, Sarclisa dose delay because of TEAEs was reported in 58.6% of patients, most frequently (≥ 3% of patients) due to neutropenia (27.0%), pneumonia (6.6%), bronchitis (4.6%), upper respiratory infection (3.9%) and diarrhea (3.9%).

Combination therapy with Sarclisa, carfilzomib and dexamethasone (Isa-Kd) in relapsed and/or refractory multiple myeloma (IKEMA study)

The safety data described in this section are based on IKEMA, a randomized, open-label clinical trial in

adult patients with previously treated multiple myeloma. In IKEMA, patients received Sarclisa 10 mg/kg in combination with carfilzomib and dexamethasone (Isa-Kd) (N=177) or carfilzomib and dexamethasone (Kd) (N=122) (see 14 Clinical Trials). Among patients who received Isa-Kd, the median duration of Sarclisa exposure was 79.9 weeks (range: 1 to 111 weeks).

The most frequent adverse reactions (in ≥20% of patients who received Isa-Kd) were upper respiratory tract infection (66.7%), infusion reactions (45.8%), fatigue (41.8%), hypertension (37.3%), pneumonia (36.2%), diarrhea (36.2%), dyspnea (28.8%), insomnia (23.7%), bronchitis (23.7%), and back pain (22.0%).

Serious adverse reactions occurred in 59.3% of patients receiving Isa-Kd and in 57.4% of patients receiving Kd. The most frequent serious adverse reactions (in >5% of patients) were pneumonia (24.9% with Isa-Kd vs 18.0% with Kd) and upper respiratory tract infections (9.0% with Isa-Kd vs 8.2% with Kd). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group and in 3.3% of patients in the Kd group (those occurring in more than 1% of patients were pneumonia and cardiac failure both occurring in 1.1% of patients in the Isa-Kd group and in 0.8% of patients in the Kd group).

Permanent discontinuation of treatment because of adverse reactions was reported in 8.5% of patients treated with Isa-Kd and in 13.9% of patients treated with Kd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Kd were infections (2.8%). Sarclisa alone was discontinued in 0.6% of patients due to infusion-related reactions.

Sarclisa dose interruptions due to an adverse reaction occurred in 32.8% of patients. The most frequent adverse reaction requiring Sarclisa dose interruption was infusion-related reaction (29.9%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Combination therapy with Sarclisa, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) in newly diagnosed multiple myeloma (IMROZ study)

Table 6 presents the adverse reactions observed during the treatment period in IMROZ study, in 263 patients with newly diagnosed multiple myeloma treated with Sarclisa 10 mg/kg in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) (see 14 Clinical Trials). Table 9 present treatment-emergent hematology laboratory abnormalities in IMROZ study.

Table 6– Adverse Reactions Reported in IMROZ study – ≥ 10% of Patients and ≥5% Higher in the Isa-VRd Group Versus VRd Group

IMROZ study						
Primary System Organ Class Preferred Term	**Sarclisa + Bortezomib + Lenalidomide + Dexamethasone (N=263)**			**Bortezomib + Lenalidomide + Dexamethasone (N=181)**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Infusion reaction	23.6%	0.4%	0%	1.1%	0%	0%
Infections and infestations						
Pneumonia[a]	39.9%	25.1%	2.3%	27.6%	15.5%	3.9%
Covid-19[c]	22.4%	0.8%	0%	16.6%	1.1%	0.6%
Blood and lymphatic system disorders						
Neutropenia	30.0%	19.0%	11.0%	21.5%	16.0%	4.4%
Eye disorders						
Cataract	38.0%	15.6%	0%	25.4%	11.0%	0%
Gastrointestinal disorders						
Diarrhea	54.8%	7.2%	0.4%	48.6%	8.3%	0%
General disorders and administration site conditions						
Fatigue	34.6%	8.0%	0%	26.5%	6.6%	0%

[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 parainfluenzae viral, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia viral, Pulmonary sepsis, Pulmonary tuberculosis, Tuberculosis.

[c] Covid-19 includes TEAEs in the SMQ "Covid-19-Narrow", except "Covid-19 pneumonia" term. Observed preferred terms are: Covid-19.

MedDRA 26.0

In IMROZ, the median duration of exposure is 53.2 months in the Isa-VRd group and 31.3 months in the VRd group

Combination therapy with Sarclisa, pomalidomide and low-dose dexamethasone (Isa-Pd) in relapsed and/or refractory multiple myeloma (ICARIA study)

Adverse reactions presented in Table 7 were observed during the treatment period in 301 patients in ICARIA-MM (see 14 Clinical Trials). At the time of analysis, the median duration of exposure was 41 weeks (range 1.3 to 76.7) in the Isa-Pd arm and 24 weeks (range 1.0 to 73.7) in the Pd arm.

Table 7: Summary of treatment-emergent adverse events with an all grades incidence ≥5% in the Isa-Pd group and with an all grades incidence difference ≥2% between Isa-Pd group and Pd group in ICARIA-MM (EFC14335) study - Safety Population

	Pd (N=149)			**Isa-Pd 10 mg/kg (N=152)**		
Primary System Organ Class[#] Preferred Term[#]	**All Grades* (n%)**	**Grade 3 (n%)**	**Grade 4 (n%)**	**All grades* (n%)**	**Grade 3 (n%)**	**Grade 4 (n%)**
Blood and lymphatic system disorders						
Neutropenia[a]	50 (33.6)	25 (16.8)	23 (15.4)	71 (46.7)	24 (15.8)	45 (29.6)
Febrile neutropenia	3 (2.0)	2 (1.3)	1 (0.7)	18 (11.8)	16 (10.5)	2 (1.3)

Table 7: Summary of treatment-emergent adverse events with an all grades incidence ≥5% in the Isa-Pd group and with an all grades incidence difference ≥2% between Isa-Pd group and Pd group in ICARIA-MM (EFC14335) study - Safety Population

	Pd (N=149)			Isa-Pd 10 mg/kg (N=152)		
Primary System Organ Class[#] Preferred Term[#]	**All Grades* (n%)**	**Grade 3 (n%)**	**Grade 4 (n%)**	**All grades* (n%)**	**Grade 3 (n%)**	**Grade 4 (n%)**
Gastrointestinal disorders						
Diarrhea	29 (19.5)	1 (0.7)	0	39 (25.7)	3 (2.0)	0
Nausea	14 (9.4)	0	0	23 (15.1)	0	0
Vomiting	5 (3.4)	0	0	18 (11.8)	2 (1.3)	0
Stomatitis	4 (2.7)	0	0	10 (6.6)	1 (0.7)	0
General disorders						
Edema peripheral	16 (10.7)	0	0	20 (13.2)	1 (0.7)	0
Immune system disorders						
Infusion related reaction[b]	0	0	0	58 (38.2)	2 (1.3)	2 (1.3)
Infections and infestations						
Upper respiratory tract infection	26 (17.4)	1 (0.7)	0	43 (28.3)	5 (3.3)	0
Pneumonia[c]	34 (22.8)	24 (16.1)	4 (2.7)	47 (30.9)	33 (21.7)	5 (3.3)
Bronchitis	13 (8.7)	1 (0.7)	0	36 (23.7)	5 (3.3)	0
Herpes viral infection [d]	4 (2.7)	0	0	15 (9.9)	1 (0.7)	0
Nasopharyngitis	7 (4.7)	0	0	14 (9.2)	0	0
Investigations						
Weight decreased	2 (1.3)	0	0	10 (6.6)	0	0
Metabolism and nutrition disorders						
Decreased appetite	7 (4.7)	1 (0.7)	0	15 (9.9)	2 (1.3)	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal chest pain	7 (4.7)	0	0	13 (8.6)	0	0
Bone pain	8 (5.4)	2 (1.3)	0	12 (7.9)	1 (0.7)	0
Muscular weakness	7 (4.7)	0	0	11 (7.2)	1 (0.7)	0
Myalgia	5 (3.4)	0	0	10 (6.6)	0	0
Nervous system disorders						
Headache	8 (5.4)	0	0	15 (9.9)	0	0
Tremor	6 (4.0)	0	0	12 (7.9)	3 (2.0)	0
Dizziness	4 (2.7)	0	0	8 (5.3)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	15 (10.1)	2 (1.3)	0	23 (15.1)	6 (3.9)	0

Table 7: Summary of treatment-emergent adverse events with an all grades incidence ≥5% in the Isa-Pd group and with an all grades incidence difference ≥2% between Isa-Pd group and Pd group in ICARIA-MM (EFC14335) study - Safety Population

	Pd (N=149)			Isa-Pd 10 mg/kg (N=152)		
Primary System Organ Class[#] Preferred Term[#]	**All Grades* (n%)**	**Grade 3 (n%)**	**Grade 4 (n%)**	**All grades* (n%)**	**Grade 3 (n%)**	**Grade 4 (n%)**

Pd: pomalidomide and dexamethasone; Isa-Pd: isatuximab in combination with pomalidomide and dexamethasone
[a] Grade 5 neutropenia was reported in 1 patient (0.7%) in the Isa-Pd arm; considered as non-related to study treatment
[b] Infusion related reaction was a TEAE considered to be related to infusion by site investigators and with onset typically within 24 hours from the start of infusion
[c] Pneumonia includes TEAEs in the narrow Standard MedDRA Query (SMQ) Infective pneumonia. Grade 5 pneumonia was reported in 1 patient (0.7%) in the Pd arm and in 2 patients (1.3%) in the Isa-Pd arm.
[d] Herpes viral infection includes the following list of terms: Herpes simplex, Herpes zoster, Herpes zoster disseminated, Oral herpes and Varicella
Note: Percentages are calculated using the number of treated patients as denominator.
[#]MedDRA 21.0
*CTCAE 4.03

Combination therapy with Sarclisa, carfilzomib and dexamethasone (Isa-Kd) in relapsed and/or refractory multiple myeloma (IKEMA study)

Table 8 and Table 11 presents the adverse reactions and abnormal laboratory findings observed during the treatment period of IKEMA in 299 patients with multiple myeloma, treated with Sarclisa 10 mg/kg in combination with carfilzomib and dexamethasone (Isa-Kd) or carfilzomib and dexamethasone (Kd) (see 14 Clinical Trials).

