Amsterdam, 26 March 2026
EMADOC-1700519818-3141936
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on an extension of marketing authorisation

Sarclisa

International non-proprietary name: Isatuximab

Procedure No. EMA/X/0000281242

Marketing Authorisation Holder (MAH): Sanofi Winthrop Industrie

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List of abbreviations

ADA: anti-drug antibody
ADCC: antibody dependent cell-mediated cytotoxicity
ADCP: antibody dependent cellular phagocytosis
ASCT: autologous stem cell transplant
BMA: bone marrow aspiration
CAT: Committee for Advanced Therapies
CD38: cluster of differentiation 38
CDC: complement dependent cytotoxicity
CHMP: Committee for Medicinal Products for Human Use
CL: clearance
CR: complete response
CSR: clinical study report
EMA: European Medicines Agency
E-R: exposure-response
EU: European Union
FIH: First in human
Fc: fragment crystallizable
IgG1: immunoglobulin G1
IKd: isatuximab in combination with carfilzomib and dexamethasone
IMids: immunomodulators
IPd: isatuximab in combination with pomalidomide and dexamethasone
IR: infusion reaction
IRC: Independent Review Committee
ISR: injection site reaction
IV: intravenous
IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone
MM: multiple myeloma
NAbs: neutralising antibodies
NCA: non-compartmental analysis
NDMM: newly diagnosed multiple myeloma
NK: natural killer
OBDS: on-body delivery system
ORR: overall response rate
OS: overall survival
PBMC: peripheral blood mononuclear cell
PD: pharmacodynamic
PI: proteasome inhibitor
PK: pharmacokinetic
PRAC: Pharmacovigilance Risk Assessment Committee
Q1: first/lowest exposure quartile
RDI: relative dose intensity
RRMM: relapsed and/or refractory multiple myeloma
RMP: Risk management plan
SC: subcutaneous
SD: standard deviation
SmPC: Summary of product characteristics
US: United States (of America)
V1: volume of distribution for the central compartment
V2: volume of distribution for the peripheral compartment
VGPR: very good partial response

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 24 June 2025, Sanofi Winthrop Industrie submitted an extension of the marketing authorisation.

The MAH applied for the following indications for Sarclisa for 1400 mg solution for subcutaneous injection:

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

- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see section 5.1).

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

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

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) (d) (e) - Extensions of marketing authorisations.

1.3. Scientific advice and protocol assistance

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
14/09/2023	Clinical	EMA/SA/0000139694 Silvijus Abramavicius, Macarena Gajardo Alvarez	The Scientific Advice pertained to the following clinical aspects: • Adequacy of the proposed development plan to support the approval of the subcutaneous isatuximab in the existing Sarclisa (IV isatuximab) indications and in the high-risk smoldering MM (HR-SMM) indication under development; manual administration in addition to the proposed on-body delivery system (OBDS); home administration; patient satisfaction and patient-reported outcomes (PROs); safety database

1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0049/2024) on the granting of a product specific waiver of a paediatric investigation plan (PIP).

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.6. Patient experience data

Table 2: Patient experience data relevant to the application

Patient experience data submitted with this application				Section where discussed (if applicable)
☒	Patient experience data submitted by the MAH:			
	☐	Clinical outcome assessments (COAs) such as		
		☒	Patient-reported outcomes (PRO)	*Section 5.3*
		☐	Other	
	☒	Patient preference studies		*Section 5.3*
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☐	Other patient experience data not submitted by the MAH but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	☐	CHMP early dialogue with patient organisations		
	☐	Third party interventions from patients and patient groups		
	☐	Other (such as medical literature, summaries/analysis from patient engagement activities - please specify)		

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Peter Mol
Co-Rapporteur:	N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur:	Monica Martinez Redondo

The application was received by the EMA on	24 June 2025
The procedure started on	17 July 2025
The CHMP Rapporteur's first Assessment Report was received on	06 October 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	14 October 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 October 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	13 November 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	26 November 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	5 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 January 2026
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	29 January 2026
The MAH submitted the responses to the CHMP List of Outstanding Issues on	22 February 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion on an extension of the marketing authorisation for Sarclisa on	26 March 2026
The CHMP adopted a report on similarity of Sarclisa with Darzalex, Farydak, Kyprolis, Ninlaro, Carvykti, Talvey and Abecma on (see Appendix on similarity)	26 March 2026

1.8. CHMP outcome

1.8.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4. of this report.

