EU-RISK MANAGEMENT PLAN FOR SARCLISA® (ISATUXIMAB)

Data Lock Point (DLP)	26-SEP-2023
Risk Management Plan (RMP) Version number	Version 2.1
Date of final sign-off	14-OCT-2024

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Alignment of indication based on response to Committee for Medicinal Products for Human Use (CHMP) Rapporteur assessment report (dated 02-Oct-2024) for type II variation extension of indication application (procedure EMEA/H/C/004977/0030) (IMROZ).
Summary of significant changes in this RMP	The following modules and annex have been updated with data supporting the new requested indication: Cover page, Part I; Part II SI and Part VI. Annex 8.

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	1.6
Approved with procedure	EMEA/H/C/004977/II/0026
Date of approval (opinion date)	22-Feb-2024

EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	Hadj Benzerdjeb[a], MD
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ACTH:	Adrenocorticotropic Hormone
ADA:	Anti-Drug Antibody
AE:	Adverse Event
ALT:	Alanine Aminotransferase
aRMM:	Additional Risk Minimization Measure
ASCT:	Autologous Stem Cell Transplant
ASIR:	Age-Standardized Incidence Rate
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
B/R:	Benefit/Risk
BBB:	Blood Brain Barrier
C1P1F1:	Cell 1, Process 1, Formulation 1
C1P2F2:	Cell 1, Process 2, Formulation 2
CD:	Cluster of Differentiation
CHMP:	Committee for Medicinal Products for Human Use
CHO:	Chinese Hamster Ovary
CI:	Confidence Interval
CNS:	Central Nervous System
CRS:	Cytokine Release Syndrome
CYP:	Cytochrome P450
DALA:	Drug Abuse Liability Assessment
DaraKd:	Daratumumab/Carfilzomib/Dexamethasone
DaraPd:	Daratumumab/Pomalidomide/Dexamethasone
DaraRd:	Daratumumab/Lenalidomide/Dexamethasone
DaraVd:	Daratumumab/Bortezomib/Dexamethasone
DaraVMP:	Daratumumab/Bortezomib/Melphalan/Prednisone
DaraVTD:	Daratumumab/Bortezomib/Thalidomide/Dexamethasone
DDI:	Drug-Drug Interaction
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
DRd:	Daratumumab/Lenalidomide/Low-dose Dexamethasone
DTT:	Dithiothreitol
ECG:	Electrocardiogram
ECO:	European Cancer Observatory
ECOG:	Eastern Cooperative Oncology Group
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
eGFR:	Estimated Glomerular Filtration Rate
EMEA:	European Medicines Agency
EPAR:	European Public Assessment Report
ESMO:	European Society for Medical Oncology
EU:	European Union
FSH:	Follicle Stimulating Hormone

GH:	Growth Hormone
GLOBOCAN:	Global Cancer Observatory
GLP:	Good Laboratory Practice
GVP:	Good Pharmacovigilance Practices
HBV:	Hepatitis B Virus
HCP:	Healthcare Professional
HIV:	Human Immunodeficiency Virus
HR:	Hazard Ratio
IARC:	International Agency for Research on Cancer
IAT:	Indirect Antiglobulin Test
ICH:	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG:	Immunoglobulin G
IMiD:	Immunomodulatory Agent
INN:	International Nonproprietary Name
IR:	Infusion Reaction
IRd:	Izaxomib/Lenalidomide/Low-dose Dexamethasone
Isa-kd:	Isatuximab/Carfilzomib/Dexamethasone
Isa-Pd:	Isatuximab/Pomalidomide/Dexamethasone
ISS:	International Staging System
IV:	Intravenous
IVRd:	Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone
Kd:	Carfilzomib/Dexamethasone
KRd:	Carfilzomib/Lenalidomide/Dexamethasone
LDH:	Lactate Dehydogenase
LH:	Luteinizing Hormone
mAb:	Monoclonal Antibody
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MM:	Multiple Myeloma
NCCN:	National Comprehensive Cancer Network
NDMM:	Newly Diagnosed Multiple Myeloma
NK:	Natural Killer
NOAEL:	No-Observed-Adverse-Effect Level
OR:	Odds Ratio
PASS:	Post-Authorization Safety Study
PCd:	Pomalidomide/Cyclophosphamide/Dexamethasone
PCL:	Plasma Cell Leukemia
Pd:	Pomalidomide/Dexamethasone
PFS:	Progression Free Survival
PI:	Proteasome Inhibitor
PK:	Pharmacokinetic
PL:	Package Leaflet
PSA:	Prostate Specific Antigen
PSUR:	Periodic Safety Update Report
PVd:	Pomalidomide/Bortezomib/Dexamethasone
QPPV:	Qualified Person Responsible for Pharmacovigilance

RBC:	Red Blood Cell
RCT:	Randomized Clinical Trials
Rd:	Lenalidomide/Dexamethasone
Rd-Elo:	Elotuzumab/Lenalidomide/Low-dose Dexamethasone
RhD:	Rhesus factor D
R-ISS:	Revised International Staging System
RMP:	Risk Management Plan
RMS:	Risk Minimization Strategy
RRMM:	Relapsed/Refractory Multiple Myeloma
Sd:	Selinexor/Dexamethasone
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
SPM:	Second Primary Malignancy
SVD:	Selinexor/Bortezomib/Dexamethasone
TLS:	Tumour Lysis Syndrome
TSH:	Thyroid Stimulating Hormone
UK:	United Kingdom
ULN:	Upper Limit of Normal
US:	United States
VCD:	Bortezomib/Cyclophosphamide/Dexamethasone
Vd-Pano:	Panobinostat/Bortezomib/Dexamethasone
VenVD:	Venetoclax/Bortezomib/Dexamethasone
VMP:	Bortezomib/Melphalan/Prednisone
VRd:	Bortezomib/Lenalidomide/Dexamethasone
VZV:	Varicella Zoster Virus

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Isatuximab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Antineoplastic agents, monoclonal antibodies (ATC code: L01FC02)
Marketing Authorization Holder (MAH)	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in European Economic Area (EEA)	Sarclisa
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Immunoglobulin G1 (IgG1) monoclonal antibody (mAb).
	Summary of mode action: Isatuximab binds to a specific extracellular epitope of cluster of differentiation (CD38) receptor and triggers several mechanisms leading to the death of CD38 expressing tumour cells.
	Important information about its composition: Isatuximab, Water for Injections, Sucrose, Histidine hydrochloride monohydrate, Histidine, Polysorbate 80. Isatuximab is a well-characterized recombinant protein product expressed in Chinese Hamster Ovary (CHO) cells manufactured without the direct use of animal-derived raw materials.
Hyperlink to the product information	Refer to electronic common technical document (e-CTD) sequence 0070, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	Current: Sarclisa is indicated: • in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy. • in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
	Proposed: Sarclisa is indicated: • in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. • in combination with carfilzomib and dexamethasone, for the treatment of adult

<table>
<tr><td></td><td>patients with multiple myeloma who have received at least one prior therapy.
• in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
The recommended dose of Sarclisa is 10 mg/kg body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone (isatuximab regimen), according to the schedule in the following Table 5a:
Table 5a - Sarclisa dosing schedule in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone
<table><tr><th>Cycles</th><th>Dosing schedule</th></tr><tr><td>Cycle 1</td><td>Days 1, 8, 15 and 22 (weekly)</td></tr><tr><td>Cycle 2 and beyond</td><td>Days 1, 15 (every 2 weeks)</td></tr></table>
Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.
For other medicinal products that are administered with Sarclisa, refer to the respective current SmPC.
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.</td></tr>
<tr><td></td><td>Proposed:
The recommended dose of Sarclisa is 10 mg/kg body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone (Isa-Pd) or in combination with carfilzomib and dexamethasone (Isa-Kd), or in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd), Sarclisa dosing schedules are provided in Table 5b and Table 5c:
Table 5b - Sarclisa dosing schedule in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone
<table><tr><th>Cycles</th><th>Dosing schedule</th></tr><tr><td>Cycle 1</td><td>Days 1, 8, 15 and 22 (weekly)</td></tr><tr><td>Cycle 2 and beyond</td><td>Days 1, 15 (every 2 weeks)</td></tr></table>
Table 5c - Sarclisa dosing schedule in combination with bortezomib, lenalidomide, and dexamethasone
<table><tr><th>Cycles</th><th>Dosing schedule</th></tr><tr><td>Cycle 1 (42-day cycle)</td><td>Days 1, 8, 15, 22, and 29</td></tr><tr><td>Cycles 2 to 4 (42-day cycles)</td><td>Days 1, 15, and 29 (every 2 weeks)</td></tr><tr><td>Cycles 5 to 17 (28-day cycles)</td><td>Days 1, 15 (every 2 weeks)</td></tr><tr><td>Cycles 18 and beyond (28-day cycles)</td><td>Day 1 (every 4 weeks)</td></tr></table>
Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.
For other medicinal products that are administered with Sarclisa, see section 5.1 and the respective current summary of product characteristics.</td></tr>
</table>

	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.
Pharmaceutical form(s) and strength(s)	Current: Concentrate for solution for infusion, 20 mg/mL.
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the European Union (EU)?	Yes

ATC: Anatomical Therapeutic Chemical; CD: Cluster of Differentiation; CHO: Chinese Hamster Ovary; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; IgG: Immunoglobulin G; INN: International Nonproprietary Name; Isa-Kd: Isatuximab/Carfilzomib/Dexamethasone; Isa-Pd: Isatuximab/Pomalidomide/Dexamethasone; Isa-VRd: Isatuximab/Bortezomib/Lenalidomide/Dexamethasone; mAb: Monoclonal Antibody; MAH: Marketing Authorization Holder; MM: Multiple Myeloma; PI: Proteasome Inhibitor; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Isatuximab is indicated:

- in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy.
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

The epidemiology of the disease is summarized in Table 6

Table 6 - Epidemiology of multiple myeloma

Indication	**Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant**
Incidence	The worldwide ASIR of multiple myeloma extracted from the Global Cancer Observatory in 2020 (1) was 1.78 (95% UI 1.69-1.87) per 100 000 people globally, corresponding to 176 404 new cases. The three world regions with the highest ASIR are Australia and New Zealand (4.86/100 000 persons; 95% UI: 4.66-5.07), North America (4.74/100 000 persons; 95% UI: 4.69-4.79) and Northern Europe (3.82/100 000 persons; 95% UI: 3.71-3.93). In 2019, the ASIR in Eastern Europe was 1.57 per 100 000 persons (95%UI: 1.35-1.78), 2.13 (95% UI: 1.69-2.46) in Central Europe, and 4.24 (95% UI: 3.51-4.90) in Western Europe. ASIR (per 100 000 persons) in High-income North America was 1.49 (95% UI: 4.12-5.87), in Tropical Latin America was 2.06 (95% UI: 1.78-2.22) and in Southern Latin America was 2.66 (95% UI: 2.08-3.41). ASIR lower than 1/100 000 were reported in Asia except in High-income Asia Pacific where ASIR was 1.96 (95% UI: 1.58-2.30) (2) Regarding trends, Huang et al (1) reported the highest European increase (average annual increase >4%) in Iceland, Denmark, Germany and Malta. In Asia, the highest increase was reported in Kuwait and Thailand. For the EU as a whole, MM incidence is projected to increase from approximately 35 000 new cases to over 43 000 by 2030. (3) RWD studies in France (4) (2013 - 2017) and in the US (5) (2011 - 2021) among adults newly diagnosed MM with a documented first-line therapy initiation reported that 71% and 76% of patients did not receive a ASCT. In the US study, ASCT was less frequent in patients aged 70 years or more than those aged less than 70 years (7% vs 45%). D'Agostino et al (6) published in 2023 a study of 10 843 NDMM patients included in RCTs from 2005 to 2016. Depending on studies, the proportion of NDMM patients not eligible to ASCT ranged from 35% to 47%.
Prevalence	The IARC using Globocan 2020 (7) reported a 5-year worldwide prevalence of 450 579, distributed as follows: • Asia: 150 210, • Europe: 138 083 • Northern America: 100 432