Table 8: Adverse Reactions (≥10%) in Patients Receiving Sarclisa, Carfilzomib, and Dexamethasone (Isa-Kd) with a Difference Between Arms of ≥5% Compared to Control Arm in IKEMA

Adverse Reactions	**Sarclisa + Carfilzomib + Dexamethasone (Isa-Kd) (N=177)**			**Carfilzomib + Dexamethasone (Kd) (N=122)**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Infusion-related reaction[a]	45.8%	0.6%	0%	3.3%	0%	0%
Infections						
Upper respiratory tract infection[b]	66.7%	9.0%	0%	57.4%	7.4%	0%
Pneumonia[c]	36.2%	19.2%	3.4%	30.3%	14.8%	2.5%
Bronchitis[d]	23.7%	2.3%	0%	13.1%	0.8%	0%
Vascular disorders						
Hypertension[e]	37.3%	20.3%	0.6%	32.0%	18.0%	1.6%
Respiratory, thoracic and mediastinal disorders						

Adverse Reactions	Sarclisa + Carfilzomib + Dexamethasone (Isa-Kd) (N=177)			Carfilzomib + Dexamethasone (Kd) (N=122)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Dyspnea[f]	28.8%	5.1%	0	23.8%	0.8%	0%
Cough[g]	22.6%	0%	0%	14.8%	0%	0%
Gastrointestinal disorders						
Diarrhea	36.2%	2.8%	0%	28.7%	2.5%	0%
Vomiting	15.3%	1.1%	0%	9.0%	0.8%	0%
General disorders and administration site conditions						
Fatigue[h]	41.8%	5.1%	0%	32.0%	3.3%	0%

[a] Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and hypersensitivity.

[b] Upper respiratory tract infection includes acute sinusitis, chronic sinusitis, H1N1 influenza, H3N2 influenza, influenza, laryngitis, laryngitis viral, nasal herpes, nasopharyngitis, pharyngitis, pharyngotonsillitis, respiratory syncytial virus infection, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, tracheitis, upper respiratory tract infection, viral rhinitis, respiratory tract infection, respiratory tract infection viral, influenza like illness, parainfluenzae virus infection, respiratory tract infection bacterial, and viral upper respiratory tract infection.

[c] Pneumonia includes atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, pneumocystis jirovecii pneumonia, pneumonia, pneumonia influenzal, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, pulmonary sepsis, and pulmonary tuberculosis.

[d] Bronchitis includes bronchitis, bronchitis viral, respiratory syncytial virus bronchitis, bronchitis chronic, and tracheobronchitis.

[e] Hypertension includes hypertension, blood pressure increased, and hypertensive crisis.

[f] Dyspnea includes dyspnea and dyspnea exertional.

[g] Cough includes cough, productive cough, and allergic cough.

[h] Fatigue includes fatigue and asthenia.

Description of Selected Adverse Reactions

Cardiac Arrhythmias

In ICARIA-MM, a higher incidence of all Grades cardiac arrhythmias TEAEs occurred in the Isa-Pd group (11.2%) compared with Pd group (2.0%). Grade ≥ 3 arrhythmias were reported in 3.3% patients in the Isa-Pd group compared with 0.7% in the Pd group. Most patients had pre-existing cardiovascular disorders. The most common TEAE in this category in the Isa-Pd group was atrial fibrillation (4.6%; Grade ≥ 3 2.0%).

Cardiac Failure

In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure and pulmonary edema) was reported in 7.3% of patients in the Isa-Kd group (4.0% of Grade ≥3) and in 6.6% of patients in 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. Fatal events of cardiac disorders occurred in 1.1% of patients in the Isa-Kd group (cardiac

failure) and in 0.8% of patients in the Kd group (acute myocardial infarction). See the current Product Monograph for carfilzomib for additional information.

Infusion-Related Reactions (IRRs)
In IMROZ, infusion-related reactions were reported in 63 patients (24.0%) treated with Isa-VRd. Grade 1 IRRs 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. Signs and symptoms of Grade 3 or 4 IRRs included hypertension, bronchospasm, and hypoxia. Isatuximab was discontinued in 0.8% of patients due to infusion-related reactions.

In ICARIA-MM, IRRs, defined as adverse reactions associated with the Sarclisa infusions, with an onset typically within 24 hours from the start of the infusion, were reported in 58 patients (38.2%) treated with Sarclisa. All patients who experienced IRRs, had the events during the 1st infusion of Sarclisa, with 3 patients (2.0%) also having IRRs at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 IRRs were reported in 3.9%, Grade 2 in 31.6%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. The incidence of infusion interruptions because of IRRs was 28.9%. The incidence of infusion interruptions because of infusion-related reactions was 28.9%. The median time to infusion interruption was 55 minutes. The median duration of Sarclisa infusion was 3.3 hours during the first infusion and 2.8 hours for the subsequent infusions.

In IKEMA, IRRs were reported in 81 patients (45.8%) treated with Isa-Kd. Grade 1 IRRs were reported in 13.6%, Grade 2 in 31.6%, and Grade 3 in 0.6% of the patients treated with Isa-Kd. Signs and symptoms of Grade 3 IRRs included dyspnea and hypertension. The incidence of Sarclisa infusion interruptions due to IRRs was 29.9%. Sarclisa was discontinued in 0.6% of patients due to infusion-related reactions.

In multiple myeloma clinical trials, anaphylactic reactions have been reported in association with infusion reactions in 5 patients (0.3%). Signs and symptoms of anaphylactic reactions included bronchospasm, dyspnea, angioedema, and swelling. No anaphylactic reactions were reported in the ICARIA-MM clinical trial and 1 patient (0.4%) experienced an anaphylactic reaction (Grade 4 infusion reaction) in the IMROZ clinical trial.
In a separate study (TCD14079 Part B) with Sarclisa 10 mg/kg administered from a 250 mL fixed infusion volume in combination with Pd, IRRs (all Grade 2) were reported in 19 patients (40.4%), at the first administration. The median duration of infusion was 3.9 hours for the first infusion, 1.9 hours for the second infusion and 1.3 hours from third infusion onwards.

In all patients treated with Sarclisa in the clinical studies, 267 patients (46.4%) had at least one IRR symptom and 28 (4.9%) experienced Grade 3 or 4 symptoms. Sarclisa was discontinued due to a Grade 3 or 4 IRR in 4 (2.6%) patients. The most common symptoms of an IRR were dyspnea, cough, nasal congestion, chills and nausea. Other reported symptoms included hypertension, hypoxia, pulmonary edema, hypotension, tachycardia, syncope, bronchospasm, cytokine release syndrome, anaphylactic reaction, face edema, and hyperglycemia

Infections
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.

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% in the Isa-Kd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 19.2% of patients in the Isa-Kd group compared to 14.8% 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 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, the 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.

Neutropenia

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 ICARIA-MM, Grade 3 and 4 neutropenia as laboratory abnormalities were reported in 24.3% and 60.5% of patients treated with Sarclisa in combination with pomalidomide and dexamethasone (Isa-Pd). Neutropenic complications included febrile neutropenia (11.8% of patients) and neutropenic infections (25% of patients). Sarclisa infusion was omitted due to neutropenia in 9.2% of patients. Pomalidomide and dexamethasone dose reduction or omission due to neutropenia occurred in 29.6% and 9.2% of patients, respectively. Use of granulocyte-colony stimulating factor (G-CSF) was required in 69.1% of the patients, either for prophylaxis or as treatment for neutropenia.

In the pivotal study IKEMA, in patients treated with Sarclisa in combination with carfilzomib and dexamethasone (Isa-Kd), neutropenia was reported as a laboratory abnormality in 54.8% 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). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

Second primary malignancies (SPMs)

In IMROZ study, at a median follow-up time of 59.7 months, SPMs were reported in 16.0% of patients in the Isa-VRd group and in 8.8% in the VRd group. SPMs were skin cancers in 8.4% of patients in the

Isa-VRd group and in 3.9% in the VRd group, were solid tumors other than skin cancer in 6.5% of patients in the Isa-VRd group and in 3.9% in the VRd group, and hematological malignancy in 1.1% of patients in each treatment group. Patients with SPM of skin cancer continued treatment after resection of the skin cancer, except one patient in each treatment group. In the Isa-VRd group (6/263) 2.3% of patients (4 with solid tumor other than skin cancer, 1 with skin cancer, and 1 with hematological malignancy) and (3/181) 1.7% of patients in the VRd group (1 with solid tumor other than skin cancer, 1 with skin cancer, and 1 with hematological malignancy) discontinued treatment due to SPM. SPMs with fatal outcome were reported in (6/263) 2.3% of patients in the Isa-VRd group (neuroendocrine carcinoma of the skin, malignant melanoma, squamous cell carcinoma of skin, squamous cell carcinoma of lung, colorectal cancer, and rectal adenocarcinoma) and in (2/181) 1.1% of patients in the VRd group (metastases to peritoneum and adenocarcinoma of colon).