1.8.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.5. of this report.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sarclisa is not similar to Darzalex, Farydak, Kyprolis, Ninlaro, Carvykti, Talvey and Abecma within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.8.3. Conditions or restrictions regarding supply and use

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

1.8.4. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of 1400 mg solution for injection of Sarclisa is favourable in the following indications:

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

- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see section 5.1).

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

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Sarclisa subject to the conditions described in the following sections.

1.8.5. Other conditions and requirements of the marketing authorisation

1.8.5.1. Periodic safety update reports

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

1.8.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.6.1. Risk management plan (RMP)

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

An updated RMP should be submitted:

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

1.8.6.2. Additional risk minimisation measures

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

The educational program is aimed at:

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

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

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

1. HCPS AND BLOOD BANKS EDUCATIONAL MATERIAL

- The HCPs and blood banks educational material includes the following elements:
- The summary of product characteristics (SmPC)
- The HCPs and blood banks brochure
- Patient card

1.1 Healthcare professionals and Blood Banks brochure

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

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

- Isatuximab 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 measures through appropriate measures:

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

1.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

2. Introduction

Therapeutic Context

Disease or condition

Isatuximab is currently registered for the treatment of newly diagnosed (ND) and relapsed/refractory (RR) multiple myeloma (MM).

This application concerns the registration of a subcutaneous (SC) administration of isatuximab for the currently approved indications, using an on-body delivery system (OBDS) or a commercially available syringe set for manual administration of the drug.

Epidemiology

MM is the second most-common adult blood cancer, with an estimated incidence in Europe of 4.5-6.0/100,000/year. More than 175,000 cases were reported in 2020, and incidence appears to be highest in countries with a higher human development index. Median age at diagnosis ranges from 65 to 74 years. MM is slightly more frequent in males than in females (approximately 1.4:1), and incidence seems to vary by ethnicity; the incidence in African Americans and Black populations is two to three times that in White populations, as shown in studies from the United States and United Kingdom. The reason for this variance is not known.

Aetiology and pathogenesis

MM is a cancer of the haemopoietic system that is characterised by uncontrolled clonal expansion of plasma cells in the bone marrow. These plasma cells produce an excess amount of abnormal antibodies (so called M protein) or fragments thereof that cause a range of health issues, including impairment of the immune system and increased blood viscosity.

Clinical presentation, diagnosis and prognosis

Patients often present with bone lesions, anaemia, hypercalcaemia and renal failure. Bone lesions are caused by expanding plasmacytomas or cytokines secreted by myeloma cells that activate osteoclasts and suppress osteoblasts. Increased bone demineralization may in turn lead to hypercalcemia. Renal failure is thought to be caused by the deposition of light chains in the distal tubules or by hypercalcemia. Anaemia develops secondary to kidney disease or is caused by suppression of erythropoiesis by cancer cells.

Diagnosis is based on serum protein electrophoresis and immunofixation electrophoresis to detect IgG/IgA monoclonal gammopathy. A plasma cell staining in a bone marrow aspirate and imaging (MRI/PET-CT) are used to confirm the MM diagnosis. The international scoring system (ISS) for MM stratifies patients into three stages based on serum β2-microglobulin level (I < 3.5 mg/L; 3.5 mg/L $\leq$ II < 5.5 mg/L; III $\geq$ 5.5 mg/L), with higher levels being unfavourable. High-risk patients are identified through cytogenetic analysis of the malignant plasma cells and Serum Lactate Dehydrogenase (LDH). The presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16) and high LDH levels are associated with a worse prognosis. The revised ISS (R-ISS) combines ISS stratification with cytogenetics and serum LDH.

Management

Since MM is still incurable, therapy is only initiated after symptoms of the disease have manifested in the form of end-organ damage.

The last two decades have seen the approval of three generations of immunomodulatory drugs (IMiDs; thalidomide, lenalidomide, and pomalidomide), two generations of proteasome inhibitors (PIs; bortezomib, then carfilzomib and ixazomib) and most recently, first generation monoclonal antibodies (mAbs), two of which target CD38 (isatuximab and daratumumab) and another targeting SLAMF7 (elotuzumab).

Agents targeting novel myeloma-specific antigens such as B-Cell Maturation Antigen (BCMA), and new modalities of treatment such as chimeric antigen receptor (CAR)-T cell therapies, are gaining traction and moving towards earlier lines of treatment.

Throughout the treatment lines, fixed combinations of drugs are approved and the choice of therapy is mostly dependent on transplant eligibility (based mainly on age and performance status).