Indication	Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant
	• Latin America and Caribbean: 36 867 • Africa: 16 363 • Oceania: 8624. The 1-year prevalence of multiple myeloma in the EU, based on data from the IARC, was 4.3/100 000 population, resulting in approximately 39 517 cases. The estimated 10-year prevalence rate in 2016 available from the Nordic EU countries, Belgium and the UK are 31.8, 32.4 and 30.0/100 000 individuals. (IARC data) (8)
Demographics of the population in the authorized indication	**In Multiple Myeloma** Sex: The global ASIR reported from the GLOBOCAN statistics in 2020 (1) was 2.2/100 000 for males and 1.5/100 000 for females. Multiple Myeloma is approximately 1.5 times more common among men than in women. The cumulative risk of being diagnosed from birth to age 74 is 0.24% among men and 0.17% among women. (9) Age gradient: The crude incidence rates in 2018 were 1.6 per 10 000 and 24.4 per 10 000 in individuals aged 0-64 years and 64 years or more respectively. Multiple Myeloma is typically observed in older adults with the median age being 69 in the US. (9) In term of prevalence, the age group 65-85 years old represents about 65% of all prevalent cases (IARC). Ethnicity: Based on the US cancer registries, blacks showed a substantially higher incidence of MM than that of whites over the three decades (9.9/100 000 versus 4.2 in 1981-1990, 10.1 versus 4.3 in 1991-2000, and 9.9 versus 4.3 in 2001-2010), and people of other races showed the lowest MM incidence (3.1 in 1981-1990, 3.2 in 1991-2000, and 3.2 in 2001-2010). (10) The discrepancy is even higher among younger black patients below age 50 (over 3 times), indicating a younger onset of disease on average among black patients. In addition, there is a greater risk of mortality among black patients with MM in contrast to Caucasians. Asians and Pacific Islanders appeared to have a decreased risk of MM, with an incidence of 6.0/100 000 among men and 3.2/100 000 among women. (9) Older age, positive family history, male sex, black race, and genetic factors have been described as risk factors for the disease. Underlying germline predisposing mutations have yet to be determined in MM. (9) Monoclonal gammopathy of undetermined significance is a condition that precedes MM and is the most important factor associated with the development of MM. Regarding environmental factors, exposure to benzene, petroleum products, and ionizing radiation, as well as agricultural or industrial occupation have been acknowledged, whereas tobacco smoking, obesity, and dietary characteristics are probably less implicated. (11) About pregnancy: Multiple Myeloma is extremely uncommon during pregnancy. Hematologic malignancies represent 25% of the cancers complicating pregnancy. In women aged 15 to 24 years, the most frequent malignant tumour is Hodgkin's lymphoma and the second is leukemia with an incidence reported at 1:75 000 to 1:10 000. (12) **In Newly Diagnosed MM patients ineligible to Stem Cell Transplant (NDMM-TI)** The following table displays demographics (13) of 17 731 US NDMM patients aged 45 years and older identified in electronic health record (Medicare and Optum) who did not receive a stem cell transplantation and received at least one line of treatment between 2007 and 2018, and of 178 NDMM aged 65 years or older, considered not eligible to

<table>
<tr><td>Indication</td><td>Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant</td></tr>
<tr><td></td><td>ASCT by the treating physician and who were initiated with either a daratumab (DRd) or a bortezomib (VRd) triplet combination (TAURUS Chart review [14]).
Table 6a - Demographic characteristics of US NDMM-TI patients in claims databases
<table>
<tr><th></th><th>US HER (N = 17 731)</th><th colspan="2">TAURUS</th></tr>
<tr><th></th><th></th><th>DRd (N=99)</th><th>VRd (N=79)</th></tr>
<tr><td>Mean age ± SD [median]</td><td>71.0 ± 9.83</td><td>76.4 ± 6.0 [77.0]</td><td>75.8 ± 6.0 [75.0]</td></tr>
<tr><td>Women</td><td>49.5%</td><td>45.5%</td><td>55.7%</td></tr>
<tr><td>Ethnicity
White
Black / African American
Other or Unknown</td><td>Not available</td><td>
55.6%
13.1%
31.3%</td><td>
51.9%
19.0%
29.1%</td></tr>
</table>
SD: Standard Deviation; DRd: Daratumumab/Lenalidomide/Low-dose Dexamethasone; VRd: Bortezomib/Lenalidomide/Dexamethasone, NDMM-T1: Newly diagnosed Multiple Myeloma patients not eligible to Stem Cell Transplant; US: United States.</td></tr>
<tr><td>Main existing treatment options</td><td><u>Newly Diagnosed Multiple Myeloma (NDMM):</u>
ESMO GUIDELINES: recommendations for MM front-line therapy, no eligibility for ASCT (15)
<u>First option:</u>
• DaraRd [I, A]
• DaraVMP [I, A]
• VRd [I, A]
<u>If first option is not available:</u>
• VMP [I, A]
• Rd [I, A]
NCCN Guidelines: primary therapy for non-transplant candidates (16)
Preferred Regimens
• Bortezomib/lenalidomide/dexamethasone
• Daratumumab/lenalidomide/dexamethasone
Relapsed /Refractory Multiple Myeloma (RRMM)
ESMO GUIDELINES: Second-line options for MM patients who received VRd and Dara-based front-line therapies (15)
• Second-line options after VRd
– Lenalidomide-sensitive: KRd [I, A] / DaraRd [I, A] / EloRd [I, A] / PomVd [I, A] / DaraKd [I, A] / IsaKd [I, A] / IxaRd [I, A] / SVd [I, A]
– Lenalidomide-refractory: PomVd [I, A] / EloRd / DaraKd [I, A] / IsaKd [I, A] /</td></tr>
</table>

Indication	Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant
	SVd [I, A] – **Bortezomib-sensitive:** KRd [I, A] / DaraRd [I, A] / EloRd [I, A] / PomVd [I, A] / DaraKd [I, A] / DaraVd [I, A] / IsaKd [I, A] / SVd [I, A] / VenVd [I, A] – **Lenalidomide and bortezomib-refractory:** DaraKd [I, A] / IsaKd [I, A] • **Second-line options after DaraRD** – **Lenalidomide-sensitive**: PomVd / Kd / EloRd / KRd / IxaRd / SVd VenVd – **Lenalidomide-refractory:** PomVd/ Kd / SVd/ VenVd • **Second-line options after DaraVMP or DaraVTD** – **Bortezomib-sensitive:** EloRd / KRd/ IxaRd / VRd / SVd / Kd / VenVd – **Bortezomib-refractory:** EloRd **NCCN Guidelines: Therapy for previously treated MM Relapsed/Refractory disease after 1-3 prior therapies (16)** **Preferred Regimens** • **Bortezomib-refractory:** - Carfilzomib/lenalidomide/dexamethasone - Daratumumab/carfilzomib/dexamethasone - Daratumumab/lenalidomide/dexamethasone - Isatuximab-irfc/carfilzomib/dexamethasone - Carfilzomib/pomalidomide/dexamethasone *After one prior therapy including lenalidomide and a PI* • **Daratumumab/pomalidomide/dexamethasone** *After two prior therapies including lenalidomide and a PI* • **Isatuximab-irfc/pomalidomide/dexamethasone** • **Lenalidomide-refractory:** - Daratumumab/bortezomib/dexamethasone - Daratumumab/carfilzomib/dexamethasone - Isatuximab-irfc/carfilzomibldexamethasone - Pomalidomide/bortezomib/dexamethasone - Selinexor/bortezomib/dexamethasone - Carfilzomib/pomalidomide/dexamethasone - Elotuzumab/pomalidomide/dexamethasone

Indication	Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant
	After one prior therapy including lenalidomide and a PI • **Daratumumab/pomalidomide/dexamethasone** *After two prior therapies including lenalidomide and a PI* • **Isatuximab-irfc/pomalidomide/dexamethasone** *After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy.* • **Ixazomib/pomalidomide/dexamethasone**
Natural history of the indicated condition in the untreated population including mortality and morbidity	Although an overall decrease in mortality overtime was observed, the Multiple myeloma remains an incurable disease. Survival in hematological cancers (17) was studied in the Nordic European countries from 2012 to 2016. The study showed a relative 5-year survival in MM ranging from 43% in Finland to 55% in Denmark. Multiple Myeloma is a heterogenous disease characterized by subsequent relapses in which the burden of the disease and previous treatments received could limit subsequent lines of therapy, as described in treatment guidelines (18). The disease becomes more aggressive after each relapse and the time between relapses is shorter, which means less duration of response per late line of treatment that could lead into treatment refractoriness. Progression free survival is shorter after each treatment line and the prognosis of the patients gets worse. Increasing the duration of treatment at relapse has a positive impact in the overall survival and in the clinical evolution of the disease. A retrospective study of 598 Japanese newly diagnosed multiple myeloma patients not eligible for transplant (19) with a median follow-up of 31.3 months reported a median PFS ranging from 12.7 to 31.7 months depending on the treatment received. Overall Survival ranged from 43.9 to 79.8 months and was not reached in one treatment regimen. A French retrospective (20) study published in 2019 and assessing 200 RRMM patients showed that a half of RRMM patients were deceased after a median follow-up of 52 months. The median PFS from the second line treatment initiation was 21.4 (15.5; 25.0) months and the median OS was 59.4 (38.8; NE). Among patients initiating the 3rd line of treatment, the median PFS was 12.8 (9.0; 16.8) months and the median OS was 31.9 (23.4; 53.3) months. 20% to 25% MM patients will present with high-risk disease and 20% to 50% have renal impairment which are less responsive to the available treatment and continues to negatively impact PFS and OS, despite advances in treatment. **Staging:** Using Fluorescence in situ hybridization analysis as a part of the routine evaluation, high risk MM is defined as having at least one of the mutations related with poor prognosis including; t(4;14) t(14;16), t(14;20), del 17p, p53 mutation, gain 1q and del 1p. M-Smart MM risk stratification guidelines proposed by the Mayo Clinic describes the presence of two of the high-risk genetic abnormalities defined as double hit MM and having any three high-risk genetic abnormalities as triple hit MM. (21) The R-ISS is currently the common staging approach used to risk-stratify patients with NDMM and has been validated in several studies. Staging is based on the amount of albumin, beta-2-microglobulin, and LDH in the blood, as well as specific gene

Indication	Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant
	abnormalities (cytogenetics) of the cancer. However, the distribution of patients in R-ISS results in the majority being classified as intermediate. Incorporating cytogenic risk factors and an improved of prognostic implications of multi-hit disease, there is a new simple additive staging system available in patients with NDMM. (22) **Morbidity:** The risk of second primary cancers in MM survivors (23) (24) was assessed in cancer registries of Germany and Sweden, treated mainly with Melphalan ± autologous transplant. (25) Significantly elevated Standardized Incidence Ratios were observed for: • acute myeloid leukemia (standardized incidence ratios = 4.9 and 2.3 in Germany and Sweden respectively), • kidney cancer (2.3), • nervous system cancer (1.9). However, one study from Swedish registers indicated that patients with a prior malignancy diagnosis had a significantly increased risk of developing a subsequent malignancy compared with MM patients without a prior malignancy diagnosis (HR 1.42, 95% CI: 1.23-1.65). (26) In a most recent study, among 737 patients with newly diagnosed multiple myeloma not eligible for ASCT and randomly assigned to daratumumab plus lenalidomide and dexamethasone or to lenalidomide and dexamethasone, respectively 8.8% and 7.1% had developed a SPM after a 28-month follow-up and 20% and 13% after 56 months of follow-up. (23) (24) Overall, the risk of SPMs in MM is low, multifactorial, and partially related to the length of patients' survival and MM intrinsic susceptibility. Studies suggest a significantly increased incidence of SPMs when lenalidomide is administered either following, or concurrently with, oral melphalan. Increased SPM incidence has also been reported with lenalidomide maintenance following high-dose melphalan, albeit to a lesser degree. In both cases, the risk of death from MM was significantly higher than the risk of death from SPMs, with lenalidomide possibly providing a survival benefit. No increase in SPM incidence was reported with lenalidomide plus dexamethasone (without melphalan), or with bortezomib plus oral melphalan, dexamethasone, or thalidomide. (27) Drugs as Melphalan, as well as autologous transplant are less/not part of treatment strategy for MM patients not eligible for transplant. The profile of SPM will evolve with time and use of different drugs like immunomodulatory agents in front line setting. Infection is a significant cause of morbidity and the leading cause of death in patients with myeloma. The risk depends on the remission status of the underlying disease, type of therapy applied, extent of prior therapy, and presence of co-morbidities and organ dysfunctions and therefore, no estimate may be provided. (28) **Mortality:** **Newly diagnosed multiple myeloma risk of early mortality:** A study conducted in Asia involving patients with NDMM (N = 460) identified that being male, having primary PCL, plasma cells of bone marrow 60%, hemoglobin <10.0 g/dL, platelets <150 000/mL, low serum albumin (<3.5 g/dL), corrected serum calcium 12 mg/dL, serum creatinine 2 mg/dL, LDH 250 U/L, serum b2M 5500 mg/L, and ECOG 2 were significant predictors for early mortality in patients with MM. Infection was identified as the direct cause of early death in the majority of patients. (29) **Multiple Myeloma:** Despite the increase in incidence over the past decades in the US, mortality from MM has

Indication	Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant
	fallen due to the drastic increase in survival. In other words, a 2.27 increase in 5-year survival over the past decades, from 23.7% in 1976 to 53.9% in 2016. The current mortality of MM in the US (3.3/100 000) is 18% below the peak of 4.0/100 000 in 1994. Approximately 12 800 people were estimated to pass away in 2020 from MM, accounting for 2.1% of all cancer deaths. According to the SEER program, the overall mortality rate has dropped for all ages from 3.3/100 000 in 2013 to 3.2/10 000 in 2017, and in the greater than 65 age groups from 21.7/100 000 in 2013 to 20.5/100 000 in 2017. (9) Mortality from MM globally has risen by 94% from 1990 to 2016. In 2018, an estimated 106 000 people globally perished of MM, accounting for 1.1% of all cancer deaths. Approximately, 59 000 of those deaths were male and 47 000 were female, equaling an age-standardized mortality of 1.3/100 000 and 0.9/100 000, respectively. The median age of death is 75 with approximately 80% of deaths occurring in patients over the age of 65. (9) The ECO reports an age-standardized (European population) mortality rate of 2.5/100 000. The risk of death from MM (GLOBOCAN 2018) was 0.15% among men and 0.10% among women, which was similar to the sex discrepancies in cancer risk and indicated a similar survival between sexes from global estimates. (9) A German population-based study published in 2023 reported the following causes of death (displayed by ICD-10 chapter) in patients with multiple myeloma: • Multiple myeloma and plasma cell neoplasms (C90) 76.8% • Cardiovascular diseases (I00-I99) 7.0% • Non-myeloma malignancies (C00-D48, excluding C90) 6.1% • Respiratory diseases (J00-J99) 1.9% • Diseases of the genitourinary system (N00-N99) 1.1% • Certain infectious and parasitic diseases (A00-B99) 1.0% • Endocrine, nutritional and metabolic diseases (E00-E90) 0.8% • Gastrointestinal diseases (K00-K93) 0.8% • Mental and behavioural disorders (F00-F99) 0.3% • Diseases of the nervous system and sensory organs (G00-H95) 0.3% • Non-informative causes of death (R00-R94, R95-R99) 1.1% • Unknown 1.5%. **Survival:** The overall survival in patients with MM has greatly improved over the last two decades, especially with the broader use of novel drugs and autologous tandem transplantation. (29) The most recent 10-year survival figures are in the range of 20% (Swedish Registry) to 32.6% (German registries) with substantial differences across age groups. (30) (31) In France, the 5-year and 10-year survival reported over 2005-2010 were 47% and 27% respectively. There is a substantial age effect with a 5-year survival of 75% in 15-55 years old, 43% in 65-75 years old and 23% in 75 years old and more. (32)
Important co-morbidities	The most frequent co-morbidity is renal disease (OR 11.0, 95% CI: 8.1-14.9), based on a Danish nationwide population-based study. (33) In a Swedish nationwide study investigating the burden of comorbidities on patients diagnosed with MM over a 23-year period, patient survival from the Swedish Cancer Registry was investigated. Over half of the population (54% of 13 656 patients) had evidence of at least one comorbidity at diagnosis. Of those patients, 55.7% were male and