In ICARIA-MM, second primary malignancies were reported after a median follow-up time of 52.4 months in 10 (6.6%) patients in the Isa-Pd group and in 3 patients (2.0%) in the Pd group. Second primary malignancies were most commonly skin cancer (3.9% of patients in the Isa-Pd group and in 2.0% in the Pd group). Other solid tumours occurred in 2.0% of patients in the Isa-Pd group (one patient also had skin cancer) compared to none in the Pd group. One hematological malignancy occurred in the Isa-Pd group (myelodysplastic syndrome [0.7%]). Two patients discontinued treatment with Isa-Pd due to second primary malignancy (one with metastatic melanoma, one with myelodyplastic syndrome). The remainder continued treatment after resection of the new malignancy.

In IKEMA, at a medium follow-up time of 20.7 months, SPMs were reported in 13 (7.3%) patients treated with Isa-Kd and in 6 (4.9%) patients treated with Kd. SPMs were skin cancers in 9 (5.1%) patients in the Isa-Kd group and in 3 (2.5%) patients in the Kd group, and were solid tumours other than skin cancer in 5 (2.8%) patients in the Isa-Kd group and in 4 (3.3%) patients in the Kd group. One (0.6%) patient in the Isa-Kd group and one (0.8%) patient in the Kd group had both skin cancer and solid tumours other than skin cancer. Patients with skin cancer continued treatment after resection of the skin cancer.

8.3 Less Common Clinical Trial Adverse Reactions

Other TEAEs of clinical relevance in the Isa-Kd arm in IKEMA include:

Eye disorders: cataract.

Ear and labyrinth disorders: vertigo.

Cardiac disorders: angina pectoris.

Gastrointestinal disorders: dyspepsia, gastroesophageal reflux disease, stomatitis.

Investigations: weight decreased.

Metabolism and nutrition disorders: decreased appetite, hyperglycemia, fluid retention.

Neoplasm benign, malignant and unspecified (incl cysts and polyps): skin cancer, solid tumour other than skin cancer.

Nervous system disorder: paresthesia.

Psychiatric disorders: anxiety.

Respiratory, thoracic and mediastinal disorders: pulmonary hypertension.

Skin and subcutaneous tissue disorders: erythema, purpura.

Other TEAEs of clinical relevance in the Isa-Pd arm in ICARIA-MM include:

Blood and lymphatic system disorders: anemia.

Eye disorders: cataract; vision blurred.

Gastrointestinal disorders: abdominal distension; abdominal pain upper; gastroesophageal reflux disease.

General disorders and administration site conditions: pyrexia.

Immune system disorders: cytokine release syndrome.

Infections and infestations: influenza; Pneumocystis jirovecii pneumonia; sepsis.

Investigations: gamma-glutamyltransferase increased.

Metabolism and nutrition disorders: diabetes mellitus; hyperglycemia.

Musculoskeletal and connective tissue disorders: joint swelling; arthralgia.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): squamous cell carcinoma of skin.

Nervous system disorders: dizziness; lethargy.

Psychiatric disorders: anxiety; confusional state; agitation; restlessness.

Renal and urinary disorders: urinary incontinence.

Respiratory, thoracic and mediastinal disorders; hiccups, pulmonary embolism.

Vascular disorders: hypertension; hot flush.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

Table 9: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-VRd Treatment Versus VRd Treatment – IMROZ study

Laboratory parameter	Sarclisa + Bortezomib + Lenalidomide + Dexamethasone (N=263)			Bortezomib + Lenalidomide + Dexamethasone (N=181)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	98.9%	17.5%	0%	97.8%	16.0%	0%
Lymphopenia	95.4%	44.9%	15.2%	92.3%	37.6%	15.5%
Thrombocytopenia	95.4%	14.8%	15.2%	84.5%	19.3%	8.3%
Neutropenia	87.5%	35.7%	18.6%	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 10: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment Versus Pd Treatment - ICARIA-MM (EFC14335)

Laboratory parameter	Pomalidomide + low-dose Dexamethasone (N=149)			Sarclisa + Pomalidomide + low-dose Dexamethasone (N=152)		
	All grades* n (%)[a]	Grade 3 n (%)[a]	Grade 4 n (%)[a]	All grades* n (%)[a]	Grade 3 n (%)[a]	Grade 4 n (%)[a]
Anemia	145 (98.6)	41 (27.9)	0	151 (99.3)	48 (31.6)	0
Neutropenia	137 (93.2)	57 (38.8)	46 (31.3)	146 (96.1)	37 (24.3)	92 (60.5)
Lymphopenia	137 (93.2)	52 (35.4)	12 (8.2)	140 (92.1)	64 (42.1)	19 (12.5)
Thrombocytopenia	118 (80.3)	14 (9.5)	22 (15.0)	127 (83.6)	22 (14.5)	25 (16.4)

[a] 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 11: Treatment emergent laboratory abnormalities in patients receiving Isa-Kd treatment versus Kd treatment – IKEMA study

Laboratory parameter	Sarclisa + Carfilzomib + Dexamethasone (N=177)			Carfilzomib + Dexamethasone (N=122)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	99.4%	22.0%	0%	99.2%	19.7%	0%
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%

Laboratory parameter	Sarclisa + Carfilzomib + Dexamethasone (N=177)			Carfilzomib + Dexamethasone (N=122)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Neutropenia	54.8%	17.5%	1.7%	43.4%	6.6%	0.8%

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

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

- Tumour Lysis Syndrome

9 Drug Interactions

9.4 Drug-Drug Interactions

The pharmacokinetics of isatuximab and pomalidomide, or bortezomib, or lenalidomide were not influenced by their co-administration. Analysis suggests administration of carfilzomib with isatuximab did not alter isatuximab pharmacokinetics or vice versa.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herb have not been established.

9.7 Drug-Laboratory Test Interactions

Interference with Serological Testing
Because CD38 protein is expressed on the surface of red blood cells, Sarclisa, 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 Sarclisa (see 7 Warnings And Precautions) . The indirect antiglobulin test was positive during Isa-Pd treatment in 67.7% of the tested patients in ICARIA-MM, and during Isa-Kd treatment in 63.3% of the tested patients in IKEMA. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by Sarclisa treatment.

Interference with Serum Protein Electrophoresis and Immunofixation Electrophoresis Tests
Sarclisa may be incidentally detected by serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE) assays used for the monitoring of M-protein and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria (see 7 Warnings And Precautions). In patients with persistent very good partial response, where interference is suspected, consider using a validated isatuximab-specific IFE assay to remove isatuximab interference and specifically visualize any remaining serum M protein, to facilitate determination of complete response. 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 Sarclisa signal from the myeloma M protein signal. In 11 out of the 22 patients, there was no residual myeloma M protein detectable at the sensitivity level of the immunofixation test (25 mg/dL); 10 of the 11 patients had IgG subtype myeloma at baseline, indicating Sarclisa interference with the immunofixation assay. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

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.

10 Clinical Pharmacology

10.1 Mechanism of Action

Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 and triggers several mechanisms leading to the death of CD38 expressing tumour cells. CD38 is a transmembrane glycoprotein with ectoenzymatic activity, expressed in hematological malignancies, including multiple myeloma cells, as well as other cell types and tissues at various levels.

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

Isatuximab inhibits the enzymatic activity of CD38 which catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR), which may contribute to immunoregulatory functions. Isatuximab inhibits the cADPR production from extracellular nicotinamide adenine dinucleotide (NAD) in multiple myeloma cells.

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 experiments using a human multiple myeloma xenograft model demonstrated that the combination of isatuximab and pomalidomide results in enhanced antitumour activity compared to the activity of isatuximab or pomalidomide alone.

10.2 Pharmacodynamics

NK Cell, CD19+ B-cell, CD4+ T-cell and TREG Cell Count

The pharmacodynamic activity of isatuximab was characterized in monotherapy. A decrease in absolute counts of total NK cells (including inflammatory $CD16^{+\,low}$ $CD56^{+\,bright}$ and cytotoxic $CD16^{+\,bright}$ $CD56^{+\,dim}$ NK cells), $CD19^{+}$ B-cells, $CD4^{+}$ T-cells and T_{REG} ($CD3^{+}$, $CD4^{+}$, $CD25^{+}$, $CD127^{-}$) was observed in peripheral blood.

In human peripheral blood mononuclear cells (PBMCs), natural killer (NK) cells express the highest CD38 levels. In vitro, isatuximab can activate NK cells in the absence of CD38 positive target tumour cells through a mechanism which is dependent of the Fc portion of isatuximab.

Also, isatuximab inhibits Tregs which express higher levels of CD38 in MM patients compared to healthy individuals. The decrease of the T_{REG} was higher in the responder patients compared to non-responder patients.