In transplant ineligible, older/frail patients, a typical first-line treatment strategy would consist of bortezomib-lenalidomide-dexamethason (VRd) combined with an anti-CD38 antibody (isatuximab/daratumumab). Autologous Stem Cell Transplant (ASCT) - eligible patients with NDMM generally receive an induction therapy with the same quadruplet combination, high-dose chemotherapy + ASCT, sometimes followed by consolidation treatment and commonly followed by lenalidomide maintenance therapy.

After relapse from PIs and IMiDs, patients are often retreated with drugs that have the same mechanism of action. Ultimately, the disease becomes refractory. Patients who are heavily pretreated and/or refractory to both a PI and IMiD have a dismal prognosis, they are difficult to get back into a durable remission, and median survival is only between 8 to 9 months (Kumar 2012; Usmani 2015, Verelst 2015). For patients who are refractory to at least 3 of the common PIs and IMiDs (bortezomib, lenalidomide, carfilzomib, or pomalidomide), the median survival decreased to only 5 months.

Isatuximab is currently administered using the intravenous (IV) formulation at the dose of 10 mg/kg. Isa-IV is administered with the fixed-volume infusion method, allowing the IV infusion to be given during 75 minutes from the third infusion. Isatuximab SC administration allows for a notably shorter duration of administration compared to the currently approved IV route, thereby optimizing the convenience of administration and minimizing the time spent in a healthcare facility.

The SC administration of isatuximab is also intended to:

- decrease the incidence of systemic infusion reactions
- reduce the administration volume (10 mL with Isa-SC versus 250 mL with Isa- IV) which may be clinically relevant in participants with cardiac or renal impairment

Unmet medical need

As survival has greatly improved over the last decades, and the disease mostly manifests at a later age, the highest unmet medical need may lie in refinement of current treatment strategies. Many drugs seem to be effective and have made it to the first line of treatment, where they are combined and given for long stretches of time. Nonetheless, MM remains incurable.

2.1. Aspects of development

The isatuximab SC programme was initiated in 2019. This dossier is based on 5 isatuximab SC studies:

- Study EFC15951 (IRAKLIA), a pivotal, randomized, multicentre Phase 3, open label study evaluating SC versus IV administration of isatuximab in combination with pomalidomide and dexamethasone (IPd) in adult patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least one prior line of therapy including lenalidomide and a PI. This study was conducted with the same treatment combination as the pivotal study EFC14335 (ICARIA) IV study, which included patients who received at least two prior lines of therapy including lenalidomide and a PI.
- Study ACT17453 (IZALCO), a randomized, multicentre, Phase 2, open label study evaluating SC administration of isatuximab in combination with carfilzomib and dexamethasone (IKd) in adult participants with RRMM who have received 1 to 3 prior lines of therapy. This study was conducted with the same treatment combination and study population as the pivotal IV study EFC15246 (IKEMA).
- Study IIT17756 (IFM IsaSoCut), an investigator-sponsored, multicentre, Phase 2 study of subcutaneous isatuximab plus bortezomib, lenalidomide and dexamethasone (IVRd) in the treatment of newly diagnosed transplant ineligible multiple myeloma (NDMM). This study was conducted with the same treatment combination and study population as the pivotal study EFC12522 (IMROZ) IV study.
- Study IIT17041 (GMMG HD8), an investigator-sponsored, randomized, multicentre, Phase 3 non-inferiority study assessing lenalidomide, bortezomib and dexamethasone induction therapy with either intravenous or subcutaneous isatuximab (IVRd) in transplant-eligible patients with NDMM. This study was conducted with the same treatment combination and study population as the IV study IIT15403 (GMMG HD7). The current submission uses study IIT17041 data from a planned interim safety analysis conducted when the first approximately 120 randomized participants will have completed induction phase in the study, with the primary objective to show consistency of efficacy of SC isatuximab with IV isatuximab, based on the VGPR+ rate (according to IMWG criteria).
- Study TCD15484, a multicentre, open-label, Phase 1b study to assess the pharmacokinetics, safety, and efficacy of subcutaneous and intravenous isatuximab (SAR650984) in combination with pomalidomide and dexamethasone, in patients with RRMM. This first in human (FIH) study for Isa-SC was conducted with the same treatment combination and study population as the pivotal study EFC14335 IV study.

As of this submission, more than 3000 participants have been treated with isatuximab in completed or ongoing studies in the multiple myeloma programme, with 522 participants having received Isa-SC and over 2600 participants having received isatuximab IV.