<table>
<tr><td>Indication</td><td>Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant</td></tr>
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44.3% were female, and the patients with a known comorbidity were generally older. Of all MM patients (N = 13 656), 24.6% had only one comorbidity listed at the MM diagnosis, 14.1% had two comorbidities, and 15.6% had three or more comorbidities at diagnosis. Of all MM patients under study, the most common comorbidities were the following (34):

Hypertension (20.4%)
Cancer (11.3%)
Arrhythmia (11.3%)
Chronic ischemic heart disease (9.2%)
Heart failure (9.2%)
Diabetes mellitus (8.4%)
Cerebrovascular disease (7.7%)
Psychological disease (6.1%)
Chronic lung disease (6.0%)

Based on a systematic literature search and random-effects meta-analysis over 34 studies (N = 3023) the most prevalent symptoms are (35):

Fatigue (98.8%, 95% CI: 98.1-99.2%);
Pain (73%, 39.9-91.7);
Constipation (65.2%, 22.9-92.2);
Tingling in the hands/feet (neuropathy) (53.4%, 0.4-99.7).

In Newly diagnosed MM patients not eligible to Stem Cell Transplant (NDMM-TI)
The following table displays main comorbidities (13) of 17 731 US NDMM patients aged 45 years and older identified in electronic health record (Medicare and Optum) who did not receive an autologous stem cell transplantation and received at least one line of treatment between 2007 and 2018, and of 178 NDMM aged 65 years or older, considered not eligible to ASCT by the treating physician and who were initiated with either a daratumab (DRd) or a bortezomib (VRd) triplet combination (TAURUS Chart review (14).
<table>
<tr><th rowspan="2"></th><th rowspan="2">US HER (N = 17 731)</th><th colspan="2">TAURUS</th></tr>
<tr><th>DRd (N=99)</th><th>VRd (N=79)</th></tr>
<tr><td>Mean Charlson comordidity Index (SD)</td><td>1.9 (2.3)</td><td>1.1 (1.4)</td><td>1.4 (1.4)</td></tr>
<tr><td>Hypertension</td><td>59.9%</td><td>71.7%</td><td>79.7%</td></tr>
<tr><td>Renal failure</td><td>30.5%</td><td>24.2%</td><td>26.2%</td></tr>
<tr><td>Diabetes</td><td>25.4%</td><td>16.2%</td><td>25.3%</td></tr>
<tr><td>Cardiac arrhythmia</td><td>23.1%</td><td>Not available</td><td>Not available</td></tr>
<tr><td>Chronic pulmonary disorders</td><td>18.5%</td><td>7.1%</td><td>13.9%</td></tr>
<tr><td>Congestive heart failure</td><td>16.7%</td><td>5.1%</td><td>6.3%</td></tr>
<tr><td>Hypothyroidism</td><td>14.9%</td><td>Not available</td><td>Not available</td></tr>
<tr><td>Valvular disease</td><td>12.8%</td><td>Not available</td><td>Not available</td></tr>
<tr><td>Peripheral neuropathy</td><td>11.2%</td><td>14.1%</td><td>11.4%</td></tr>
</table>
SD: Standard Deviation; DRd: Daratumumab/Lenalidomide/Low-dose Dexamethasone; VRd: Bortezomib/Lenalidomide/Dexamethasone, US: United States.
A review article examined the disease characteristics and demographics of patients with relapsed MM, focusing predominantly on those who have relapsed early in their treatment course (ie, after 1-3 prior lines of treatment) and who were enrolled in phase II or III
</td></tr>
</table>

Indication	Multiple Myeloma including relapsed, refractory and, newly diagnosed ineligible for autologous stem cell transplant
	interventional trials or observational studies (36): • Peripheral neuropathy is a common occurrence in patients with relapsed MM, resulting from complications of the disease and treatment related toxicities. Based on exclusion rate from clinical trials, the prevalence ranges from 36% to 83%. (36)

ASCT: Autologous Stem Cell Transplant; ASIR; Age-Standardized Incidence Rate; b2M: Beta-2 microglobulin; CI: Confidence Interval; DaraKd: Daratumumab/Carfilzomib/ Dexamethasone; DaraPd: Daratumumab/Pomalidomide/Dexamethasone; DaraRd: Daratumumab/Lenalidomide/Dexamethasone; DaraVd: Daratumumab/Bortezomib/Dexamethasone; DaraVMP: Daratumumab/Bortezomib/Melphalan/Prednisone; DaraVTD: daratumumab/bortezomib/thalidomide/dexamethasone; DRd: Daratumumab/Lenalidomide/Low-dose Dexamethasone; ECO: European Cancer Observatory; ECOG: Eastern Cooperative Oncology Group; EloRd: Elotuzumab/Lenalidomide/Dexamethasone; ESMO: European Society for Medical Oncology; EU: European Union; GLOBOCAN: Global Cancer Observatory; HR: Hazard Ratio; IARC: International Agency for Research on Cancer; IMiDs: Immunomodulatory Agents; IRd: Izaxomib/Lenalidomide/Low-dose Dexamethasone; Isa-Kd: Isatuximab/Carfilzomib/Dexamethasone; Isa-Pd: Isatuximab/Pomalidomide/Dexamethasone; Kd: Carfilzomib/ Dexamethasone; KRd: Carfilzomib/Lenalidomide/Dexamethasone; LDH: Lactate dehydrogenase; N: Number; MABs: Monoclonal Antibodies; MM: Multiple Myeloma; NCCN: National Comprehensive Cancer Network; NDMM: Newly Diagnosed Multiple Myeloma; NDMM-T1: Newly diagnosed Multiple Myeloma patients not eligible to Stem Cell Transplant; PomVd: Pomalidomide/Bortezomib/Dexamethasone; OR: Odds Ratio; PCd: Pomalidomide/Cyclophosphamide/Dexamethasone; PCL: Plasma Cell Leukemia; Pd: Pomalidomide/Dexamethasone; PFS: Progression Free Survival; PI: Proteasome Inhibitor; RCT: Randomized Clinical Trials; Rd: Lenalidomide/Dexamethasone; Rd-Elo: Elotuzumab/Lenalidomide/Low-dose Dexamethasone; R-ISS: Revised International Staging System; RWD: Real-World Evidence; Sd: Selinexor/Dexamethasone; SPM: Second Primary Malignancy; SVD: Selinexor/Bortezomib/Dexamethasone; UK: United Kingdom; US: United States; VCD: Bortezomib/Cyclophosphamide/Dexamethasone; VenVd: Venetoclax/Bortezomib/Dexamethasone; VMP: Bortezomib/Melphalan/Prednisone; VRd: Bortezomib/Lenalidomide/Dexamethasone; VTD: Bortezomib/Thalidomide/Dexamethasone; Vd-Pano: Panobinostat/Bortezomib/Dexamethasone.

RISK MANAGEMENT PLAN – PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Isatuximab is specific for the human CD 38 protein. Consequently, in the absence of a relevant animal species for toxicity testing or a relevant surrogate antibody, the overall non-clinical safety evaluation of isatuximab was limited to a repeat-dose intravenous (IV) (once weekly for 3 weeks) toxicity study in cynomolgus monkeys (preceded by a small exploratory study) in order to evaluate potential non-targeted and non-specific general toxicity, a local tolerance study in rabbits and an in vitro compatibility study with human whole blood and plasma.

In the repeat-dose (once weekly for 3 weeks) IV toxicity study conducted in cynomolgus monkeys (a non-pharmacologically-reactive species), isatuximab in its clinical formulation (cell 1, process 2, formulation 2 [C1P2F2]) did not produce compound-related changes in any parameters evaluated and the no-observed-adverse-effect level (NOAEL) was 100 mg/kg/week (highest dose tested).

Even if the cynomolgus monkey is not a pharmacologically reactive species, some safety pharmacology endpoints were evaluated in the weekly repeat-dose Good Laboratory Practice (GLP) IV toxicity study conducted with isatuximab in this animal species. No isatuximab-related effects were noted in this study on electrocardiogram (ECG) parameters, blood pressure, gross behavior profile (including body temperature) and respiratory function up to the highest dose tested of 100 mg/kg/week.

The local tolerance evaluation of isatuximab in its clinical formulation (cell 1, process 1, formulation 1 [C1P1F1]) in rabbits (a non-pharmacologically-reactive species) demonstrated that isatuximab was well tolerated after IV injections, the intended route of administration for clinical use, as well as after intramuscular, intra-arterial, subcutaneous or paravenous injections (non-intended routes that might occur accidentally) up to 5 mg/mL (the maximum concentration tested). In addition, isatuximab in its clinical formulation (C1P2F2) did not produce compound-related macroscopic or microscopic changes at the injection sites following once weekly IV infusion for 3 weeks in cynomolgus monkeys up to 20 mg/mL (the maximum concentration tested).

Isatuximab prepared in its clinical formulation (C1P1F1) did not induce hemolysis of human whole blood cells and was found to be compatible with human plasma up to a final concentration in blood or plasma of 2.5 mg/mL (the maximum concentration tested).

In addition, different in vitro studies were conducted to characterize the presence of CD38 on human blood cells and evaluate the in vitro biological effects of isatuximab on the different types of human blood cells, including the potential effects of isatuximab on cytokine release. Overall, no significant cytokine release, cellular activation, or depletion was induced by isatuximab in in vitro assays with normal human peripheral blood mononuclear cells, despite some induction of apoptosis in purified natural killer (NK) cells.

Based on a literature review on $CD38^{-/-}$ mice, main side effects noted in these knockout animals included deficiencies in humoral immune responses (37), impaired glucose tolerance and reduced

serum insulin level (38), reduced bone mineralization (39), deficits in learning and memory (40), impaired maternal nurturing behavior postpartum under stressful condition and impaired male social recognition. (41) However, data obtained in these genetically modified animals are only indicative of potential adverse effects and should be considered with caution. (42)

Target organs identification for potential toxicity in human could not be performed due to the lack of relevant animal species for isatuximab testing as well as lack of relevant animal surrogate antibody. Therefore, the identification of target organs for potential toxicity of isatuximab in humans is based on in vitro studies using human tissues. The GLP tissue cross-reactivity study using normal human tissues demonstrated isatuximab specific binding in the lymphoid tissues (spleen, thymus, lymph node, and tonsil) and in the bone marrow as expected, and in the pituitary gland (endothelial cells) and prostate gland (glandular epithelial cells). In addition, specific isatuximab binding was detected in infiltrating or resident round cells (macrophages and/or lymphocytes) in most tissues, including Kupffer's cells in the liver. In a previous non-GLP tissue cross-reactivity study using a different batch of isatuximab, additional staining was observed in the brain (astrocytes) and the lung (bronchial epithelium), but this was not reproduced in the GLP study. Staining of non-lymphoid tissue elements (prostate, pituitary gland, lung, and brain) was interpreted as evidence of cross-reactivity that may possibly indicate potential unintended target sites.

The presence of specific staining in some non-lymphoid human tissue elements as described above resulted, as a precautionary measure, in the implementation of systematic monitoring of the safety profile of isatuximab including the evaluation of prostate, pituitary and respiratory function before each infusion in the first-in-human Phase 1 single agent trial (TED10893) via the dosage of prostate specific antigen (PSA) levels, pituitary hormones levels (growth hormone [GH], follicle stimulating hormone [FSH]/luteinizing hormone [LH], adrenocorticotropic hormone [ACTH], thyroid stimulating hormone [TSH]) and the implementation of pulmonary function tests (Spirometry, Diffusion Capacity) and chest X-rays. Regarding the staining noted in the brain, no specific monitoring was conducted in patients, because isatuximab is unlikely to penetrate the blood-brain barrier (BBB) to any significant degree based on its large molecular size (molecular weight: about 150 000 Da) and the restrictive nature of the BBB.

No relevant laboratory abnormalities to the above listed tests and no adverse events (AEs) were reported suggesting an effect of the study treatment on these organs/functions. Therefore, those systematic laboratory assessments during study treatment were not considered necessary in the subsequent clinical studies.