T-cell receptor (TCR) DNA sequencing was used to quantify expansion of individual T-cell clones, each of them having a unique TCR conferring antigen specificity. In multiple myeloma patients, Sarclisa monotherapy induced clonal expansion of the T-cell receptor repertoire.

In multiple myeloma patients treated with Sarclisa combined with pomalidomide and dexamethasone, a decrease in absolute counts of total NK cells (including inflammatory $CD16^{+\,low}$ $CD56^{+\,bright}$ and cytotoxic $CD16^{+\,bright}$ $CD56^{+\,dim}$ NK cells) and $CD19^{+}$ B-cells was observed in peripheral blood. An increase of $CD4^{+}$ T-cells and T_{REG} ($CD3^{+}$, $CD4^{+}$, $CD25^{+}$, $CD127^{-}$) was observed.

Cardiac Electrophysiology

The relationship between isatuximab plasma concentration and QT interval and other electrocardiogram parameters was analyzed by PK/PD modeling. Patients included in the modeling

received single agent Sarclisa up to 20 mg/kg QW which resulted in an isatuximab plasma concentration consistent with the predicted steady state C_{max} of isatuximab administered at the recommended dose.

Isatuximab had no apparent effect on Frederica-corrected QT interval (QTcF) change from baseline and on PR or QRS interval.

A concentration-related effect on heart rate (HR) was demonstrated by the PK/PD modeling. The predicted geometric mean HR change from baseline for Sarclisa administered at the recommended dose is 13 beats per minute (bpm) (95% CI: 9.3, 16.6).

10.3 Pharmacokinetics

The pharmacokinetics of isatuximab were characterized primarily by population pharmacokinetics in 476 patients with multiple myeloma treated with Sarclisa intravenous infusion as a single agent or in combination with pomalidomide/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) increased 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 was observed between 5 and 20 mg/kg following every week for 4 weeks followed by every 2 weeks schedule.

After Sarclisa administration at the recommended dose (10 mg/kg administration every week for 4 weeks followed by every 2 weeks), the median time to reach steady state was 8 weeks with a 3.1-fold accumulation. In ICARIA-MM (Sarclisa 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.

In IKEMA (Sarclisa in combination with carfilzomib and dexamethasone), the mean (CV%) predicted maximum plasma concentration C_{max} and AUC at steady state were 637 µg/mL (30.9%) and 152,000 µg.h/mL (37.8%), respectively.

In IMROZ (Sarclisa in combination with bortezomib, lenalidomide, and dexamethasone), the mean (CV%) predicted maximum plasma concentration Cmax and AUC_{2weeks} at steady state were 494 µg/mL (25.5%) and 119,000 µg.h/mL (31.8%), respectively.

Distribution:

The mean (CV%) predicted total volume of distribution of isatuximab is 8.13 L (26.2%).

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. The mean (CV%) clearance of isatuximab decreases over time by 50% to a steady state value of 0.00840

L/h [0.202 L/day] (58.8%). This is associated with a mean (CV%) terminal half-life of 37 days (50%).

Special Populations and Conditions

- **Pediatrics**: Sarclisa should not be used in pediatrics outside of a clinical trial setting (see 7 WARNINGS and PRECAUTIONS, General above).
- **Geriatrics:** The population pharmacokinetic analyses of 476 patients aged 36 to 85 years showed no clinically meaningful difference in exposure to isatuximab in patients < 75 years old versus > 75 years old (n=70).
- **Sex:** Based on population pharmacokinetic analyses, gender had no clinically meaningful effect on the pharmacokinetics of isatuximab.
- **Ethnic Origin:** Based on population pharmacokinetic analyses, race (Caucasian, Black, Asian and other races) had no clinical meaningful effect on isatuximab pharmacokinetics.
- **Hepatic Insufficiency:** No formal studies of Sarclisa in patients with hepatic impairment have been conducted. Out of the 476 patients of the population pharmacokinetic analyses, 65 patients presented with mild hepatic impairment (total bilirubin 1 to 1.5 times upper limit of normal [ULN] or aspartate amino transferase [AST] > ULN and 1 patient had moderate hepatic impairment (total bilirubin> 1.5 to 3 times ULN and any AST). Mild hepatic impairment had no clinically meaningful effect on the pharmacokinetics of isatuximab. The effect of moderate (total bilirubin >1.5 times to 3 times ULN and any AST) and severe hepatic impairment (total bilirubin >3 times ULN and any AST) on isatuximab pharmacokinetics is unknown.
- **Renal Insufficiency:** No formal studies of Sarclisa in patients with renal impairment have been conducted. The population pharmacokinetic analyses on 476 patients included 192 patients with mild renal impairment (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate [e-GFR] <90 mL/min/1.73 m^2), 163 patients with moderate renal impairment (30 mL/min/1.73 m^2≤ e-GFR < 60 mL/min/1.73 m^2) and 12 patients with severe renal impairment (e-GFR <30 mL/min/1.73 m^2). Analyses suggested no clinically meaningful effect of mild to severe renal impairment on isatuximab pharmacokinetics compared to normal renal function.

  A pharmacokinetics analysis on 22 patients with End-Stage Renal Disease (ESRD) including patients on dialysis (eGFR <15 mL/min/1.73 m^2) showed no clinically meaningful effects of ESRD on isatuximab pharmacokinetics compared to those of normal, mild, or moderate renal function. No dose adjustment of Sarclisa is needed in patients with mild, moderate, severe or end-stage renal impaired function.

10.4 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity to Sarclisa. Overall, across 9 clinical studies in relapsed or refractory multiple myeloma (RRMM) with Sarclisa single agent and combination therapies including ICARIA-MM and IKEMA (N= 1023), the incidence of treatment emergent anti-drug antibodies (ADAs) was <2%. In ICARIA-MM and IKEMA, no patients with RRMM tested positive for ADA. Therefore, the neutralizing ADA status was not determined. In RRMM, no effect of ADAs was observed on pharmacokinetics, safety or efficacy of Sarclisa.
Across 3 clinical studies in newly diagnosed multiple myeloma (NDMM) with Sarclisa 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 Sarclisa 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 Sarclisa, including those with neutralizing antibodies, no meaningful impact of ADAs on safety or efficacy of Sarclisa was observed.

11 Storage, Stability And Disposal

Vials of Sarclisa concentrate for solution for infusion should be stored between 2°C and 8°C (36°F to 46°F) and protected from light. Do not freeze. Do not shake.

After Dilution

Sarclisa infusion solution should be prepared in sodium chloride 0.9% or dextrose 5%. Microbiological, 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. No protection from light is required for storage in the infusion bag.

Disposal

Unused portions of solution must be discarded. All materials that have been utilized for dilution and administration should be disposed of according to standard procedures.

12 Special Handling Instructions

Sarclisa must not be mixed with other medicinal products except those mentioned in the 4 Dosage And Administration section.

The preparation of the infusion solution must be done under aseptic conditions (refer to 4 Dosage And Administration).

Part 2: Scientific Information

13 PHARMACEUTICAL INFORMATION

Drug Substance

Non-proprietory name:	Isatuximab
Chemical name:	Immunoglobulin G1, anti – (human CD38 antigen) (human-Mus musculus monoclonal hu38SB19 heavy chain), disulfide with human-Mus musculus monoclonal hu38SB19 light chain, dimer
Molecular formula and molecular mass:	Isatuximab is composed of light and heavy chains. Each light chain consists of 214 amino acid residues and each heavy chain consists of 450 amino acid residues. The heavy chain N-terminal glutamine residue is fully converted to pyroglutamate. The majority of the heavy chain C-terminal K450 is clipped (between 9 and 11 % of C-terminal K450 using reduced peptide mapping). Isatuximab contains 32 cysteines leading to 16 disulfide bonds and two glycosylation sites located on Asparagine N300 of heavy chain. 147 825 Da (G_0F-G_0F glycosylated form)
Structural formula:	Isatuximab is an IgG_1 derived-monoclonal antibody binding selectively the human CD38 membrane protein. The protein structure is composed of 2 kappa light chains each with molecular weight of approximately 23 kDa and 2 IgG1 heavy chains each with a molecular weight of approximately 49 kDa (deglycosylated form) linked through disulfide bridges.
Physicochemical properties:	The concentrate for solution for infusion is a colorless to slightly yellow solution, essentially free of visible particulates.
Pharmaceutical standard:	Professed
Product Characteristics:	Isatuximab is produced by recombinant deoxyribonucleic acid (DNA) technology from a mammalian cell line (Chinese Hamster Ovary, CHO). The manufacture of isatuximab is based on a CHO master and working cell bank system, where the master and working cell banks have been thoroughly characterized and tested for adventitious contaminants and

endogenous viruses. Results from genetic characterization studies also demonstrated stability of these cell banks. The manufacturing process of isatuximab consists of a series of steps which include cell culture, harvest, purification (including viral inactivation/removal steps), and formulation buffer exchange. The purification process includes a combination of chromatographic steps.

Isatuximab is produced by recombinant deoxyribonucleic acid (DNA) technology from a mammalian cell line (Chinese Hamster Ovary, CHO). The manufacture of isatuximab is based on a CHO master and working cell bank system, where the master and working cell banks have been thoroughly characterized and tested for adventitious contaminants and endogenous viruses. Results from genetic characterization studies also demonstrated stability of these cell banks. The manufacturing process of isatuximab consists of a series of steps which include cell culture, harvest, purification (including viral inactivation/removal steps), and formulation buffer exchange. The purification process includes a combination of chromatographic steps.