2.2. Description of the product

Isatuximab is an IgG1 monoclonal antibody directed against cluster of differentiation (CD) 38, which is highly expressed on plasma cells, with particularly high surface density on MM cells. However, B cell, T cells and natural killer (NK) cells can also upregulate CD38 surface expression to similar levels upon activation. In vitro experiments have shown that isatuximab acts by flagging CD38-expressing cells for Fc-dependent immune-mediated clearance through antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). The enzymatic activity of CD38, resulting in extracellular conversion of NAD+ to the immunosuppressive factor adenosine (ADO), has been shown to be inhibited by isatuximab in vitro.

3. Quality aspects

Introduction

This line extension application has been submitted to register a new subcutaneous presentation for all currently approved indications of the existing MAA of Sarclisa (concentrate for solution for intravenous (IV) infusion, EMEA/H/C/004977). This extension will result in a change in the strength (1400 mg), pharmaceutical form (solution for injection), formulation and route of administration (subcutaneous use).

The finished product (FP) is presented as a solution for subcutaneous injection containing 1400 mg of Isatuximab as active substance (AS). Other ingredients are: arginine hydrochloride, histidine, histidine hydrochloride monohydrate, poloxamer 188, sucrose and water for injections.

Sarclisa SC 1400 mg is available in a 20 mL type I colourless clear glass vial closed with an ETFE (copolymer of ethylene and tetrafluoroethylene)- coated bromobutyl stopper. The vials are crimped with an aluminium seal with a green flip-off cap. Sarclisa SC 1400 mg is supplied in a pack size of one vial.

Sarclisa 1400 mg is administered as a subcutaneous injection with CirCLIQ on-body delivery system (OBDS) or with a syringe and infusion set for manual administration (using commercially available syringe and infusion set). CirCLIQ OBDS is packaged separately.

3.1. Active substance

The active substance of Sarclisa is Isatuximab, a monoclonal antibody targeted against CD38.

Isatuximab SC is formulated at the AS level, and not at the FP level. Isatuximab SC active substance is formulated at 140 mg/mL isatuximab, compared to 20 mg/mL for Isatuximab IV. Consequently, the formulation change that is part of the line extension has a significant impact on the AS part of the dossier.

3.1.1. General information

The nomenclature, structure and mechanism of action of isatuximab are not impacted by this line extension.

In brief, isatuximab is an IgG1 derived-monoclonal antibody binding selectively the human CD38 membrane protein. The protein structure is composed of two kappa light chains each with molecular weight of approximately 23 kDa and two IgG1 heavy chains each with a molecular weight of approximately 49 kDa (deglycosylated form) linked through disulfide bridges.

3.1.2. Manufacture, characterisation, and process controls

3.1.2.1. Description of manufacturing process and process controls

Manufacturers

Isatuximab SC bulk active substance is manufactured using the Process 3 Formulation 3 (P3F3) manufacturing process at the Sanofi site in Vitry, France.

All the active substance manufacturing sites are GMP compliant.

Manufacturing process

The proposed P3F3 manufacturing process for Isatuximab SC bulk active substance is an adaptation of the approved P3F2 process for the manufacture of Isatuximab IV . The P3F3 process is compared to the approved P2P2 process which is used for the manufacture of Isatuximab IV at the same site as the intended site for the manufacture of Isatuximab SC (Sanofi Vitry) (see section below).

The MAH has provided clear and sufficiently detailed descriptions of the P3F3 manufacturing process of Isatuximab active substance through flow diagrams and narratives. The manufacturing process is typical for a monoclonal antibody based on recombinant DNA technology.

Reprocessing is not performed at any of the manufacturing steps for Isatuximab P3F3.

The cleaning regimen and storage conditions of the columns and filters are described and raises no concerns. A validation of the lifetime of column resins was performed. The filters used for concentration/diafiltration are re-used and the maximum number of uses is being validated under a continuous lifetime protocol.

The microbial control strategy for the AS manufacturing process is described and includes a detailed list and diagram of the sampling points. The microbial control strategy is considered acceptable.

Control of Materials

The source, history and generation of the cell substrate is not impacted by the line extension and was previously approved for Isatuximab IV (P3F2 and P2F2).

The cell banking system of Isatuximab SC and Isatuximab IV is the same and therefore not impacted by this line extension.