The key non-clinical findings are presented in the following table:

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • **Key issues identified from Acute or repeat-dose toxicity studies** No relevant animal species for isatuximab toxicity testing or	Not relevant.

Key Safety Findings	Relevance to human usage
relevant surrogate antibody were available. In a repeat-dose (once weekly for 3 weeks) IV toxicity study conducted in cynomolgus monkeys (a non-pharmacologically-reactive species), isatuximab in its clinical formulation did not produce compound-related changes in any parameters evaluated and the NOAEL was 100 mg/kg/week (highest dose tested). • **Reproductive/developmental toxicity studies** As isatuximab is a biologic agent intended for the treatment of late-stage cancer patients, reproductive and developmental toxicity studies are generally not warranted with the exception of an embryofetal toxicology assessment. In the case of isatuximab and in the absence of a relevant animal species for non-clinical safety evaluation, no embryofetal toxicity studies were conducted. • **Genotoxicity** Monoclonal antibodies, such as isatuximab, are not expected to interact directly with DNA or other chromosomal material. Therefore, no genotoxicity studies were performed with isatuximab. • **Carcinogenicity** As isatuximab is a biologic agent intended for the treatment of late-stage cancer patients, carcinogenicity studies were not conducted.	Because of the absence of reproductive toxicity studies and clinical experience with the use of isatuximab in pregnant or women of childbearing potential not taking effective contraception, appropriate caution for use in the patients of reproductive ability is stated in the SmPC. Not relevant: it is not expected that biotechnology-derived pharmaceuticals would interact directly with DNA or other chromosomal material (ICH S6 R1) and no genotoxic effects are expected in humans. Second Primary Malignancies are considered AEs of special interest in the clinical studies of isatuximab administered in oncologic indications.
Immunogenicity Some ADAs were noted in monkeys with a batch of isatuximab beyond current shelf-life.	Immunogenicity following administration of human proteins in monkeys is known to be a poor predictor of similar responses in humans. Immunogenicity is a known class effect observed with other monoclonal antibodies, but risk of immunogenicity was expected to be low with isatuximab since isatuximab is a naked IgG1 antibody. No signal for autoimmune disorder has been identified during the clinical trials. No positive ADA samples were identified in the 151 evaluable patients during the on-treatment period for ICARIA (EFC14335) study, nor in the 168 evaluable patients during the on-treatment period for IKEMA (EFC15246) study, the incidence of ADA positive was 9.1% in 275 patients for IMROZ (EFC12522) study (global + Chinese expansion). In addition, among those with treatment-induced ADA, 15 had a neutralizing response resulting in an NAb incidence of 5.5%. Among the 383 patients with NDMM treated with isatuximab in combination with VRd and evaluable for ADA (with at least one treatment sample), the ADA incidence range from 9.1% to 21.6%, depending on the study. Although the ADA incidence is higher in NDMM patients compared to RRMM patients (<2%, N = 1023), the ADA + kinetics in NDMM patients exhibited the same pattern than those in RRMM patients: Most of the response were transient with only 1 out of the

Key Safety Findings	Relevance to human usage
	45 treatment-induced ADA positive patients showing persistent ADA kinetics and 3 patients with indeterminate ADA response with a median onset of 0.7 to 1 month. While no impact on PK was noted in the RRMM patients, a trend to lower exposure was observed in patients with ADA + across studies (ie $\leq$ 30% for AUC4W and CT4W in IMROZ). However, this impact of ADA was considered not clinically meaningful as no impact on safety and efficacy was evidenced. To conclude, a higher incidence of ADA + associated with an early onset observed in NDMM patients is likely attributed to a more immunocompetent status in NDMM patients compared to RRMM patients. As isatuximab is targeting B-cells that express CD38 and also produce ADA, these factors, together, explain the transient nature of ADA kinetics in both MM populations. Despite a trend to lower exposure in NDMM patients with ADA positive, no evidence of an impact of ADA could be demonstrated on safety and efficacy when isatuximab is given in combination with VRd.
Safety pharmacology Even if the cynomolgus monkey is not a pharmacologically-reactive species, some safety pharmacology endpoints were evaluated in the weekly repeat-dose GLP IV toxicity study conducted with isatuximab in this animal species. No isatuximab-related effects were noted in this study on ECG parameters, blood pressure, gross behavior profile (including body temperature) and respiratory function up to the highest dose tested of 100 mg/kg/week.	Isatuximab is not likely to cross the BBB, there is no clinical evidence of CNS effects and the potential for intentional misuse for illegal purpose is considered minimal (see [Part II Module SVI]). In addition, there were no preclinical findings on vital signs that would appear to have relevance to humans. No clinically meaningful changes of ECG parameters, blood pressure, body temperature, and respiratory function were observed from the analysis of the results of the randomized, controlled, Phase III studies EFC15246 (IKEMA), EFC14335 (ICARIA) or EFC12522 (IMROZ).
Other toxicity-related information or data • **In vitro tissue cross reactivity studies with normal human tissues** Isatuximab staining of the lymphoid tissues (spleen, thymus, lymph node, and tonsil) and in the bone marrow was expected. Staining of non-lymphoid tissue elements such as prostate, pituitary gland, lung and brain was interpreted as evidence of cross-reactivity that may possibly indicate potential unintended target sites.	The presence of specific staining in some non-lymphoid human tissue elements resulted, as a precautionary measure, in the implementation of systematic monitoring of the safety profile of isatuximab including the evaluation of prostate, pituitary and respiratory function before each infusion in the first-in-human Phase 1 single agent trial (TED10893) by monitoring PSA levels, pituitary hormones levels (GH, FSH/LH, ACTH, TSH) and implementing pulmonary function tests (Spirometry, Diffusion Capacity) and chest X-rays. Regarding the staining noted in the brain, no specific monitoring was conducted in patients, because isatuximab is unlikely to penetrate the BBB to any significant degree based on its large molecular size (molecular weight: about 150 000 Da) and the restrictive nature of the BBB. Staining of astrocytes in the brain and bronchial epithelium cells in the lungs, however, was not observed in the definitive GLP tissue cross-reactivity study. Furthermore, among the 89 patients treated in Study TED10893 Phase 1, laboratory abnormalities and AEs did not suggest evidence of an effect of the study treatment on these organ functions. Therefore, systematic

Key Safety Findings	Relevance to human usage
	laboratory assessments during study treatment have no longer been considered necessary in the subsequent clinical studies. Within the clinical trials experience with isatuximab, PSA and pituitary hormones were evaluated in Study TED10893 Phase 1. Fluctuations in the median values were observed in all treatment dose groups; the median of the last on-treatment value, however, was similar to the baseline. These fluctuations do not correspond to AEs suggesting no effect of the treatment on these organ functions. There was an increase in the incidence of dyspnea, all grade and grade $\geq$3 in both EFC14335 (ICARIA) and EFC15246 (IKEMA) studies, but these were mostly due to either pre-existing respiratory conditions, treatment emergent respiratory infections, or disease progression and dyspnea was therefore not considered an important independent risk. In study EFC12522 (IMROZ), there were less cases of dyspnea in the IVRd arm than in the VRD arm. Respiratory infections, as stated above, are known to occur with CD38 antibody treatment and are well managed with dose reductions, colony stimulating factors and anti-infective agents as needed. In these two trials, no AEs of the pituitary or prostate were observed that suggested an effect of the treatment on these organ functions.
• **Literature review on CD38 knockout mice** Main side effects noted in these CD38-/- animals included deficiencies in humoral immune responses, impaired glucose tolerance and reduced serum insulin level, reduced bone mineralization, deficits in learning and memory, impaired maternal nurturing behavior postpartum under stressful condition and impaired male social recognition.	Data obtained in genetically modified animals such as knockout mice are only indicative of potential effects and should be considered with caution because potential secondary and parallel effects from genetic manipulations may confound results. Knockout mice may have uncharacterized compensatory mechanisms or redundant pathways that are not readily apparent to replace the function of the absent protein or target. Finally, knockout mice that lack a target throughout embryogenesis and development may not accurately reflect the clinical scenario where the protein function may be nullified only during adulthood. Therefore, their use in assessing safety is more supportive rather than providing definitive safety data.

ACTH: Adrenocorticotropic Hormone; ADA: Anti-Drug Antibody; AE: Adverse Event; BBB: Blood Brain Barrier; CD: Cluster of Differentiation; CNS: Central Nervous System; DNA: Deoxyribonucleic Acid; ECG: Electrocardiogram; FSH: Follicle Stimulating Hormone; GH: Growth Hormone; GLP: Good Laboratory Practice; ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IgG: Immunoglobulin G; Isa-Pd: Isatuximab/Pomalidomide/Dexamethasone; IV: Intravenous; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; LH: Luteinizing Hormone; MM: Multiple Myeloma; N: Number; NDMM: Newly Diagnosed Multiple Myeloma; NOAEL: No-Observed-Adverse-Effect Level; PK: Pharmacokinetic; PSA: Prostate Specific Antigen; RRMM: Relapsed refractory multiple myeloma; SmPC: Summary of Product Characteristics; TSH: Thyroid Stimulating Hormone; VRd: Bortezomib/Lenalidomide/Dexamethasone.

No additional non-clinical data have been collected on the use of isatuximab in any special populations.

The analyses of safety data for the extension of indication in NDMM patients, are based on the following presentation strategy:

- Isa-VRD in patients with NDMM not eligible for transplant (Study EFC12522/IMROZ) global portion, excluding patients from Chinese expansion and data after crossover): Indication 3 in Tables below.
- All-Isa pool. The All-Isa pool aims to provide pooled safety data for NDMM patients (from Studies EFC12522/IMROZ, IIT15403 and TCD13983). This is further supplemented with comprehensive safety data from all studies in which patients were exposed to isatuximab including those with NDMM and RRMM. In these studies, a total of 1787 patients were treated with isatuximab.

Table 8 – Duration of exposure – Cumulative and by indication

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Number of patients treated by isatuximab	692	177	244	498	1787
Duration of exposure (n [%])					
At least 1 month	669 (96.7)	172 (97.2)	230 (94.3)	423 (84.9)	1656 (92.7)
At least 3 months	652 (94.2)	163 (92.1)	196 (80.3)	266 (53.4)	1395 (78.1)
At least 6 months	322 (46.5)	148 (83.6)	157 (64.3)	164 (32.9)	872 (48.8)
At least 9 months	310 (44.8)	134 (75.7)	131 (53.7)	110 (22.1)	743 (41.6)
At least 12 months	296 (42.8)	124 (70.1)	110 (45.1)	75 (15.1)	649 (36.3)
At least 15 months	283 (40.9)	110 (62.1)	97 (39.8)	46 (9.2)	572 (32.0)
At least 18 months	269 (38.9)	101 (57.1)	83 (34.0)	18 (3.6)	499 (27.9)
At least 21 months	264 (38.2)	90 (50.8)	70 (28.7)	13 (2.6)	461 (25.8)
At least 24 months	259 (37.4)	81 (45.8)	63 (25.8)	8 (1.6)	433 (24.2)
>24 months	259 (37.4)	81 (45.8)	63 (25.8)	8 (1.6)	433 (24.2)

Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR: Estimated Glomerular Filtration Rate, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_s_t.sas
OUT=REPORT/OUTPUT/cdc_isa_cat_p1_s_t_i.rtf (14FEB2024 9:35)
Note: Percentages are calculated using the number of patients treated as denominator.
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

Table 9 - Exposure by age group and gender – Cumulative and by indication

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Number of patients treated by isatuximab	692	177	244	498	1787
Gender [n(%)]					
Male	390 (56.4)	99 (55.9)	145 (59.4)	265 (53.2)	993 (55.6)
Female	302 (43.6)	78 (44.1)	99 (40.6)	233 (46.8)	794 (44.4)
Age group (years) [n(%)]					
<65	281 (40.6)	87 (49.2)	95 (38.9)	224 (45.0)	763 (42.7)
65-74	326 (47.1)	74 (41.8)	103 (42.2)	193 (38.8)	772 (43.2)
75-84	83 (12.0)	15 (8.5)	44 (18.0)	78 (15.7)	243 (13.6)
≥85	2 (0.3)	1 (0.6)	2 (0.8)	3 (0.6)	9 (0.5)

Note: Percentages are calculated using the number of patients treated as denominator.

Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.

PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_s_t.sas
OUT=REPORT/OUTPUT/cdc_isa_cat_p1_s_t_i.rtf (14FEB2024 9:35)

AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

Table 10 - Exposure by age group and gender (person-years) – Cumulative and by indication

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Isatuximab exposure (person-years)	1242.6	399.7	344.6	240.3	2388.5
Gender (person-years)					
Male	669.6	225.6	204.1	132.7	1314.5
Female	573.0	174.1	140.5	107.6	1074.0
Age group (years) (person-years)					
<65	157.1	195.1	136.6	96.1	628.2
65-74	831.7	176.2	154.1	91.1	1359.0
75-84	250.8	27.9	53.2	51.9	395.7
≥85	3.0	0.6	0.7	1.2	5.7

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**

Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
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OUT=REPORT/OUTPUT/cdc_isa_cat_py_p1_s_t_i.rtf (14FEB2024 9:36)
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

Table 11 - Exposure by ethnic origin – Cumulative and by indication

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Number of patients treated by isatuximab	692	177	244	498	1787
Ethnicity [n(%)]					
Hispanic or Latino	4 (0.6)	12 (6.8)	12 (4.9)	36 (7.2)	76 (4.3)
Not Hispanic or Latino	249 (36.0)	142 (80.2)	209 (85.7)	347 (69.7)	1083 (60.6)
Not Reported or Unknown	439 (63.4)	23 (13.0)	23 (9.4)	115 (23.1)	628 (35.1)

Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
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OUT=REPORT/OUTPUT/cdc_isa_cat_p1_s_t_i.rtf (14FEB2024 9:35)
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

Table 12 - Exposure by ethnic origin (person-years) – Cumulative and by indication

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Isatuximab exposure (person-years)	1242.6	399.7	344.6	240.3	2388.5
Ethnicity (person-years)					
Hispanic or Latino	13.5	31.6	12.3	21.3	85.1
Not Hispanic or Latino	818.6	316.1	312.3	178.5	1719.9
Not Reported or Unknown	410.6	52.0	20.0	40.6	583.6

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**

Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_py_s_t.sas
OUT=REPORT/OUTPUT/cdc_isa_cat_py_p1_s_t_i.rtf (14FEB2024 9:36)
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

Table 13 - Exposure by race – Cumulative and by indication

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Number of patients treated by isatuximab	692	177	244	498	1787
Race [n(%)]					
White	566 (81.8)	130 (73.4)	199 (81.6)	349 (70.1)	1386 (77.6)
Black or African American	4 (0.6)	5 (2.8)	6 (2.5)	25 (5.0)	53 (3.0)
Asian	56 (8.1)	25 (14.1)	23 (9.4)	61 (12.2)	175 (9.8)
Other	9 (1.3)	3 (1.7)	2 (0.8)	21 (4.2)	36 (2.0)
Not Reported or Unknown	57 (8.2)	14 (7.9)	14 (5.7)	42 (8.4)	137 (7.7)

Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_s_t.sas
OUT=REPORT/OUTPUT/cdc_isa_cat_p1_s_t_i.rtf (14FEB2024 9:35)
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

Table 14 - Exposure by race (person-years) – Cumulative and by indication

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Isatuximab exposure (person-years)	1242.6	399.7	344.6	240.3	2388.5
Race (person-years)					
White	849.0	289.8	289.7	163.9	1734.0

	Isatuximab				
	IVRd (N=692) (Indication 3)	**Ikd (N=177) (Indication 2)**	**Ipd (N=244) (Indication 1)**	**Isa (±Dex) (N=498)**	**All (N=1787)**
Black or African American	6.7	9.2	1.7	9.8	32.6
Asian	178.9	70.3	42.1	43.1	343.4
Other	22.0	7.3	2.0	8.2	40.6
Not Reported or Unknown	186.2	23.0	9.1	15.2	237.8

Note: Percentages are calculated using the number of patients treated as denominator.

Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.

PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_py_s_t.sas
OUT=REPORT/OUTPUT/cdc_isa_cat_py_p1_s_t_i.rtf (14FEB2024 9:36)

AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

RISK MANAGEMENT PLAN – PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 15 – Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not including as missing information)
Pregnant or breastfeeding females, or females who intend to become pregnant during the participation in a study.	To avoid potential harm to an unborn fetus or a newborn through exposure of drug from breast milk.	No	Not included as per CHMP request in initial dossier.
ICARIA (EFC14335): Patients with total bilirubin >2 × ULN; AST and/or ALT >3 × ULN. IKEMA (EFC15246): Patients with total bilirubin >1.5 × ULN; except for known Gilbert syndrome. IMROZ (EFC12522): Total bilirubin >1.5 × ULN, except for known Gilbert syndrome. AST and/or ALT >3 × ULN. TCD13983: AST and/or ALT ≥3 times normal level and/or serum bilirubin ≥1.5 × ULN if not due to hereditary abnormalities such as Gilbert's disease.	Based on the pomalidomide label, patients with bilirubin values >2 were not enrolled in their trials. Aspartate aminotransferase and ALT >3 was already in all protocols including the single agent TED10893 as there were no data.	No	Isatuximab is not cleared via hepatic clearance and no safety concern associated with the use of isatuximab in hepatic impaired patients is anticipated.
ICARIA (EFC14335): Renal function (eGFR) <30 mL/min/1.73 m^2 IKEMA (EFC15246): Renal function (eGFR) <15 mL/min/1.73 m^2 IMROZ (EFC12522): Renal function eGFR <30 mL/min/1.73 m^2 TCD13983: Patients with severe renal insufficiency (Creatinine Clearance <30 mL/min)	Impairment of renal function is an important complication of multiple myeloma, and a predictor of poor prognosis. For this reason, severe renal impairment was an exclusion criterion in study EFC14335, to ensure that the study patients had adequate renal function and to avoid confounding safety results in patients who may be requiring dialysis.	No	Based on population PK analyses using data from phase 1 to phase 3 studies (N = 823 patients), no dosage adjustment is necessary for patients with moderate and severe renal impairment. Approximately 33% of patients enrolled in study EFC14335 had moderate renal impairment (≥30 to <60 mL/min/1.73 m2) at baseline: no apparent difference in the safety profile could be observed in these patients. An eGFR of ≥30 to <60 mL/min/1.73 m^2 was present at baseline in 145/263 (55.1%) the isatuximab arm of study IMROZ (EFC12522).

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not including as missing information)
			An eGFR of <60 mL/min/1.73 m^2 was present at baseline in 65/331 (19.6%) the isatuximab arm of study TCD13983.
Significant cardiac dysfunction; myocardial infarction within 12 months; unstable, poorly controlled angina pectoris. IMROZ (EFC12522): Second/third degree heart block; Poorly controlled hypertension; Myocardial infarction; Severe/unstable angina pectoris;Coronary/peripheral artery bypass graft; New York Heart Association class III or IV congestive heart failure; Grade ≥3 arrhythmias, Stroke or transient ischemic attack. In the 6 months prior to randomisation. Left-ventricular ejection fraction <40%.	Patients with significant cardiac dysfunction were systematically excluded from trials with isatuximab in combination with pomalidomide, because of restrictions inherent to the use of pomalidomide. Based on the warning in the lenalidomide label that myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. In addition, these criteria ensure that in case of drug-induced cardiac complications, these effects can be detected without the interference of important confounding morbidities at baseline.	No	The absence of safety data in this population does not constitute a safety concern.
Known HIV+ status or hepatitis A, B or C active infection	These conditions interfere with CD4+ lymphocytes, weakening the immune system, and are known risk factors for infections, cancer, and mortality.	No	The absence of safety data in this population does not constitute a safety concern.
Any of the following within 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease,	Based on the carfilzomib label, there is a warning about thrombocytopenia, hemorrhage, and	No	The absence of safety data in this population does not constitute a safety concern. Isatuximab safety data does not indicate an imbalance of hemorrhage or

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not including as missing information)
diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.	thrombotic microangiopathy. Thrombocytopenia is a major dose limiting toxicity of lenalidomide and included in warnings and precautions in label, and physicians and patients are advised of increased risk of bleeding.		thrombotic events.
IMROZ (EFC12522): Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide (as an example: hereditary problems of galactose intolerance, Lapp lactose deficiency).	To ensure that lenalidomide is absorbed	No	The absence of safety data in this population does not constitute a safety concern.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CD: Cluster of Differentiation; CHMP: Committee for Medicinal Products for Human Use; eGFR: Estimated Glomerular Filtration Rate; HIV: Human Immunodeficiency Virus; PK: Pharmacokinetic; ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAM

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

- Rare adverse reactions should be understood as (≥1/10 000 to <1/1000).
- Adverse reactions with a long latency: While the duration of follow-up during a clinical study is normally not sufficient to detect adverse reactions with a long latency (with a long interval between the last administration and the onset of the adverse reaction), post-treatment adverse events are systematically monitored using routine pharmacovigilance. However, the extended follow ups of the RRMM trials and the NDMM program included patients with longer exposure.
- Adverse reactions caused by prolonged or cumulative exposure: The median exposure to isatuximab in the pool of isatuximab clinical studies from the integrated summary of safety with data cut-off of 26 September 2023 (including RRMM and NDMM studies) was 24.36 weeks, and the maximum exposure was 299.0 weeks. A total of 27.9% (499 patients) had exposure for ≥18 months and 24.2% (433 patients) for >24 months. No adverse events from cumulative drug exposure, which suggest off-target organ effects, have been observed during the clinical development program. Diseases that develop with long cumulative exposure or with long latency, such as SPMs have been observed in the clinical study

program and will also be monitored using routine pharmacovigilance. Although SPMs have been observed more frequently in the isatuximab arm of several studies the exposure adjusted differences are less marked and the rate currently observed in the pooled database (6.0%) is below the upper end of the range of frequencies reported in multiple myeloma studies (1.7% to 6.6%).

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAM

Table 16 - Exposure of special populations included or not in clinical trial development programmes

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Pregnant women</td><td rowspan="2">Not included in the clinical development program</td></tr>
<tr><td>Breastfeeding women</td></tr>
<tr><td>Pediatric patients</td><td>Not included in the clinical development program</td></tr>
<tr><td>Elderly patients</td><td>
<table>
<tr><th></th><th colspan="5">Isatuximab</th></tr>
<tr><th></th><th>IVRd (N = 692)</th><th>IKd (N = 177)</th><th>IPd (N = 244)</th><th>Isa (±Dex) (N=498)</th><th>All (N=1787)</th></tr>
<tr><td>Number of patients treated by isatuximab</td><td>692</td><td>177</td><td>244</td><td>498</td><td>1787</td></tr>
<tr><td>Age group (years) (n [%])</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td><65</td><td>281 (40.6)</td><td>87 (49.2)</td><td>95 (38.9)</td><td>224 (45.0)</td><td>763 (42.7)</td></tr>
<tr><td>65-74</td><td>326 (47.1)</td><td>74 (41.8)</td><td>103 (42.2)</td><td>193 (38.8)</td><td>772 (43.2)</td></tr>
<tr><td>75-84</td><td>83 (12.0)</td><td>15 (8.5)</td><td>44 (18.0)</td><td>78 (15.7)</td><td>243 (13.6)</td></tr>
<tr><td>≥85</td><td>2 (0.3)</td><td>1 (0.6)</td><td>2 (0.8)</td><td>3 (0.6)</td><td>9 (0.5)</td></tr>
</table>
Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
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ICARIA (EFC14335): A population PK analysis using data form Phase 1 to 3 studies from 476 patients aged 36-85 years old (14.7% of patients in the dataset were ≥75 years of age) has demonstrated no effect on isatuximab PK in this elderly population.
IKEMA (EFC15246): Pharmacokinetics data from IKEMA study confirmed no meaningful impact of age on isatuximab exposure (N = 15, 8.7% of patients in the</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td></td><td>dataset were ≥75 years of age). No dose adjustments are considered necessary. In addition, no clinically meaningful differences could be seen in safety on the basis of age.

IMROZ (EFC12522): Furthermore, the pharmacokinetics data from IMROZ study confirmed no meaningful impact of age on isatuximab exposure (N = 68, 24.2% of patients in the dataset were ≥75 years of age). No dose adjustments are considered necessary. An increase in Grade 5 TEAEs was observed in patients in the IVRd group ≥70 years of age compared to those <70 years of age. This appears to have been due to an increase in COVID-19 related infections during the first two years of the COVID-19 pandemic and may also have been related to imbalances of certain risk factors such as, ISS stage.</td></tr>
<tr><td>Patients with relevant co-morbidities
• Patients with hepatic impairment</td><td>
<table>
<tr><th></th><th colspan="5">Isatuximab</th></tr>
<tr><th></th><th>IVRd (N=692)</th><th>IKd (N=177)</th><th>IPd (N=244)</th><th>Isa (±Dex) (N=498)</th><th>All (N=1787)</th></tr>
<tr><td>Number of patients treated by isatuximab</td><td>692</td><td>177</td><td>244</td><td>498</td><td>1787</td></tr>
<tr><td>Hepatic status (n [%])</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Normal</td><td>605 (87.4)</td><td>160 (90.4)</td><td>213 (87.3)</td><td>402 (80.7)</td><td>1532 (85.7)</td></tr>
<tr><td>Mild impairment</td><td>74 (10.7)</td><td>15 (8.5)</td><td>31 (12.7)</td><td>63 (12.7)</td><td>203 (11.4)</td></tr>
<tr><td>Moderate impairment</td><td>1 (0.1)</td><td>2 (1.1)</td><td>0</td><td>1 (0.2)</td><td>7 (0.4)</td></tr>
<tr><td>Severe impairment</td><td>1 (0.1)</td><td>0</td><td>0</td><td>0</td><td>1 (<0.1)</td></tr>
</table>
Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin <=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_s_t.sas OUT=REPORT/OUTPUT/cdc_isa_cat_p1_s_t_i.rtf (14FEB2024 9:35)
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

ICARIA (EFC14335): A population PK analysis with data form Phase 1 to 3 studies (N = 476 patients) has demonstrated no effect of mild hepatic insufficiency on isatuximab PK.

IKEMA (EFC15246): In addition, IKEMA PK data (N = 15, 8.7% of the patients with mild hepatic insufficiency) confirmed no meaningful impact on mild hepatic insufficiency on isatuximab exposure. No dose adjustments are considered necessary in this patient population.