The manufacturing of Sarclisa (the drug product) consists of steps which include drug substance thawing, pooling and homogenization, prefiltration, sterilizing filtration of the pre-filtered solution at the point of fill, aseptic filling into glass vials, and stoppering and crimping of the vials. The drug product manufacturing process uses appropriate aseptic process techniques, equipment, and facilities.

14 Clinical Trials

14.1 Clinical Trials by Indication

Sarclisa (Isatuximab for injection) is indicated in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant (ASCT)

Study IMROZ (EFC12522)

Study demographics and trial design

Study #	Trial design	Dosage, route of administration and duration		Study subjects (n)	Mean age, years (Range)	Sex
IMROZ EFC12522	Phase 3 Multicenter, international, randomized, open-label, 2-arm study in patients with newly diagnosed multiple myeloma who are not eligible for stem cell transplantation.	Induction period: 42-day cycles Isa-VRd; Sarclisa (10mg/Kg IV) [a] + bortezomib (1.3 mg/m² SC) [b] + lenalidomide (25 mg PO)[c] + dexamethasone (20 mg IV/PO)[d] VRd: bortezomib (1.3 mg/m² SC) [b] + lenalidomide (25 mg PO)[c] + dexamethasone (20 mg IV/PO)[d]	Continuous period: 28-day cycles Isa-Rd: Sarclisa (10mg/Kg IV)[e] + lenalidomide (25 mg PO)[f] + dexamethasone (20 mg IV/PO)[g] Rd: lenalidomide (25 mg PO)[f] + dexamethasone (20 mg IV/PO)[g]	Total:446 Isa-VRd: 265 VRd: 181	72 (range: 60-80)	Male: 237 (53.1%) Female: 209 (46.9%)

[a] on day 1, 8, 15, 22, and 29, in the first cycle and on day 1, 15, and 29, from cycle 2 to 4
[b] on days 1, 4, 8, 11, 22, 25, 29, and 32 of each cycle
[c] from day 1 to 14 and from day 22 to 35 of each cycle
[d] IV on the days of isatuximab infusions, and PO the other days; 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
[e] on day 1 and 15 from cycle 5 to 17, and on day 1 from cycle 18
[f] from day 1 to 21 of each cycle
[g] IV on the days of isatuximab infusions, and PO the other days; on days 1, 8, 15, and 22 of each cycle
IV = Intravenous; PO = Taken orally

The efficacy and safety of Sarclisa in combination with bortezomib, lenalidomide, and dexamethasone were evaluated in IMROZ (EFC12522), a multicenter, international, randomized, open-label, 2-arm, phase III study in patients with newly diagnosed multiple myeloma who are not eligible for stem cell transplantation.

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 IV 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 (IV 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 IV 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 (IV 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. 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.

Study Results

Progression-free survival (PFS) was the primary efficacy endpoint of IMROZ. 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. Key secondary endpoints were complete response (CR) rate, minimal residual disease (MRD) negativity rate in patients with CR, very good partial response (VGPR) or better rate, and overall survival (OS).

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

Efficacy results are presented in Table 12 and Kaplan-Meier curves for PFS are provided in Figure 1:

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

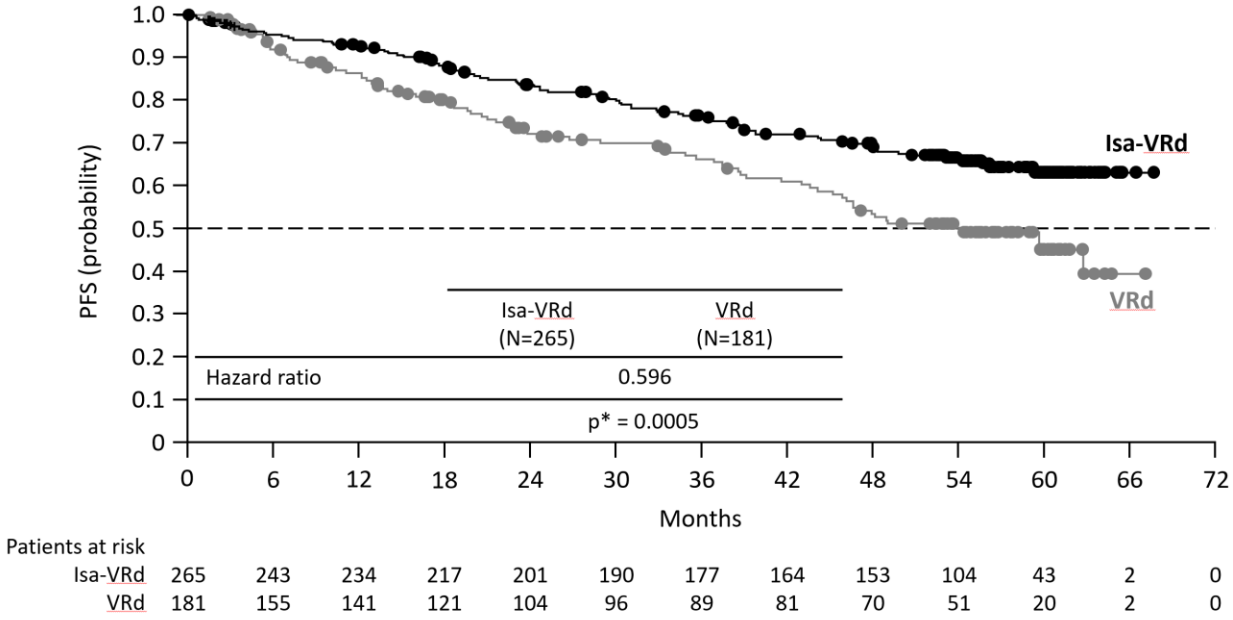
Endpoint	Sarclisa + bortezomib + lenalidomide + dexamethasone N =265	Bortezomib + lenalidomide + dexamethasone N = 181
Progression-Free Survival [a]		
Median (months)	NR	54.34
[95% CI]	[NR-NR]	[45.21-NR]
Hazard ratio [b] [98.5% CI]	0.596 [0.406-0.876]	
p-value (Stratified Log-Rank test, 1-sided)[b]	0.0005	
CR or better (sCR and CR)	74.7%	64.1%
[95% CI][c]	[0.690-0.798]	[0.566-0.711]
p-value (Stratified Log-Rank test, 1-sided)[b]	0.0080	
Minimal Residual Disease negativity[d] **CR**	55.5%	40.9%
[95% CI][c]	[0.493-0.616]	[0.337-0.484]
p-value (stratified Cochran-Mantel-Haenszel, 1-sided) [b]	0.0013	

[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.
CR: complete response; sCR: stringent complete response
Cut-off date of 26 September 2023. Median follow-up time=59.73 months.
NR: not reached.

The ORR was 91.3% in the IVRd group and 92.3% in the VRd group. A statistically significantly higher rate of CR (including sCR) was observed in the IVRd group (74.7%) than in the VRd group (64.1%). The very good partial response (VGPR) and partial response (PR) rates were 14.3% and 2.3%, respectively in IVRd group compared to 18.8% and 9.4%, respectively in VRd group.

At a median follow-up time of 59.73 months, the median overall survival was not reached for either treatment group, and 26.0% 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). The 60-month survival rate estimates were respectively 72.3% (95% CI: 66.1 to 77.5) in the Isa-VRd group and 66.3% (95% CI: 58.5 to 73.1) in the VRd group.

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



Patients at risk

Isa-VRd	265	243	234	217	201	190	177	164	153	104	43	2	0
VRd	181	155	141	121	104	96	89	81	70	51	20	2	0

*one-sided p-value derived from a stratified log-rank test

SARCLISA (isatuximab for injection) is indicated in combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.**Study ICARIA-MM (EFC14335)**

Study demographics and trial design

Table 13 Summary of Patient Demographics in ICARIA-MM (EFC14335)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age, years (Range)	Sex
ICARIA-MM (EFC14335)	Phase 3 Multicenter, multinational, randomized, open-label, 2-arm clinical study in patients with relapsed and refractory multiple myeloma (MM)	Isa-Pd: Sarclisa (10mg/kg; IV)[a] + pomalidomide (4mg; PO)[b] + low-dose dexamethasone (40mg PO/IV; 20mg for patients ≥ 75)[c] Pd: Pomalidomide (4mg; PO)[b] + low-dose dexamethasone (40mg PO/IV; 20mg for patients ≥ 75)[c] 28-day cycle	Total: 307 Isa-Pd: 154 Pd: 153	67 (range 36-86)	Male: 148 (48.2%) Female: 159 (51.8%)

[a] administered as an IV weekly in the first cycle and every two weeks thereafter
[b] 4mg taken orally once daily from day 1 to day 21 of each 28-day cycle
[c] Given on days 1, 8, 15 and 22 for each 28-day cycle
IV = Intravenous; PO = Taken orally

The efficacy and safety of Sarclisa in combination with pomalidomide and low-dose dexamethasone were evaluated in ICARIA-MM (EFC14335), a multicenter, multinational, randomized, open-label, 2-arm, phase III study in patients with relapsed and refractory multiple myeloma. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor. All patients had refractory disease to the last prior therapy.