The MAH has presented information on the quality, grade and control of raw materials used in the P3F3 manufacturing process of Isatuximab active substance. This includes the qualitative composition of culture media and the specifications and manufacturers of chromatography resins. For non-compendial raw materials, specifications and control strategies are defined. No raw materials of animal origin are used in the manufacturing process with the exception of the CHO cell line.

The provided information on raw materials is sufficient and raises no concerns.

Controls of critical steps and intermediates

Prior to initiation of process performance qualification (PPQ), a formal process control program was implemented with action limits and acceptance criteria established based on process understanding and capabilities as determined from process experience and characterization activities. Limit of in-vitro cell age (LIVCA), resin lifetime cycle limits, proven acceptable ranges for selected parameters, and other parameters and attributes have been incorporated into the process control program. After PPQ campaign, an updated process control program was implemented for commercial manufacturing batches with the purpose to initiate formal monitoring and trending of data using statistical process control, where appropriate.

The process controls and process parameters, critical and key process parameters, key process attributes and in-process controls (CPP, KPPs, KPAs and IPCs) for the P3F3 manufacturing process of Isatuximab are adequately described. Assessment and classification of the criticality as well as

the development of each of the controls is described in the control strategy development. For each process step, CPP, KPPs, KPAs and IPCs selected for control of the commercial manufacturing process have been established and suitably discussed. The rationale for classification of the process parameters and establishment of respective ranges for commercial manufacturing has been provided and adequately discussed and justified. Acceptance criteria and action limits are defined based on manufacturing experience and prior knowledge. The information provided is adequate and sufficient.

Analytical procedures and where applicable information on method validation for methods used for in-process control testing are provided in a separate document and raise no concerns.

For the safety related in-process controls of the unprocessed bulk it is clearly indicated that they are part of the release process. Therefore, not meeting the acceptance criteria would lead to batch rejection. Overall, the assignment of the controls with action limits or acceptance criteria (rejection limits) is considered acceptable.

Some of the controls for critical steps of P3F3 are changed compared to P2F2 (IV) but are nearly identical compared to P3F2 (IV). A major difference between the P3F2 and P3F3 Isatuximab AS manufacturing processes is the final formulation of the AS, especially the protein concentration (20 mg/mL vs 140 mg/mL). The number of diafiltration volumes was adequately investigated as well.

The information provided is adequate.

3.1.2.2. Manufacturing process development

The MAH provided an overview of the history of the isatuximab manufacturing process history. The P3F3 process evolved from the P2F2 process that is used to supply active substance for manufacturing Isatuximab IV commercial materials. Besides the changes introduced in the formulation steps of the manufacturing process (to facilitate the subcutaneous formulation), changes were implemented that are similar to improvements made during the introduction of P3F2. A detailed comparison of the P2F2 and P3F3 processes has been provided.

Comparability between P3F3 Phase I and P3F3 Phase III processes

Two versions of the P3F3 manufacturing process have been used to manufacture isatuximab SC. P3F3 Phase 1 was used to manufacture AS for FP batches for Phase I clinical trials.

P3F3 Phase 3 was used to manufacture AS for FP batches for Phase III clinical trials and is representative for the process used to manufacture commercial materials. Comparability between P3F3 Phase 1 and P3F3 Phase 3 materials is further described and assessed in the next part of this section of the AR.

The MAH has provided detailed comparisons between the P3F3 phase 1 and P3F3 phase 3 processes in CTD section 3.2.S.2.6. A separate report describes the comparability study between the two processes. The design of comparability study is considered appropriate and has investigated the similarities between active substance from the two processes based on release test data, characterisation data and stress stability studies on active substance batches and on finished product batches manufactured with the two active substances. The comparability results are clearly presented.

Taking all the presented data into consideration the conclusion of comparability between P3F3 Phase I and P3F3 Phase III is agreed.

Analytical comparability between P2F2 (IV) and P3F3 Phase 3 (SC) materials

Comparability of the AS P3F3 and P2F2 processes was studied to support the use of the P2F2 reference standards for the P3F3 program. The P3F3 batches used for the comparability exercise are the primary stability batches (GMP1 and GMP3) which are representative for the intended commercial P3F3

manufacturing process. The acceptance criteria for the study are well described and are based on the comparison of results from release and characterization tests and comparative stress stability studies. Where appropriate, statistical evaluation of historical data obtained for P2F2 batches was applied. Taken together, the results presented of the analytical comparability study between P2F2 (IV) and P3F3 Phase 3 (SC) materials in CTD section 3.2.S.5 support the use of the P2F2 reference for testing P3F3 materials.