IMROZ (EFC12522): Furthermore, IMROZ PK data (N = 22, 7.8% of the patients with mild hepatic insufficiency) confirmed no meaningful impact on mild hepatic insufficiency on isatuximab exposure, confirming that no dose adjustment is considered necessary in this patient population.</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>• Patients with renal impairment</td><td>
<table>
<tr><th></th><th colspan="5">Isatuximab</th></tr>
<tr><th></th><th>IVRd (N=692)</th><th>IKd (N=177)</th><th>IPd (N=244)</th><th>Isa (±Dex) (N=498)</th><th>All (N=1787)</th></tr>
<tr><td>Number of patients treated by isatuximab</td><td>692</td><td>177</td><td>244</td><td>498</td><td>1787</td></tr>
<tr><td>Renal status (mL/min/1.73m^2) (n [%])</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Normal</td><td>180 (26.0)</td><td>37 (20.9)</td><td>43 (17.6)</td><td>102 (20.5)</td><td>395 (22.1)</td></tr>
<tr><td>Mild impairment</td><td>316 (45.7)</td><td>83 (46.9)</td><td>98 (40.2)</td><td>191 (38.4)</td><td>774 (43.3)</td></tr>
<tr><td>Moderate impairment</td><td>131 (18.9)</td><td>39 (22.0)</td><td>87 (35.7)</td><td>143 (28.7)</td><td>447 (25.0)</td></tr>
<tr><td>Severe impairment</td><td>8 (1.2)</td><td>4 (2.3)</td><td>2 (0.8)</td><td>16 (3.2)</td><td>30 (1.7)</td></tr>
<tr><td>End stage</td><td>0</td><td>0</td><td>0</td><td>2 (0.4)</td><td>2 (0.1)</td></tr>
</table>
Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m^2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_s_t.sas OUT=REPORT/OUTPUT/cdc_isa_cat_p1_s_t_i.rtf (14FEB2024 9:35)
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal.

ICARIA (EFC14335): A population PK analysis with data from Phase 1 to Phase 3 studies (N = 476 patients) has demonstrated no effect of mild, moderate and severe renal impairment on isatuximab PK.

IKEMA (EFC15246): Pharmacokinetic data from IKEMA study confirmed no meaningful impact of renal function on Isatuximab exposure. However, it could be noted a trend towards lower exposure in the 5 patients with severe renal impairment, but these patients had confounding baseline characteristics that are known to impact isatuximab PK (ie, β2 microglobulin levels at baseline ≥5.5 mg/L with 3 patients were classified ISS III and 2 as ISS II). In addition, no clinically meaningful differences could be seen in safety. Therefore, no dose adjustments are considered necessary in this population.

IMROZ (EFC12522): In addition, the pharmacokinetic data from IMROZ study confirmed no meaningful impact of renal function on isatuximab exposure (N=69;24.6% of the patients with moderate renal insufficiency and N=5, 1.8% of the patients with severe renal impairment). Except for subsequent events of chronic kidney disease, no clinically meaningful differences could be seen in safety. Altogether, no dose adjustments are considered necessary in this population.
</td></tr>
<tr><td>• Patients with significant cardiovascular impairment</td><td>Not included in the clinical development program.</td></tr>
<tr><td>• Immunocompromised patients</td><td>Not included in the clinical development program.</td></tr>
</table>

Type of special population	Exposure
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Populations with relevant different ethnic origin	

	Isatuximab				
	IVRd (N=692)	**IKd (N=177)**	**IPd (N=244)**	**Isa (+/- Dex) (N=498)**	**All (N=1787)**
Number of patients treated by isatuximab	692	177	244	498	1787
Race (n[%])					
White	566 (81.8)	130 (73.4)	199 (81.6)	349 (70.1)	1386 (77.6)
Black or African American	4 (0.6)	5 (2.8)	6 (2.5)	25 (5.0)	53 (3.0)
Asian	56 (8.1)	25 (14.1)	23 (9.4)	61 (12.2)	175 (9.8)
Other	9 (1.3)	3 (1.7)	2 (0.8)	21 (4.2)	36 (2.0)
Not Reported or Unknown	57 (8.2)	14 (7.9)	14 (5.7)	42 (8.4)	137 (7.7)
Ethnicity (n[%])					
Hispanic or Latino	4 (0.6)	12 (6.8)	12 (4.9)	36 (7.2)	76 (4.3)
Not Hispanic or Latino	249 (36.0)	142 (80.2)	209 (85.7)	347 (69.7)	1083 (60.6)
Not Reported or Unknown	439 (63.4)	23 (13.0)	23 (9.4)	115 (23.1)	628 (35.1)

Note: Percentages are calculated using the number of patients treated as denominator.
Note: Hepatic status is defined as follows, Normal: Total bilirubin <= ULN and AST <= ULN, Mild: ULN< Total Bilirubin<=1.5×ULN and AST = Any or Total Bilirubin <=ULN and AST >ULN, Moderate: 1.5×ULN < Total Bilirubin <=3×ULN and AST = Any, Severe: Total Bilirubin >3×ULN and AST = Any. Renal status (eGFR, mL/min/1.73m2) is defined as follows, Normal: >=90, Mild: >=60 to <90, Moderate: >=30 to <60, Severe: >=15 to <30, End stage renal disease: <15.
PGM=PRODOPS/SAR650984/SAR650984POOL5/POOL5/REPORT/PGM/cdc_isa_cat_s_t.sas OUT=REPORT/OUTPUT/cdc_isa_cat_p1_s_t_i.rtf (14FEB2024 9:35).
AST: Aspartate Aminotransferase; Dex: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; ULN: Upper Limit of Normal..

ICARIA (EFC14335): Pharmacokinetic analysis with data from Phase 1 to 3 studies (N = 476 patients)) has identified race (Asian versus non-Asian) as a significant covariate influencing isatuximab PK. However, as the impact was limited to V_1 (ie, 24% lower in a typical Asian patient compared to a typical non-Asian patient), it did not translate into a meaningful impact on exposure to require dose adjustment.

IKEMA (EFC15246): Data from IKEMA study confirmed no meaningful impact of race (Asian versus non-Asian) on isatuximab exposure (N = 26, 13.2% of the dataset).

Data from **IMROZ (EFC12522)** study confirmed no meaningful impact of race (Asian versus non-Asian) on isatuximab exposure. However, a trend to lower

Type of special population	Exposure
	exposure (ie ,28%) was observed in Asian patients (N=54, 19.2% of the dataset) compared to Caucasian patients. However, there is a trend of a lower exposure in Chinese patients (N=30) but not in Japanese (N=17). These Chinese patients had confounding baseline characteristics as these patients presented slightly more advanced disease characteristics (ie, more patients with ISS-III), and slightly lower body weight which may have amplified the effect.
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development program. To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of isatuximab in the currently proposed indication(s).

AST: Aspartate Aminotransferase; COVID-19: Coronavirus Disease 2019; DEX: Dexamethasone; eGFR: Estimated Glomerular Filtration Rate; ECOG: Eastern Cooperative Oncology Group; IKd: Isatuximab in combination with Carfilzomib and low-dose Dexamethasone; IPd: Isatuximab in combination with Pomalidomide and Dexamethasone; Isa: Isatuximab; ISS: International Staging System; IVRd: Isatuximab in combination with bortezomib, lenalidomide and dexamethasone; PK: Pharmacokinetic; TEAEs: Treatment Emergent Adverse Events; ULN: Upper Limit of Normal.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

The MAH is currently utilizing the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience since December 2019. The MARCO application collects data monthly, as a result, the data may not correspond precisely to the current reporting interval but to 30 September 2023.

Methodology.

Total patients exposed were estimated assuming that all vials sold have been used and that each patient, with an average body weight of 73.8 kg, received a mean of nine cycles of chemotherapy with isatuximab at the dosage of 10 mg/kg given four times in first cycle and two times in subsequent cycles and at 89.67% dose intensity, as recommended in the reference document effective during the reference period ie, -

Cycle 1: 10 mg/kg × 73.8 kg × 4 infusions = 2952 mg.

Cycles 2 to 9: 10 mg/kg × 73.8 kg × 2 infusions per cycle × 8 cycles = 11 808 mg.

A total of 14 760 mg expected per patient for all nine cycles, the total drug received per patient is 14 760 × 0.8967 (dose intensity) equals to 13 235 mg/patient or 13.2 g/patient for all nine cycles. The total number of patients exposed were calculated by dividing total sales in grams with 13.2 g.

SV.1.2 Exposure

Cumulatively up to 30 September 2023, 18 749 patients have been exposed to isatuximab in the postmarketing setting.

	ISATUXIMAB						ISATUXIMAB Total
	CONCENTRATE SOLUTION (INFUSION)		INFUSION, LIQUID (SOLUTION)		INJECTION, LIQUID (SOLUTION)		
COUNTRY	100 MG/5 ML	500 MG/25 ML	100 MG/5 ML	500 MG/25 ML	100 MG/5 ML	500 MG/25 ML	
[redacted]	2003	1259					3262
	4572	3381					7953
	5246	2832					8078
	4346	1709					6055
	24 008	13 801					37 809
	673	450					1123
	30	10					40
	3976	2486					6462
	58 873	65 502	2740	2			127 117
	12	4					16

	ISATUXIMAB						ISATUXIMAB Total
	CONCENTRATE SOLUTION (INFUSION)		INFUSION, LIQUID (SOLUTION)		INJECTION, LIQUID (SOLUTION)		
COUNTRY	100 MG/5 ML	500 MG/25 ML	100 MG/5 ML	500 MG/25 ML	100 MG/5 ML	500 MG/25 ML	
[redacted]	35 285	23 248					58 533
	1448	1373					2821
	194	175					369
	130	135					265
	2	2					4
	180	108					288
	30 600	21 698					52 298
					99 204	72 187	171 391
	112	53					165
	2	2					4
		60					60
	236	778					1014
	527	516					1043
	1714	1291					3005
	3903	2332					6235
	56	14					70
	55	38					93
	856	683					1539
	1761	809	0	0			2570
	42	22					64
	732	605	118				1455
	48	16					64
	12 041	6995					19 036
	48	34					82
	783	1456					2239
	137	321					458
	142	1002					1144
	22 572	12 737					35 309
	37	19					56
	2696	1606					4302
	39	15					54
	5	2					7
	551	406					957
	71 470	47 621					119 091
	146 063	93 407	10 965	3525			253 960

	ISATUXIMAB						ISATUXIMAB Total
	CONCENTRATE SOLUTION (INFUSION)		INFUSION, LIQUID (SOLUTION)		INJECTION, LIQUID (SOLUTION)		
COUNTRY	100 MG/5 ML	500 MG/25 ML	100 MG/5 ML	500 MG/25 ML	100 MG/5 ML	500 MG/25 ML	
Grand Total	438 206	311 013	13 823	3527	99 204	72 187	937 960
Sales in mgs	43 820 600	155 506 500	1 382 300	1 763 500	9 920 400	36 093 500	
Total sales in mgs	247 486 80						
Total sales in grams	247 486.8						
Total patients exposed	18 749						

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

A drug abuse liability assessment (DALA) study was not performed with isatuximab as the compound has only a limited ability to cross the BBB with negligible exposure in the brain. Potential for misuse of isatuximab for illegal purposes is considered low as this product is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use, such as known pharmacological addictive effects.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Besides the standard recommendations in the RMP guidance, the following topics were considered as safety concerns because of the nature and mechanism of action of the biological product (IgG mAb), as class effects or because of common concerns in the target population. These safety concerns, however, were assessed as either not relevant to isatuximab based on the currently available clinical evidence or not benefiting from additional pharmacovigilance or additional risk minimization activities. These non-important safety concerns, evaluated in Section SVII.1.1, are as follows:

- Immunogenicity
- Decrease in NK cells
- Intravascular haemolysis
- Infections
- Infusion reactions (IRs) including cytokine release syndrome (CRS)
- Effect on QTc interval
- Respiratory adverse events
- Drug-Drug interactions (DDIs)
- Tumor lysis syndrome (TLS)
- Second primary malignancies (SPMs)

The following safety topics were considered important for inclusion in the list of safety concerns in the initial RMP version 0.1. They are discussed in section SVII.1.2.

- **Important identified risk**
  - Interference with indirect antiglobulin test (indirect Coombs' test) and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay, transfusion haemolysis)
- **Important potential risk**
  - Viral reactivation
- **Missing information**
  - None

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

Risks known to be associated with other therapeutic IgG1 mAbs, but assessed as not relevant to isatuximab and its benefit/risk balance, based on the currently available evidence or which would not benefit from additional risk minimization activities or from further evaluation:

- *Immunogenicity:*

In Study EFC14335, no evidence of immunogenicity was demonstrated through ADA positivity. In the clinical experience prior to Study EFC14335, no clinical impact on the risk-benefit profile could be demonstrated. The incidence of treatment emergent ADAs was low (2.3%) and most of these responses were transient, with only 2 out of the 13 treatment-induced ADA positive patients showing persistence (0.35%), in the data pooled across the single agent and combination studies (N = 564).

- *Decrease in NK cells:*

Decrease in NK cells is only one of the laboratory changes observed during immunoprofiling of peripheral blood immune cell subsets during Isa-Pd treatment (eg, also a decrease in neutrophil count - see Module 5.3.5.1 [Study EFC14335] - and an increase in CD3+ T-cells was noted - see Module 5.3.5.3 [tcd14079-immune-biomarker-report]). It is therefore unclear what the isolated effect of decrease in NK cells on the safety profile of the Isa-Pd regimen is. No AE of decrease in NK cells was reported in the isatuximab program.

- *Intravascular haemolysis:*

No red blood cells (RBCs) transfusion-related complications associated with interference for blood typing were reported during any of the clinical trials.