Key eligibility criteria included patients aged ≥18 years with a known diagnosis of multiple myeloma with evidence of measurable disease who had received prior treatment with at least 2 prior lines of therapy for multiple myeloma including lenalidomide and a proteasome inhibitor (PI) alone or in combination, and demonstrated disease progression on or within 60 days of completion of the last therapy. Eligible patients should have Eastern Cooperative Oncology Group (ECOG) status of 0-2, platelets ≥75,000 cells/mm^3, absolute neutrophil count ≥1 × 10^9/L, creatinine clearance ≥30 mL/min (MDRD formula), and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN). Patients who had primary refractory disease or who received prior anti-CD38 therapy were not eligible.

A total of 307 patients were randomized in a 1:1 ratio to receive either Sarclisa in combination with pomalidomide and low-dose dexamethasone (Isa-Pd, 154 patients) or pomalidomide and low-dose dexamethasone (Pd, 153 patients). Randomization was stratified by age (<75 years versus ≥75 years) and number of previous lines of therapy (2 or 3 versus more than 3).

Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. Sarclisa 10 mg/kg was administered as an IV 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. Low-dose dexamethasone (PO/IV) 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. The median patient age was 67 years (range 36-86), 19.9% of patients were ≥ 75 years, 10.4% of patients entered the study with a history of chronic obstructive pulmonary disease (COPD) or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m^2) was 38.7% in Isa-Pd group versus 33.8% in Pd group. The International Staging System (ISS) Stage at initial diagnosis was I in 25.1%, II in 31.6% and III in 28.0% of patients. Overall, 19.5% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14) and t(14;16) were present in 12.1%, 8.5% and 1.6% 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, 56.4% of patients received prior stem cell transplantation, and 93.5% of patients received prior alkylating agents. The majority of patients were refractory to lenalidomide (92.5%), to a proteasome inhibitor (75.9%), and to both an immunomodulator and a proteasome inhibitor (72.6%); 59% of patients were refractory to lenalidomide at last prior line of therapy.

The median duration of treatment was 10.3 months for the Isa-Pd group compared to 6 months for the Pd group.

Progression free survival (PFS) was the primary efficacy endpoint of ICARIA-MM. PFS results were assessed by an Independent Response Committee (IRC) based on central laboratory data for M-protein and central radiologic imaging review using the 2016 International Myeloma Working Group (IMWG) criteria. Key secondary efficacy endpoints included overall response rate (ORR) as per IMWG criteria and overall survival (OS).

Study Results

Progression-Free Survival (PFS) was significantly prolonged in the Isa-Pd group compared to the Pd group. The median PFS was 11.6 months (95% confidence interval [CI]: 8.9-13.9) in the Isa-Pd group versus 6.5 months (95% CI: 4.5-8.3) in the Pd group (hazard ratio [HR] = 0.596; 95% CI: 0.436-0.814, p=0.0010) , representing a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-Pd (Table 14, Figure 2).

Key efficacy results are presented in the following table.

Table 14 Efficacy of Sarclisa in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Endpoint	Sarclisa + pomalidomide + low-dose dexamethasone (N = 154)	Pomalidomide + low-dose dexamethasone (N = 153)
Progression-Free Survival		
Median (months) [95%CI]	11.5 [8.9-13.9]	6.5 [4.5-8.3]
Hazard Ratio[a] [95%CI]	0.596 [0.44-0.81]	
p-value[a] (stratified-log-rank test)	0.0010	
Overall Response Rate[b]		
Responders (sCR+CR+VGPR+PR) n(%)	93 (60.4)	54 (35.3)
[95% CI][c]	[0.522-0.682]	[0.278-0.434]
p-value (stratified Cochran-Mantel-Haenszel)[a]	< 0.0001	
Stringent Complete Response (sCR) + Complete Response (CR) n(%)	7 (4.5)	3 (2.0)
Very Good Partial Response (VGPR) n(%)	42 (27.3)	10 (6.5)
Partial Response (PR) n(%)	44 (28.6)	41 (26.8)

a. Stratified on age (<75y vs ≥75 y) and number of previous lines of therapy (2 or 3 vs >3) according to IRT. The p-value for PFS was derived based on stratified log-rank test. A pre-defined hierarchical procedure allows for testing of an endpoint only when the previous one is statistically significant, in the following order: PFS, ORR and OS.
b. sCR, CR, VGPR and PR were evaluated by the IRC using the IMWG response criteria (2016)
c. Estimated using Clopper-Pearson method.

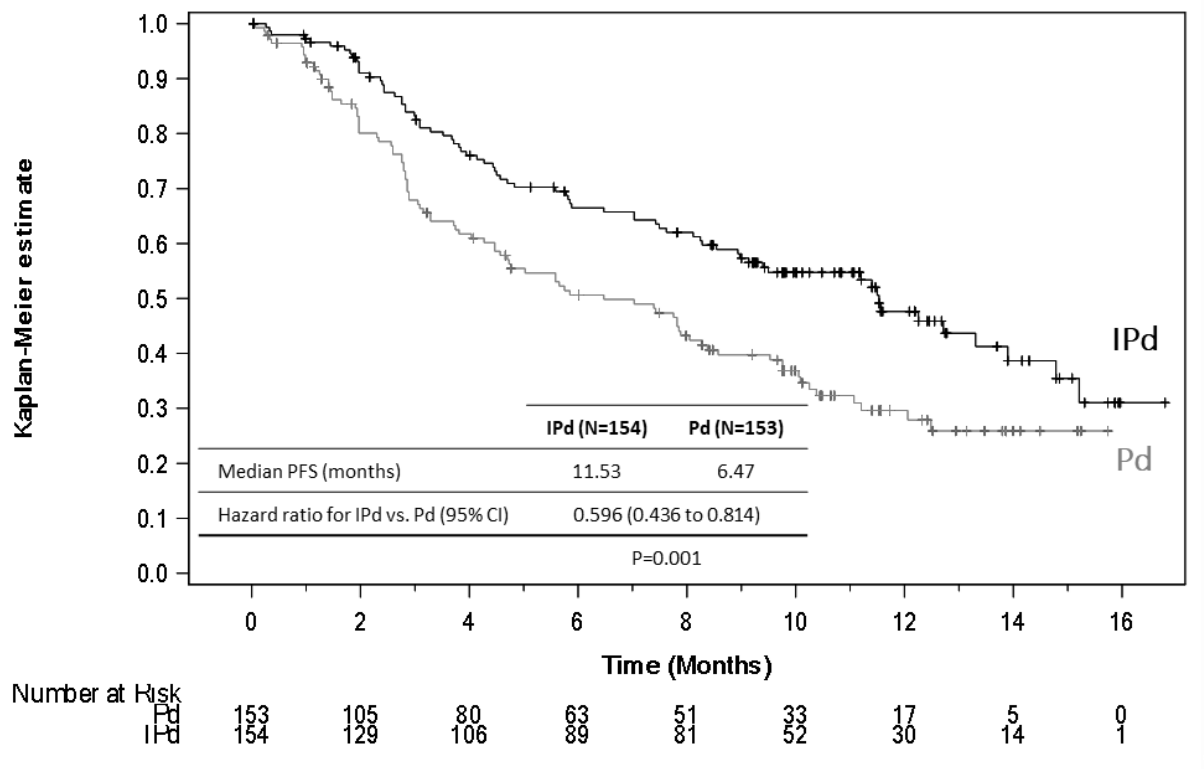
CI= Confidence Interval. CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowle.

The median duration of response was 13.3 months (95% CI: 10.6-NR) in the Isa-Pd group versus 11.1 months (95% CI: 8.5-NR) in the Pd group.

Subgroup analyses based on PFS hazard ratio were generally consistent with that of the primary PFS analysis across the pre-defined subgroups, including patients with high-risk cytogenetics, > 75 years, with ISS stage III at study entry, with baseline creatinine clearance < 60 ml/min/1.73 m^2, with > 3 prior lines of therapy, refractory to lenalidomide or proteasome inhibitor, and refractory to lenalidomide at the last line before the study entry.

The median time to first response was 35 days in the Isa-Pd group versus 58 days in the Pd group. The median duration of response was 13.3 months (95% CI: 10.6-not reached [NR]) in the Isa-Pd group versus 11.0 months (95% CI: 8.5-NR) in the Pd group.

Figure 2: Kaplan-Meier Curves of PFS – ITT population – ICARIA-MM (assessment by the IRC)



Overall Survival (OS) was analyzed at a preplanned interim analysis when the primary analyses for PFS and ORR were conducted. The OS was not mature at the time of the interim analysis. At the pre-specified primary OS analysis, conducted after 220 events had occurred (median follow-up time = 51.09 Months), median overall survival was estimated to be 24.6 months in the Isa-Pd group and 17.7 months in Pd group (HR=0.776; 95% CI: 0.594 to 1.015). The results did not achieve statistical significance.