Comparability studies to support the line extension

The MAH is including with this line extension application an additional route of administration (subcutaneous injection) to the existing MAA for Sarclisa, which is administered intravenously. As part of this line extension, a new version of the manufacturing process of the active substance Isatuximab, P3F3, is proposed.

Comparability between Sarclisa IV and Sarclisa SC is considered sufficiently assessed according to the principles of ICH Q5E and the approach taken is adequately described in CTD section 3.2.S.2.6. It is considered demonstrated that the proposed changes do not impact the quality, safety and efficacy of Sarclisa that was clinically demonstrated at initial MAA of Sarclisa IV.

3.1.2.3. Characterisation

The MAH presented data from studies that characterized the structural and physico-chemical properties of Isatuximab and impurities that arise during the manufacturing process of the molecule. The information gathered in these studies have been used to develop the Isatuximab SC control strategy and the release and stability acceptance criteria in the specifications.

Elucidation of structure and other characteristics

A set of physical, chemical and biological tests were used to extensively characterize the Isatuximab active substance. Characterization was initially performed on active substance manufactured with the P2F2 and P3F2 process (as part of Isatuximab IV) and the current studies mainly serve to show the consistency between the characteristics of the molecule generated with the IV and SC processes. The presented data on the primary, secondary and tertiary structures, charge isoform profile, glycosylation, aggregation and fragmentation profile, and biological activity is adequate and seems consistent between the materials generated with the IV and SC processes.

Process related impurities

The MAH has evaluated Isatuximab AS for the presence of potential process-related impurities and the clearance capabilities of these impurities by the P3F3 manufacturing process. The control strategies for each of the process related impurities is described.

Taken together, the information provided in this section shows that the P3F3 manufacturing process is robust and capable of consistently clearing process related impurities. The control strategy for process related impurities is endorsed.

Product related impurities

The MAH has evaluated Isatuximab AS for the presence of potential product-related impurities and the control strategies for each of the product related impurities is described.

3.1.3. Specification

3.1.3.1. Specifications

The active substance specifications include tests for identification, appearance, protein concentration, CDC and ADCC bioassays, purity, impurities, bioburden and bacterial endotoxins.

The MAH describes and justifies the methods and acceptance criteria for the release and stability of Isatuximab SC active substance. The parameters selected for release and stability are considered appropriate and are based on the international guidelines (e.g. ICH Q6B), pharmacopeia (Ph.Eur. Monograph 2031 on monoclonal antibodies for human use) and the Isatuximab SC control strategy. Although the specifications are mostly identical to the specifications for Isatuximab IV, the justifications of the acceptance criteria that are based on process capability are specific for Isatuximab SC P3F3 process.

The acceptance criterion for ADCC is new for Isatuximab SC and was not present in the AS specification for Isatuximab IV. Justifications to exclude several parameters has been adequately provided.

The principles applied for the determination of the acceptance criteria are clearly described and take into account the AS process capability, characterization, data from stability studies and FP process capability, where applicable. The batches used for process capability assessment are also used in clinical phase III studies as well as primary stability studies. In general, the approaches and the set limits are considered appropriate.

Analytical procedures

Descriptions of the non-compendial analytical procedures from the Isatuximab P3F3 active substance specification are provided. The analytical procedures in the active substance specification are described in sufficient detail. Methods are highly similar but not identical to the methods used for Isatuximab IV. The main differences are related to the sample preparation due to the increased Isatuximab concentration, which raises no concerns.

Compendial methods have been verified to be suitable for Isatuximab active substance, and non-compendial methods have been validated according to ICH Q2 guideline. Most of the non-compendial methods were co-validated at two sites and subsequently transferred to a testing site that will be responsible for testing of commercial batches. The receiving site in most of the transfers is the Sanofi-Aventis site, which is also a registered testing site for active substance manufactured with P3F2 and P2F2.

Validation and transfer reports are clearly written with separate sections for the validation and transfer activities at the involved sites. Taken together, the validation data presented for the analytical procedures of Isatuximab active substance show that they are suitable for their intended purpose.

Batch analysis

Results from batch analyses of batches of Isatuximab active substance manufactured according to the P3F3 process are presented. The P3F3 Phase I process batches are representative of early development (see 3.2.S.2.6) and the Phase III P3F3 process batches are representative of the materials used for Phase III clinical trials and the intended commercial process of Isatuximab SC. Together with the information provided in 3.2.S.2.6 and 3.2.P.5.4, the MAH provides traceability of the batches and corresponding manufacturing processes that were used to manufacture finished product batches for Phase I and Phase III clinical trials.