- *Infections:*

In the controlled, randomized Study EFC14335, neutropenia and infections were more frequent in the Isa-Pd arm than in the Pd (control) arm; the incidence of infections leading to definitive treatment discontinuation, or leading to fatal outcome, however, were similar between the treatment arms (2.6% in Isa-Pd versus 4.0% in Pd). When adjusted for the longer duration of exposure in the Isa-Pd arm, the incidence of treatment-emergent serious infections was also similar (0.72 versus 0.67 incidence rate per patient year in the Isa-Pd and Pd arms, respectively. The risk of infections is well recognized, characterized, and adequately managed (with the use of colony stimulating factors, dose reductions of pomalidomide and dexamethasone, and antibiotic/antiviral agents) according to the product information.

- *Infusion reactions including cytokine release syndrome:*

Infusion reactions are well recognized as a very common class effect of mAbs: throughout the isatuximab program, they have occurred in 46.2% of the patients with limited clinical impact: a Grade 3 severity has been reported in 2.6% of the patients, while Grade 4 IRs are uncommon (0.9%). The onset of an IR occurs most frequently (in 97.0% of the patients) at the 1st infusion, and most patients (89.1%) do not experience further episodes at subsequent infusions of isatuximab. Overall, IRs led to dose interruptions of isatuximab in 33.9% of patients and to treatment discontinuation of isatuximab in 3.3% of the patients (required by protocol if Grade 3 or higher). Infusion reactions are well managed with pre-infusion prophylaxis, monitoring of symptoms, and dose interruption, medications, or permanent discontinuation of the treatment. Thus, the risk of IRs is well-characterized and its management in the target population is well

understood, and it would not benefit from additional pharmacovigilance or risk minimization activities besides routine measures.

- *Respiratory adverse events:*

In preliminary non-GLP tissue cross-reactivity studies using a different isatuximab batch and different mAb concentrations, additional staining was also observed in the lung (bronchial epithelium). Staining of all non-lymphoid tissue elements was interpreted as evidence of cross-reactivity, indicating potential unintended off-target sites (see [Part II SII]), of isatuximab that included the evaluation of respiratory function before each infusion in the first-in-human Phase 1 single agent trial (TED10893) via the implementation of pulmonary function tests (spirometry, diffusion and capacity) and chest X-rays. In Study EFC14335, notwithstanding a higher incidence of dyspnea in the Isa-Pd arm, the occurrence of clinically meaningful dyspnea was not different between the treatment arms: the incidence of severe dyspnea was not substantially different between the two arms (Grade ≥3: 9.2% in Isa-Pd versus 6.7% in the Pd control arm), and the incidence of serious treatment emergent dyspnea was also not substantially different (2.6% in Isa-Pd versus 1.3% in Pd).

Risk with minimal clinical impact on patients

- Effect on QTc interval:

The potential for an effect on QTc interval was systematically considered as a theoretical risk during the clinical development of isatuximab. (43) Among the completed studies throughout the isatuximab program, no reports of ECG QT interval abnormal, ECG QT prolonged, long QT syndrome, torsade de pointes, or ventricular tachycardia occurred as AEs. Furthermore, a thorough analysis of ECG monitoring data collected in Study TED10893 Phase 1 does not suggest any clinically meaningful QTcF prolongation induced by isatuximab at any dose level.

Other risks considered as not important

- *Drug-drug interactions:*
  - Effect of isatuximab on other drugs: Direct DDI via cytochrome P450 (CYP) enzymes or transporters is not expected because isatuximab is a mAb. However, potential risks of DDI caused by isatuximab due to the alteration of cytokine levels, especially interleukin 6, which has been shown to impact drug metabolizing enzymes, such as CYP enzymes in humans, were taken into consideration. Given the extent and transient nature of isatuximab-induced cytokine elevation, its impact on exposures to CYP450 substrates is likely to be limited. Isatuximab does not alter the pharmacokinetics of lenalidomide, pomalidomide, or cyclophosphamide.
  - Effect of drugs on isatuximab: Isatuximab, a mAb, is likely to be eliminated by proteolytic degradation, thus drugs that impact CYP or transporter expressions are not anticipated to alter the pharmacokinetic of isatuximab. No impact of high dose dexamethasone, lenalidomide/dexamethasone, pomalidomide/dexamethasone, cyclophosphamide/bortezomib/dexamethasone, has been observed on isatuximab pharmacokinetic.

Overall, isatuximab does not alter the pharmacokinetics of, lenalidomide, pomalidomide, or cyclophosphamide and vice-versa, indicating a lack of DDI between isatuximab and these combination drugs.

- *Tumor lysis syndrome:*

  The risk of TLS will be closely monitored and further characterized via routine pharmacovigilance activities. No additional pharmacovigilance and/or risk minimization activities is proposed for the risk of TLS. Tumor lysis syndrome is not included in the list of safety concerns in the RMP, consistent with the European Guideline on Good Pharmacovigilance Practices (GVP), Module V Rev. 2.

- *Second primary malignancies:*

  The risk of SPMs will be closely monitored and further characterized via routine pharmacovigilance activities. No additional pharmacovigilance and/or risk minimization activities is proposed for the risk of SPMs. Second primary malignancies is not included in the list of safety concerns in the RMP, consistent with the European Guideline on GVP, Module V Rev. 2.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 17 - Important identified risk considered for inclusion in the list of safety concerns: Interference with indirect antiglobulin test (indirect Coombs' test) and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay, transfusion haemolysis)

Interference with indirect antiglobulin test (indirect Coombs' test) and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay, transfusion haemolysis)	
Scientific evidence that has led to the inclusion	Isatuximab binds to endogenous CD38 found at low levels on RBCs and may interfere with blood bank compatibility testing, including antibody screening and cross-matching. Lack of RBC phenotyping prior to isatuximab treatment could result in delaying a transfusion because of the need to address false positive indirect Coombs' test results. In the case of an urgent transfusion, using non-cross-matched ABO/RhD-compatible RBC could result in a small risk of transfusion-related haemolysis. No RBC transfusion-related complications associated with interference with blood typing were reported during any of the clinical trials.
Risk-benefit impact	Considering the clinical setting in which the patients are being treated, the fact that no haemolysis associated with RBC transfusions has been observed in clinical trials with isatuximab, and consequently the low likelihood of this risk to result in important clinical outcomes, the impact on the risk-benefit balance is deemed to be limited.

CD: Cluster of Differentiation; RBC: Red Blood Cell; RhD: Rhesus factor D.

Table 18 - Important potential risk considered for inclusion in the list of safety concerns: Viral reactivation

Viral Reactivation	
Scientific evidence that has led to the inclusion	In the case of MM, both the underlying disease and some chemotherapeutic agents used to treat it (such as corticosteroids) may cause immunosuppression that predisposes to viral reactivation. Reactivated viruses may include Herpes zoster or HBV. Hepatitis B Virus reactivation has uncommonly been observed, including fatal cases, for another anti-D38 mAb which, like isatuximab targets CD38 that is used in similar combination regimens that may cause immunosuppression.

Viral Reactivation	
Risk-benefit impact	Given the improved survival outcome in patients with RRMM, it is likely that reactivation of a viral disease will have limited impact on the B/R balance.

B/R: Benefit/Risk; CD: Cluster of Differentiation; HBV: Hepatitis B Virus; mAb: Monoclonal Antibody; MM: Multiple Myeloma; RRMM: Relapsed/Refractory Multiple Myeloma.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

There are no new safety concerns compared to the previous version of the RMP.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following important risks and missing information have been identified for isatuximab:

- Important identified risk:
  - Interference for blood typing (minor antigen) (positive indirect Coombs' test)
- Important potential risk:
  - Viral reactivation
- Missing information:
  - None

SVII.3.1 Presentation of important identified risks and important potential risks

Table 19 - Identified risk: Interference for blood typing (minor antigen) (positive indirect Coombs' test)

Identified risk	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
Potential mechanism	Human RBCs express low levels of CD38 compared to MM cells, and binding of isatuximab to endogenous CD38 has been found on RBCs, causing panreactivity in vitro. (44) Thus, isatuximab may interfere with routine blood bank compatibility tests. This interference is limited to the minor blood groups (not affecting the ABO and Rh typing).
Evidence source(s) and strength of evidence	Class effect: isatuximab binds to RBCs and may interfere with routine blood bank compatibility tests. Interference for blood typing has occurred during clinical trials.
Characterization of the risk	Lack of RBC phenotyping prior to isatuximab treatment could result in delaying a transfusion because of the need to address false positive indirect Coombs' test results. In the case of an urgent transfusion, using non-cross-matched ABO/RhD-compatible RBC could result in a small risk of transfusion-related haemolysis. There is no in vitro haemolytic effect or plasma incompatibility when isatuximab was mixed with human blood in the non-clinical safety studies. In Study ICARIA (EFC14335), the indirect Coombs' test was positive on treatment in 67.7% of the tested Isa-Pd patients; no RBC transfusion complications or haemolysis were observed and no cases of transfusion related haemolysis has been observed. In study IKEMA (EFC15246), the indirect Coombs' test was positive during study

Identified risk	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
	treatment in 63.3% of patients among the 150 patients in the Isa-Kd arm with negative test at baseline and at least one test during study treatment. No cases of hemolysis were reported among the patients with positive indirect Coombs' test who received transfusions. In study IMROZ (EFC12522), the indirect Coombs' test was positive during treatment in 136 (51.7%) patients amongst the 222 patients in the IVRd arm with a negative test at baseline and at least one test during study treatment. There were no reports of haemolysis within 8 days of a blood transfusion.A search of the isatuximab GPV database from the IBD of 2-Mar-2020 until 26-Sep-2023 for the SMQ hemolytic disorders retrieved 13 cases (9 unsolicited including 1 literature, and 4 solicited). There was one case of a post-platelet transfusion reaction (transfusion reaction) in an [redacted] old male, with an unknown latency of drugs isatuximab, pomalidomide, dexamethasone. All drugs were continued and the event resolved. This event is not related to this risk which refers to red blood cell reactions. There have therefore been no events fulfilling the criteria for this risk in the postmarketing setting. Background incidence/prevalence: Interference and risk of transfusion related haemolysis is specific to human monoclonal IgG1 κ antibody against CD38 antigen, and does not occur in untreated patients with MM. No transfusion-related cases of haemolysis were identified in the global safety database for daratumumab. (45)
Risk factors and risk groups	Patients with MM may require blood transfusions (occurred in 30% of the patients in the isatuximab arm of the study ICARIA (EFC14335),26% of the patients in the isatuximab arm of the study IKEMA (EFC15246) and 20.5% of patients in the isatuximab arm of the study IMROZ (EFC12522), because of morbidity from MM and its treatment.
Preventability	All the isatuximab study protocols contain instructions about phenotyping of patients before the start of treatment with isatuximab. In the postmarketing setting, educational material distributed to healthcare professionals (HCPs) and blood banks (See [Part V] and [Annex 6] for details) are proposed to increase awareness about the risk of interference and the possible resulting adverse clinical consequences for the patient and provide guidance on how to minimize it: • Recommendation for the patients to be blood-typed and screened prior to initiating treatment with isatuximab; phenotyping according to local practice; • Use of DTT treated reagent RBCs (44) (or any locally validated methods); • Use of a patient card to inform any HCPs treating a patient that he/she is using isatuximab and that this treatment is associated with the risk of interference.
Impact on the benefit-risk balance of the product	Low impact. No delays in blood transfusions or haemolysis associated with RBC transfusions was observed in clinical trials.
Public health impact	Low impact. No event of haemolysis associated with RBC transfusions have been observed in clinical trials, or the postmarketing setting. Educational materials are provided to HCPs. No significant public health impact is expected.

CD: Cluster of Differentiation; DTT: Dithiothreitol; GPV: Global Pharmacovigilance; HCP: Healthcare Professional; IBD: International Birth Date; IgG: Immunoglobulin G; Isa-Kd: Isatuximab/Carfilzomib/Dexamethasone; Isa-Pd: Isatuximab/Pomalidomide/Dexamethasone; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; MM: Multiple Myeloma; RBC: Red Blood Cell; Rh: Rhesus; RhD: Rhesus factor D; SMQ: Standardized MedDRA Query.