SARCLISA (isatuximab for injection) is indicated in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

Study IKEMA (EFC15246)

Study demographics and trial design

Table 15 Summary of Patient Demographics for IKEMA (EFC15246)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age, years (Range)	Sex
IKEMA (EFC15246)	Phase 3 Multicenter, multinational, randomized, open-label, 2-arm study in patients with relapsed and/or refractory multiple myeloma who had received one to three prior therapies.	Isa-Kd: Sarclisa (10 mg/Kg IV)[a] + carfilzomib IV[b] + dexamethasone (20 mg IV/PO)[c] Kd: Carfilzomib IV[d] + dexamethasone (20 mg IV/PO)[e] 28-day cycle	Total:302 Isa-Kd: 179 Kd: 123	63.1 (range: 33-90)	Male: 169 (56%) Female: 133 (44%)

[a] administered as an IV weekly in the first cycle and every two weeks thereafter
[b] 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
[c] IV on the days of isatuximab and/or carfilzomib infusions, and PO the other days; given on days 1, 2, 8, 9, 15, 16, 22 and 23 for each 28-day cycle
IV = Intravenous; PO = Taken orally

The efficacy and safety of Sarclisa in combination with carfilzomib and dexamethasone were evaluated in IKEMA (EFC15246), a multicenter, multinational, randomized, open-label, 2-arm, phase III study in adult patients with relapsed and/or refractory multiple myeloma. Patients had received one to three prior lines of therapy. Eligible patients had an ECOG status of 0-2, platelets ≥50,000 cells/µL if <50% of bone marrow nucleated cells were plasma cells and ≥30,000 cells/µL if ≥50% of bone marrow nucleated cells were plasma cells, absolute neutrophil count ≥1 x 10^9/L, creatinine clearance ≥15 mL/min/1.73 m^2 (MDRD formula), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN). Patients with primary refractory disease 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. Sarclisa10 mg/kg was administered as an intravenous (IV) infusion weekly in the first cycle and every two weeks thereafter. Carfilzomib was administered as an IV 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 orally on the other days) 20 mg was given on days 1, 2, 8, 9, 15, 16, 22 and 23 for each 28-day cycle. On the days where both Sarclisa and carfilzomib were administered, dexamethasone was administered first, followed by Sarclisa infusion, then followed by carfilzomib infusion.

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. The proportion of patients with renal impairment (eGFR<60 mL/min/1.73 m^2) was 24.0% in the Isa-Kd group versus 14.6% in the Kd group. The International Staging System (ISS) stage at study entry was I in 53.0%, II in 31.1%, and III in 15.2% of patients. 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.

Study Results

Progression-free survival (PFS) was the primary efficacy endpoint of IKEMA. PFS results were assessed by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using the IMWG criteria.

Efficacy results are presented in Table 16 and Kaplan-Meier curves for PFS are provided in Figure 3:

Table 16: Efficacy of Sarclisa in combination with carfilzomib and dexamethasone versus carfilzomib and dexamethasone in the treatment of multiple myeloma in IKEMA (intent-to-treat analysis)*

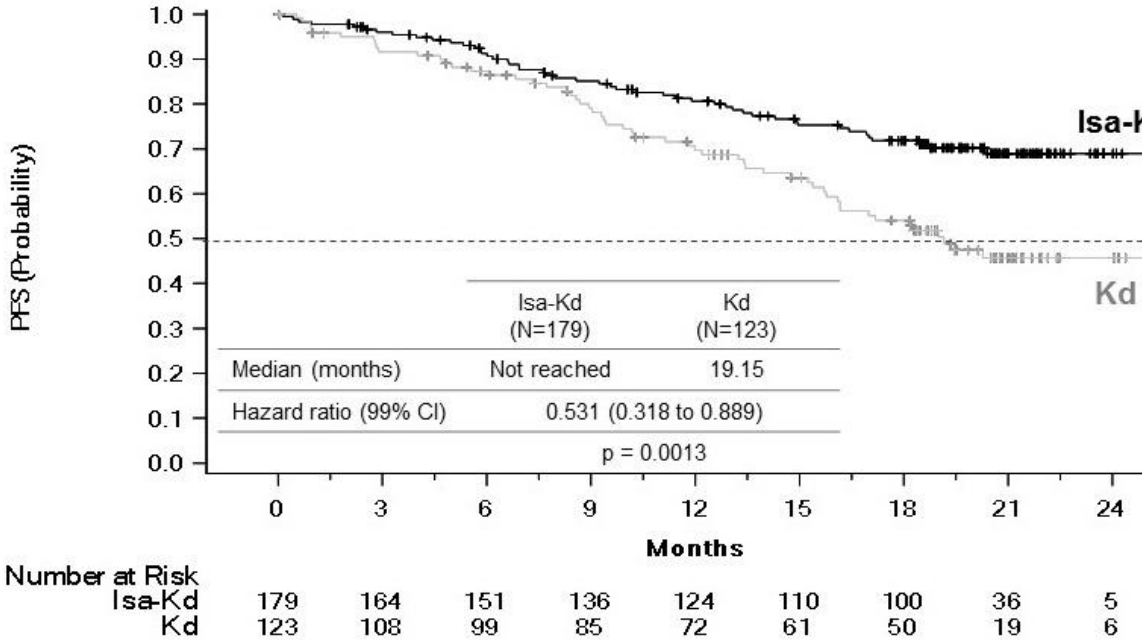
Endpoint	Sarclisa + carfilzomib + dexamethasone N = 179	Carfilzomib + dexamethasone N = 123
Progression-Free Survival[a]		
Median (months)	NR	19.15
[95%CI]	[NR -NR]	[15.77-NR]
Hazard Ratio[b] [99%CI]	0.531 [0.318-0.889]	
p-value (stratified-log-rank test)[b]	0.0013	
Overall Response Rate[c]		
Responders (sCR+CR+VGPR+PR) n (%)	155 (86.6)	102 (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) n (%)	71 (39.7)	34 (27.6)
Very Good Partial Response (VGPR) n (%)	59 (33.0)	35 (28.5)
Partial Response (PR) n (%)	25 (14.0)	33 (26.8)

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 (2016)
d. Estimated using Clopper Pearson method.

*Results are based on a prespecified interim analysis. Cut-off date of 7 February 2020. Median follow-up time 20.7 months

NR: not reached.

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



At a median follow-up time of 44 months, final PFS analysis showed a median PFS of 35.6 months (95%CI: 25.8 to 44) for Isa-Kd group compared to 19.2 months (95%CI: 15.8 to 25.0) for Kd group. Final complete response, determined using an isatuximab-specific IFE assay to remove isatuximab interference (see 9.7 Drug-Laboratory Test Interactions), was 44.1% (n=79) in Isa-Kd group compared to 28.5% (n=35) in Kd group. Note that in the Isa-Kd group, 4 patients who achieved VGPR at the interim analysis were reclassified to CR using the isatuximab-specific IFE.

At a median follow-up time of 56.6 months, median overall survival was not reached in the Isa-Kd group (95% CI: 52.2-NR) and was 50.60 months in Kd group (95% CI: 38.9-NR) (HR=0.855; 95% CI: 0.6-1.2).
The percentage of patients achieving a best overall response of VGPR or better, defined as patients with sCR, CR, or VGPR by the IRC using the IMWG response criteria, was 72.6% in the Isa-Kd group and 56.1% in the Kd group.

Subgroup analyses based on PFS hazard ratio were consistent across the pre-specified subgroups including patients with high-risk cytogenetics, ≥ 65 years of age, with baseline eGFR (MDRD) < 60 mL/min/1.73 m^2, with >1 prior line of therapy, or with ISS stage III at study entry.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

Carcinogenicity: Carcinogenicity studies have not been conducted with Sarclisa.

Genotoxicity: Genotoxicity studies have not been conducted with Sarclisa.

Reproductive and Developmental Toxicology: Reproductive, developmental toxicity and embryofetal toxicity studies have not been conducted with Sarclisa.

17 Supporting Product Monographs

1. Pomalyst® (pomalidomide)[1] (capsule, 1 mg, 2 mg, 3 mg and 4 mg), Submission Control Number 243491, Product Monograph. Date of revision: February 2, 2021
2. Dexamethasone Product Monograph
3. Kyprolis® (carfilzomib for injection) [2] Product Monograph. Date of revision: January 27, 2021.
4. Velcade® (bortezomib for injection)[3] Product Monograph. Date of revision: February 7, 2022
5. Lenalidomide Product Monograph

[1] Pomalyst® is a registered trademark of Celgene Corporation
[2] Kyprolis is a registered trademark of Onyx Pharmaceuticals, Inc.
[3] Velcade® is a registered trademark of Janssen, Inc

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr SARCLISA ®

Isatuximab for injection

This patient medication information is written for the person who will be taking **Sarclisa**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Sarclisa**, talk to a healthcare professional.

What Sarclisa is used for:

Sarclisa is used in adults 18 years or older to treat a type of cancer called multiple myeloma. This is a cancer of your plasma cells which are found in your bone marrow.

Sarclisa is used together with two other medicines in patients who have received treatments for multiple myeloma before:

- pomalidomide and dexamethasone or
- carfilzomib and dexamethasone.

Sarclisa is used together with three other medicines in patients with a newly diagnosed multiple myeloma:

- bortezomib, lenalidomide, and dexamethasone.

How Sarclisa works:

Sarclisa is a cancer medicine that contains the active substance isatuximab (ee-sah-TUKS-i-mab). It belongs to a group of medicines called “monoclonal antibodies”.

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

The ingredients in Sarclisa are:

Medicinal ingredients: Isatuximab

Non-medicinal ingredients: Histidine, Histidine hydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injection

Sarclisa comes in the following dosage forms:

Sarclisa is provided as a concentrate that must be diluted and is then administered by intravenous infusion. It comes in vials. Each vial of 5 mL concentrate contains 100 mg of isatuximab (concentration of 20 mg/mL). Each vial of 25 mL concentrate contains 500 mg of isatuximab (concentration of

20 mg/mL).