All results complied with the specification limits effective at the time of release. Overall, but in particular the results for the three PPQ batches indicate consistent manufacturing of the P3F3 isatuximab active substance.

Reference standards or materials

The reference materials section is impacted by the line extension as new materials for the ADCC and protein content determination are added.

Overall, the information provided for the qualification and control of reference materials for Isatuximab SC is considered acceptable.

3.1.3.2. Container closure

Isatuximab manufactured with P3F3 process is stored in bottles. Stability samples are stored in equivalent containers of reduced size. The manufacturer of the containers is described by the MAH. Extractables studies and screening leachable studies performed with the containers raise no concerns. Compatibility of the container with Isatuximab AS was confirmed during long term stability studies and stability studies under accelerated conditions. The same storage container was used for storage of isatuximab active substance intended for use in clinical trials.

Taken together, the information provided by the MAH on the container closure system for isatuximab SC active substance is considered sufficient and the selection of the container is considered justified.

3.1.4. Stability

The shelf-life claim for the active substance is based on stability studies at the long-term storage condition and at the accelerated condition in line with relevant ICH guidelines. Primary stability studies include three production scale batches representative of the intended commercial P3F3 process. For all three batches, long-term stability data and stability data at the accelerated conditions are available and these studies are therefore completed. Studies at the stress condition are also completed. The analytical procedures used in the stability studies correspond to the tests included in the AS specification and are in line with the stability indicating methods as confirmed by the forced degradation studies. The results of the primary stability studies are summarized as follows:

At the long term storage condition, all available results are within the acceptance criteria and no significant change was observed in any of the measured attributes.

No significant changes were observed for any of the measured attributes during 6 months at the accelerated storage conditions. After 6 months at the stress condition, changes are observed. These changes are in line with the changes observed in the heat stress forced degradation study. Overall, the results from the primary stability studies show a favourable stability profile and raise no concerns.

The MAH has performed forced degradation studies with Isatuximab SC material to assess the stability and degradation aspects of Isatuximab. The selected test methods and stress conditions are considered acceptable. As Isatixumab AS and FP are formulated the same, a combination of AS and FP batches were used which were manufactured with the intended commercial process. The design of the forced degradation studies is acceptable.

Supporting stability study data was generated with the PPQ batches from the P3F3 process validation studies which were manufactured with extended processing times. These studies are still ongoing but the available data follows the same trends as the primary stability studies and raise no concerns.

Taken together, the results from the primary stability studies and supporting stability studies show that Isatuximab SC is sufficiently stable at the long term storage and accelerated conditions. The MAH commits to complete the ongoing supporting stability studies according to the protocol presented in CTD section 3.2.7.1. The MAH additionally commits to perform annual stability studies at the long term storage conditions on at least 1 batch of active substance every year. The presented annual stability protocol is considered acceptable.

3.2. Finished medicinal product

3.2.1. Description of the product and pharmaceutical development

3.2.1.1. Description of the product

The isatuximab finished product is available as a sterile 140 mg/mL solution for subcutaneous injection in a single-use vial presentation: 1400 mg/10 mL.

The finished product solution (SC) contains 1400 mg of Isatuximab as active substance. Other ingredients are: arginine hydrochloride, histidine, histidine hydrochloride monohydrate, poloxamer 188, sucrose and water for injections. All excipients are compendial grade and no novel excipients were used.

The finished product is packaged in 20 mL (ISO 20R) tubular type I colorless clear glass vials closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stoppers. The stoppered vials are crimped with an aluminum seal (non-product contact) covered with a green flip-off cap.

The solution for injection is intended for subcutaneous administration using on-body delivery system (OBDS) or by manual administration (using commercially available syringe and infusion set).

For the presentation of 1400 mg/10 mL, an overfilling is applied to guarantee a compliant extractable volume, each vial is filled with 10.77 mL of finished product to ensure that 10.0 mL can be withdrawn.

Pharmaceutical development

The Quality Target Product Profile (QTPP) and CQAs that were used as an input for the development of the formulation of Isatuximab SC finished product are described. The provided QTPP and CQAs raise no concerns. The iterative process of the formulation development is described in detail. The focus was on the reduction of the viscosity considering Isatuximab is administered as a relatively high volume (10 mL) subcutaneously.