Table 20 - Potential risk: Viral Reactivation

Potential risk	Viral Reactivation
Potential mechanism	Immunosuppression either by the underlying MM disease process or by the immunosuppressive action of drugs used to MM, such as dexamethasone may predispose to viral reactivation. (46)
Evidence source(s) and strength of evidence	Viral reactivation has been identified for another anti-CD38 antibody approved for the treatment of MM.
Characterization of the risk	No cases of HBV viral reactivation have been observed to date associated with isatuximab in the clinical development program. One case of HBV reactivation was reported from TCD13983 study but on MAH review of the case it was noted that the patient had IgM Hepatitis B antibodies and therefore this was not a reactivation. Herpes zoster was reported in 15 (5.7%) patients receiving isatuximab in the IMROZ (EFC12522) study with similar exposure adjusted rates in the two groups (IVRd vs VRd: 0.017 v 0.20 events per person-years). In the integrated summary of safety analyses, 2.1% of patients (n=11) in the VRD group and 2.5 % of patients (n=45) in the "All isatuximab group" (NDMM and RRMM) were reported to have PT: herpes zoster infection. There were an additional two cases of PT: Herpes Zoster disseminated in the All isatuximab group. Cases of other viruses have been observed in patients exposed to isatuximab in the clinical development program (ie, cytomegalovirus, Epstein-Barr virus, adenovirus). A search of the isatuximab safety database from IBD of 2-Mar-2020 until 26-Sep-2023 for the following HLTs: Adenoviral infections; Cytomegaloviral infections; Epstein-Barr viral infections; Herpes viral infections; Papilloma viral infections; Retroviral infections; Polyomavirus infections; Hepatitis virus infections retrieved 69 cases. There were 37 events in 36 case reports of viral reactivation including Herpes Zoster, and including non-sponsored clinical trial reports there were 24 cases (7 solicited Non-sponsored, 7 solicited other, 7 unsolicited non-literature and 3 Japan Non clnical trial solicited). There were 9 cases of CMV reactivation, 1 of Epstein-Barr Reactivation, 6 of Hepatitis B reactivation, 7 Herpes Zoster and 1 of Herpes Simplex reactivation. In none of the 6 cases of Hepatitis B reactivation there were laboratory evidence provided to assess/confirm the diagnosis. For one case the regimen was not provided but for the other 5, all were on regimens containing different combinations of dexamethasone, lenalidomide, bortezomib or carfilzomib. <u>Background incidence/prevalence:</u> Viral infections are now the most frequently reported infections in MM (47). Individuals diagnosed with MM are reported to have a 10fold higher risk of developing a viral infection and a 15-fold higher risk of herpes zoster infection compared to general population controls (48). The rate of VZV infection in the daratumumab arms of the pivotal studies for relapsed/refractory myeloma ranged from 2% to 5%. (49) Data on 148 patients from daratumumab clinical trials were combined showed that 2% of patients developed herpes zoster. (50)
Risk factors and risk groups	<u>Documented previous viral exposure:</u> • For HBV: serology; • For Herpes Zoster: clinical evidence of varicella zoster exposure (eg, shingles); • Any other viruses: standard evidence of viral exposure. <u>Immunosuppression</u>: • History of previous treatment with immunosuppressive drugs such as high dose corticosteroids; (46) • Clinical or laboratory data supportive of immunosuppression.

Potential risk	Viral Reactivation
Preventability	• Hepatitis B virus status (by clinical history or previous serology) should be documented at baseline. - For patients with evidence of positive HBV serology, manage according to local or national clinical guidelines; - In patients who develop reactivation of HBV while on isatuximab, suspend treatment with isatuximab and institute appropriate treatment; - Resumption of isatuximab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV. • All known exposures to any viruses capable of reactivation should be documented and managed according to local or national guidelines.
Impact on the benefit-risk balance of the product	Low impact.
Public health impact	Low impact. Hepatitis B virus status can be obtained at baseline and treated according to local and national guidelines. (51) Patients with a history of Herpes zoster or other viruses can be managed according to local or national guidelines.

CD: Cluster of Differentiation; CMV: Cytomegalovirus; HBV: Hepatitis B Virus; HLT: High-level term; IBD: International Birth Date; IVRd: Isatuximab in combination with Bortezomib, Lenalidomide and Dexamethasone; MAH: Marketing Authorization Holder; MM: Multiple Myeloma; NDMM: Newly Diagnosed Multiple Myeloma; PT: Preferred Term; VRd: Bortezomib/Lenalidomide/Dexamethasone; RRMM: Relapsed Refractory Multiple Myeloma; VZV: Varicella Zoster Virus.

SVII.3.2 Presentation of the missing information

Not applicable

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
Important potential risk	Viral reactivation
Missing information	None

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The following routine pharmacovigilance activity beyond adverse reactions reporting and signal detection is in place:

- Specific adverse reaction follow-up questionnaire for “Viral reactivation”.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities ongoing or planned for this product. Completed post-authorization safety studies (PASS) are presented in [Annex 2].

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities ongoing or planned for this product.

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for isatuximab.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 21 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	**Routine risk communication:** SmPC section 4.5. PL section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2).
Viral reactivation	**Routine risk communication:** SmPC section 4.8. PL section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.2 and 4.4. **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2).

HCP: Healthcare Professional; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 22 - Additional risk minimization measures

HCPs and blood banks brochure	
Objectives	Increase awareness about the risk of interference and its possible adverse clinical consequences for the patient and provide guidance on how to manage it. Re-inforce the communication between HCPs (hematologists, oncologists, nurses etc.), blood transfusion centers/banks, laboratory and patients and share reliable and prompt information.
Rationale for the additional risk minimization activity	Future prescribers/dispensers/other HCPs are not all aware of the risk of interference, its possible adverse clinical consequences for the patient and its management has not become clinical practice everywhere (especially in peripheral centers).

HCPs and blood banks brochure	
Target audience and planned distribution path	Target audience: • HCPs who are expected to prescribe and dispense isatuximab (eg, oncologists, hematologists, nurses etc.). • Blood banks/transfusion centers. Planned distribution path: • Mail, e-mail or face to face distribution.
Plans to evaluate the effectiveness of the interventions and criteria for success	A PASS survey of effectiveness was conducted between May-2022 and Jun-2023. Based on the PASS survey results, the overall effectiveness of aRMM is considered satisfactory and no change in the current RMS is needed (CHMP Positive Opinion received on 11-Jan-2024).
Patient card	
Objectives	Inform the HCPs/Blood banks treating the patient at any time, including in conditions of emergency, that the patient is using isatuximab and that this treatment is associated with the risk of interference with IAT.
Rationale for the additional risk minimization activity	Ensure that any HCPs/Blood banks treating a patient are aware that the patient is taking isatuximab.
Target audience and planned distribution path	Target audience/ Planned distribution path: Patients will receive the card at the time of the initial dispensation by the treating HCP who will show the card to the patient and explain objective, content and how to use it.
Plans to evaluate the effectiveness of the interventions and criteria for success	A PASS survey of effectiveness was conducted between May-2022 and Jun-2023. Based on the PASS survey results, the overall effectiveness of aRMM is considered satisfactory and no change in the current RMS is needed (CHMP Positive Opinion received on 11-Jan-2024).

aRMM: Additional Risk Minimization Measure; CHMP: Committee for Medicinal Products for Human Use; HCP: Healthcare Professional; IAT: Indirect Antiglobulin Test; PASS: Post-Authorization Safety Study; RMP: Risk Management Plan; RMS: Risk Minimization Strategy.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 23 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	**Routine risk minimization measures:** SmPC sections 4.4 and 4.5. PL section 2. **Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2). **Additional risk minimization measures:** Healthcare Professionals and blood banks educational material (brochure) and patient card.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Viral reactivation	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8. PL section 2. **Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2). **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire. **Additional pharmacovigilance activities:** None

HCP: Healthcare Professional; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN – PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Sarclisa (Isatuximab)

This is a summary of the RMP for Sarclisa. The RMP details important risks of Sarclisa how these risks can be minimized, and how more information will be obtained about Sarclisa's risks and uncertainties (missing information).

Sarclisa's SmPC and its PL give essential information to HCP and patients on how Sarclisa should be used.

This summary of the RMP for Sarclisa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Sarclisa's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Sarclisa is authorized:

- in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

  in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Sarclisa is proposed:

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

It contains isatuximab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Sarclisa's benefits can be found in Sarclisa's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/sarclisa

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Sarclisa, together with measures to minimize such risks and the proposed studies for learning more about Sarclisa's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCP;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Sarclisa, these measures are supplemented with aRMMs mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Sarclisa are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Sarclisa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 24 - List of important risks and missing information

Important identified risk	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
Important potential risk	Viral reactivation
Missing information	None

II.B Summary of important risks

Table 25 - Important identified risk: Interference for blood typing (minor antigen) (positive indirect Coombs' test) with corresponding risk minimization activities and additional pharmacovigilance activities

Interference for blood typing (minor antigen) (positive indirect Coombs' test)	
Evidence for linking the risk to the medicine	Class effect: isatuximab binds to RBCs and may interfere with routine blood bank compatibility tests. Interference for blood typing has occurred during clinical trials.
Risk factors and risk groups	Patients with MM may require blood transfusions (occurred in 30% of the patients in the isatuximab arm of the study ICARIA (EFC14335),26% of the patients in the isatuximab arm of the study IKEMA (EFC15246) and 20.5% of patients in the isatuximab arm of study IMROZ (EFC12522), because of morbidity from MM and its treatment.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.4 and 4.5. PL section 2. **Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2). **Additional risk minimization measures:** Healthcare Professionals and blood banks educational material (brochure) and patient card.

HCP: Healthcare Professional; MM: Multiple Myeloma; PL: Package Leaflet; RBC: Red Blood Cell; SmPC: Summary of Product Characteristics.

Table 26 - Important potential risk: Viral reactivation with corresponding risk minimization activities and additional pharmacovigilance activities

Viral reactivation	
Evidence for linking the risk to the medicine	Viral reactivation has been identified for another anti-CD38 antibody approved for the treatment of MM.
Risk factors and risk groups	Documented previous viral exposure: • For HBV: serology; • For Herpes Zoster: clinical evidence of Herpes simplex exposure (eg, shingles); • Any other viruses: standard evidence of viral exposure. Immunosuppression: • History of previous treatment with immunosuppressive drugs such as high dose corticosteroids; (46) • Clinical or laboratory data supportive of immunosuppression.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8. PL section 2. **Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2). **Additional risk minimization measures:** None

CD: Cluster of Differentiation; HBV: Hepatitis B Virus; HCP: Healthcare Professional; MM: Multiple Myeloma; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Sarclisa.

II.C.2 Other studies in post-authorization development plan

There are no studies for Sarclisa.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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Isatuximab (*Sarclisa*®) – Infection

Targeted Follow-up Form (coversheet)

Please provide the below requested information in the dedicated sections of the support used to provide the data (i.e., safety collection form or Sanofi Portal).

- **Suspect Product(s):**

  - The following information on the patient's isatuximab dosing regimen prior to the infection:
    - Start date
    - Dosing regimen

- **Concomitant Medicines (e.g., drugs, devices, vaccines):**

  - All concomitant medications the patient was taking including prescription medications, over the count products, dietary supplements, vitamins, and herbs at time of event onset.

- **Medical History/Risk Factors:**

  - Pregnancy status
  - Does the patient have a history of the following conditions? If yes, provide date of onset, treatment with dates, other details:
    - Hepatitis B
    - Hepatitis C
    - Cytomegalovirus
    - Shingles (herpes Zoster, varicella zoster virus reactivation)
  - Provide other relevant medical or social risk factors for blood borne pathogen exposure.

- **Description of the Reported Event(s)/Clinical Course:**

  - Race/ethnicity of the patient
  - Provide the infection diagnosis (i.e. HIV, Hepatitis B, Hepatitis C, other) and date of diagnosis.
  - Was the patient's infection diagnosed prior to the first dose of isatuximab? State if unknown.
  - The time elapsed between the first dose of isatuximab and onset of infection
  - The time elapsed between the last dose of isatuximab and onset of infection
  - Was isatuximab temporarily or permanently discontinued because of the infection event? If so, specify the date, reason, and whether the infection event improved, resolved, or abated.
    - Was isatuximab later resumed? If so, specify the date, dosing regimen, and whether the infection event recurred or worsened after restarting.
  - If isatuximab was discontinued, what was the patient's regimen after the event (provide product name, dose, and frequency)?
  - Provide details on the chief complaint and any presenting symptoms and signs, relevant findings including onset dates.
  - Was the patient hospitalized or required an ER visit? If yes, provide the ER/ hospitalization diagnosis, date(s) of hospitalization, and a copy of the discharge report or provide details, if available.
  - Attach or list the management/treatment (e.g., products, procedures, dates) of the infection
  - Provide the outcome of the infection event (recovered, not yet recovered, recovered with sequelae, unknown, and death) and date of resolution if applicable.

    - If the patient recovered with sequelae, describe the sequelae.
    - If the outcome was death, provide a copy of the death certificate and autopsy results.
- Attach or provide additional information to assist in the evaluation of this report.

- **<u>Complementary Investigations (including lab tests):</u>**

    - Details of any relevant laboratory investigations, procedures or tests (e.g., blood work, urinalysis, etc.). Provide testing dates, units of measurement and reference ranges
    - Any serology for HBV or HCV available both BEFORE and AFTER diagnosis (include dates if available):
        - HBsAg
        - anti-HBs
        - anti-HBc IgG
        - anti-HBc IgM
        - HCV antibody
        - HCV RNA level
    - Provide any information about immune status.

Discharge summary should be attached if needed/applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Key messages of the additional risk minimization measures

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

The educational program is aimed at:

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

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

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

1. HCPS AND BLOOD BANKS EDUCATIONAL MATERIAL

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

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

1.1 Healthcare professionals and Blood Banks brochure

The HCPs and Blood Banks brochure will contain the following key information:
Relevant information of the safety concern "Interference for blood typing (minor antigen) (positive indirect Coombs test)":

- Isatuximab binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test).
- The determination of a patient's ABO and Rh blood type are not impacted.

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

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

- The interference with the indirect Coombs test may persist for at least 6 months after the last isatuximab infusion therefore the HCP should advise the patient to carry the patient card until at least 6 months after the treatment has ended.
- The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt isatuximab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.
- In case of urgent need for transfusion, non-cross matched ABO/Rh compatible RBC units can be administered as per local bank practices.
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the risk of interference with indirect antiglobulin tests.
- Emphasize the need to consult the SmPC.
- Instruct the HCP regarding the need to give the patient card to the patients and to advise them to consult the package leaflet (PL).

1.2 Patient Card

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

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