Do not use Sarclisa if:

- You are allergic to isatuximab or any other ingredients in Sarclisa.

If you are not sure, talk to your doctor or nurse before you receive Sarclisa.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sarclisa. Talk about any health conditions or problems you may have, including if you:

- Are pregnant, think you might be pregnant, or are planning to have a baby. If you become pregnant while being treated with Sarclisa, tell your doctor or nurse immediately. You and your doctor will decide if the benefit of receiving Sarclisa is greater than the risk to your baby. Women who are being treated with Sarclisa must use effective contraception during treatment and for at least 5 months after treatment.
- Are producing breast milk. You and your doctor will decide if the benefit of breast feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known if it will affect the baby.
- Have had shingles (herpes zoster).

Other warnings you should know about:

Infusion-Related Reactions

Infusion-related reactions can happen during Sarclisa infusion or after the infusion and may be serious. Tell your doctor or nurse immediately if you feel unwell during or after infusion of Sarclisa. These symptoms may include:

- Feeling short of breath
- Cough
- Stuffy or runny nose
- Chills
- Nausea
- Vomiting

Severe symptoms of infusion reaction are less common, including:

- High blood pressure (hypertension)
- Low oxygen level in the blood (hypoxia)
- Low blood pressure (hypotension)
- Fast heartbeat (tachycardia)
- High level of blood sugar (hyperglycemia)
- Swollen face, lips, mouth, tongue or throat

If you have an infusion-related reaction, you may need other medicines to treat your symptoms, or the infusion may need to be slowed down or stopped. When these reactions go away or get better, the infusion can be started again.

Blood Transfusion

If you need a blood transfusion, you will have a blood test first to match your blood type. Sarclisa can affect the results of this blood test. Tell the person doing the test that you are using Sarclisa. Your doctor should do blood tests to match your blood type before you start treatment with Sarclisa.

Decreased Number of White Blood Cells
Sarclisa can decrease the number of your white blood cells, which are important in fighting infections. Your doctor will monitor for your white blood cells during Sarclisa treatment. You may receive other medications to treat low white blood cells. Your doctor may prescribe an antibiotic or antiviral medicine (for example, for herpes zoster) to help prevent infection, or a medicine to help increase your white blood cell counts during treatment with Sarclisa.

Infections
Sarclisa when combined with other drugs including pomalidomide and dexamethasone or carfilzomib and dexamethasone may increase the risk of infections. These infections can be severe or life-threatening. Tell your doctor right away if you have a fever or chill, feel very tired, have a cough or have flu-like symptoms.

Children and Adolescents
Sarclisa is not to be used in children and adolescents under the age of 18 unless part of a clinical trial.

Driving and Using Machines
Fatigue and dizziness have been reported by patients taking Sarclisa. If you experience side effects of this medicine, do not drive or use machines before discussing with your doctor, pharmacist or nurse.

Heart Problems
Sarclisa can cause heart problems and/or make your heart beat faster. Tell your doctor or nurse if you have any heart problems, or if you have ever taken a medicine for your heart. During Sarclisa treatment, if you feel your heart racing, an irregular heartbeat, dizziness, shortness of breath, chest pain, cough or leg swelling, contact your doctor or nurse immediately.

New Cancers
New cancers have happened in patients during treatment with Sarclisa. It is not clear if Sarclisa causesnew cancers. Your doctor will monitor you for new cancers.

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Tell your doctor or nurse before Sarclisa treatment if you have ever taken a medicine for your heart.

How to take Sarclisa:

- Your doctor or nurse will give you Sarclisa in your vein (intravenously) as a drip infusion.

Usual dose:

Your doctor will determine your dose of Sarclisa. This will depend on your body weight. The recommended dose is 10 mg of Sarclisa per kilogram of your body weight.

Sarclisa is used in treatment cycles of 28 days (4 weeks) together with either pomalidomide and

dexamethasone or carfilzomib and dexamethasone:

- In Cycle 1: Sarclisa is administered weekly on days 1, 8, 15 and 22
- In Cycle 2 and beyond: Sarclisa is administered every 2 weeks on day 1 and 15

When Sarclisa is used with three other medicines, bortezomib, lenalidomide, and dexamethasone, the treatment cycles last 42 days (6 weeks) from cycle 1 to 4 and last 28 days (4 weeks) from cycle 5 and onwards.

- In cycle 1: Sarclisa is administered on days 1, 8, 15, 22, and 29,
- From cycle 2 to 4: Sarclisa is administered every 2 weeks - on days 1, 15, and 29,
- From cycle 5 to 17: Sarclisa is administered every 2 weeks - on days 1 and 15,
- From cycle 18 and onwards: Sarclisa is administered every 4 weeks - on day 1.

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

Medicines given before an infusion of Sarclisa
You must receive the following medicines before infusion of Sarclisa to help reduce possible infusion-related reactions:

- Medicine to reduce allergic reactions (anti-histamine)
- Medicine to reduce inflammation (corticosteroid)
- Medicine to reduce pain and fever

Overdose:

Sarclisa will be given to you by your doctor or nurse. In the unlikely event that you are given too much (an overdose), your doctor will monitor you for side effects.

If you think you, or a person you are caring for, have taken too much Sarclisa, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is very important that you go to all your appointments to make sure your treatment works. If you miss any appointments, call your doctor or nurse as soon as possible to reschedule your appointment. Your doctor or nurse will decide how your treatment should be continued.

Possible side effects from using Sarclisa:

These are not all the possible side effects you may have when taking Sarclisa. If you experience any side effects not listed here, tell your healthcare professional.

- Headache
- Dizziness
- Feeling tired
- Decreased appetite
- Hiccups

- Runny or stuffy nose, sneezing, coughing, sore or scratchy throat (infection of the upper airways, such as nose, sinuses or throat)
- Nausea, vomiting
- Diarrhea
- Abdominal pain or discomfort
- Heartburn
- Swelling of the hands or legs
- Muscle, bone or joint pain
- Decreased body weight
- Feeling anxious
- Blurred vision
- High blood sugar
- Loss of bladder control (urinary incontinence)
- High blood pressure (hypertension)
- Hot flushes
- Covid-19
- Clouding of your eye (cataract)

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON (1 in 10 people)			
Cataract		✓	
Infusion-related reactions Symptoms can include one or more of the following: feeling short of breath, cough, stuffy or runny nose, chills, nausea, high blood pressure (hypertension), fast heartbeat, low blood pressure, swollen face, lips, mouth, tongue or throat.			✓
Low number of blood cells such as: • Platelets (thrombocytopenia) (symptoms like unusual bruising or bleeding) • White blood cells (neutropenia or lymphopenia) • Red blood cells (anemia) (symptoms like fatigue, loss of energy, weakness, shortness of breath)		✓	
Lung infection such as pneumonia, bronchitis, lower respiratory tract infections Symptoms can include congestion, cough (may produce phlegm), body ache, tiredness, wheezing, shortness		✓	

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
of breath, chest pain when breathing or cough, fever, sweating and chill, and confusion or change of mental awareness (mostly in older patients).			
Second primary malignancies		✓	
Shortness of breath		✓	
COMMON (less than 1 in 10, but more than 1 in 100)			
Herpes viral infection The infection can present as a cold sore. Symptoms can include a sore on the lip or in the mouth, painful blisters on the skin, fever, feeling tired, body ache, rash, or red spots and blisters over the entire body. The infection can also present as herpes zoster (shingles), a viral herpes infection affecting the nerves whose symptoms can include painful rashes of small blisters along a nerve path, arising in one or more affected areas.	✓		
Irregular or rapid heartbeat Symptoms can include heart racing, irregular heartbeat, dizziness, shortness of breath and chest pain.		✓	
Other cancers, most commonly cancers of the skin (e.g., squamous cell carcinomas) with some new solid tumours and blood cancers. The skin cancers may appear as a firm, red pumps, or flat sores with rough scaly patches on the skin, lips or inside the mouth		✓	
Pulmonary embolism. Symptoms can include sudden feeling short of breath, sharp chest pain, cough, heart racing, sweating, feeling anxious and fainting.			✓
Heart problems, which may present as difficulty breathing, cough, or leg swelling when Sarclisa is given with carfilzomib and dexamethasone		✓	
UNCOMMON (less than 1 in 100, but more than 1 in 1000)			
Serious allergic reaction (anaphylactic reaction), which may include rash, itching, difficulty breathing, shortness of breath, swelling of the face, mouth, throat, or tongue, cold, clammy skin,			✓

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
palpitations, dizziness, weakness or fainting			
FREQUENCY NOT KNOWN			
Tumour lysis syndrome (a fast breakdown of cancer cells): irregular heartbeat, convulsions, confusion, muscle cramps, or decrease in urine output			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Sarclisa should not be used after the expiry date which is stated on the label and carton.

Sarclisa should be stored in a refrigerator (2°C to 8°C), in its original package to protect from light.

Do not freeze.

Keep out of reach and sight of children.

If you want more information about Sarclisa:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; sanofi-aventis Canada website https://www.sanofi.com/en/canada/, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

Date of Authorization: 2025-04-17

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