The selected formulation was confirmed by manufacturing one FP batch with active substance of process 3, formulation 3 (P3F3). This P3F3 finished product batch was assessed in a set of stability studies according to specification effective at the time of the study. The results met all the acceptance criteria and the developed P3F3 formulation was in line with the QTPP. There were no changes to the formulation made from Phase 1b clinical trials to Phase III clinical trials and the intended commercial finished product.

The viscosity of the selected formulation at different temperatures is described. As the viscosity of Isatuximab SC finished product solution is significantly higher at the long term storage condition than at room temperature it is recommended to ensure proper equilibration at room temperature before withdrawing the product from the primary container. This is reflected by the section 6.6 Special

precautions for disposal and other handling of the SmPC, where it is mentioned "Prepare and administer SARCLISA 1 400 mg subcutaneously using clean technique. Prior to use, allow SARCLISA subcutaneous to reach room temperature for approximately 20 minutes to minimize pain during the injection."

The history and development of the manufacturing process of Isatuximab SC finished product 1400 mg/10 mL is described in sufficient detail.

The Isatuximab SC finished product manufacturing process is developed using an iterative approach that combined lab scale and industrial studies, risk assessment, process characterization studies and the PPQ campaign. The progression of the control strategy throughout development is described in sufficient detail. The classification of the CPPs, KPPs, KPAs and IPCs is harmonized with active substance. This is endorsed.

The MAH has performed an assessment regarding the leachables and extractables from single use systems used in the manufacturing process. These studies were performed in line with international guidelines such as ICH M7 to determine the Threshold of Toxicological Concern (TTC). It is concluded that the single use materials are suitable for use and not of toxicological concern.

The information provided is sufficient.

3.2.2. Manufacture of the product and process controls

Manufacturers

Isatuximab SC EU batch release is performed at Sanofi-Aventis Deutschland GmbH in Frankfurt. All finished product manufacturing sites are GMP compliant.

Manufacturing process

The manufacturing process for Isatuximab SC finished product is described through flow diagrams which includes the process controls, parameters and attributes. The process is straightforward as no compounding step is included. In brief, the manufacturing process consists of the following steps: thawing of formulated isatuximab active substance, pooling and homogenization, prefiltration of the solution, sterilizing filtration of the pre-filtered solution at the point-of-fill, aseptic filling, stoppering and crimping, visual inspection, container closure integrity testing (CCIT) of the filled vials, labelling and packaging.

Sterilization and depyrogenation of the container closure system is described. Glass vials are supplied sterile and ready-to-use. The sterilization and depyrogenation process performed by the supplier are described in sufficient detail, in line with the EMA guideline "Sterilisation of the medicinal product, active substance, excipient and primary container".

Hold times are described for several steps. The duration of the sterile filtration at point of fill and the filling duration and interruption time are defined. Media fills and other aseptic processes were included in the process validation.

3.2.2.1. Process controls

The controls of critical steps and intermediates of the finished product manufacturing process of Isatuximab SC FP are adequately described. The controls (CPPs, KPPs, KPAs and IPCs) were classified and developed based on the process and control strategy development described as part of the pharmaceutical development.

Filter integrity is tested before and after sterile filtration and before and after pre-filtration. Validation of the sterile filtering process is described adequately.

Overall, the proposed controls of critical steps and their limits are described in sufficient details, are well justified and considered acceptable.

3.2.2.2. Process validation

The MAH presents the results of a set of studies that were performed to validate the Isatuximab SC finished product manufacturing process through a PPQ campaign.

A bracketing approach was used in order to validate the commercial batch size range described in the batch formula. Three full scale PPQ batches were manufactured with processing times set to support the validation of the allowed time out of refrigeration and maximum holding times. The process controls as well as additional controls were evaluated for each of the manufacturing steps. Results are provided in sufficient detail and raise no concerns.

The process time from the start of sterilizing filtration and end of filling, stoppering and crimping was included in the validation and at any time limited by the performed media fill validation. For sterile filter validation, the applicant has included a separate report which also supports the operational parameters for sterile filtration and filter integrity testing.

The PPQ batches complied with the acceptance criteria for Isatuximab SC finished product. The available stability study results of these batches raise no concerns.

The validation of the microbiological aspects of the aseptic process is described. The time between the start of sterilizing filtration and end of filling, stoppering and crimping is supported by media fill studies. Elements from the EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container regarding filter validation were included, adsorption, chemical compatibility, retention capacity (bacterial challenge), integrity test limits and extractable and leachable.

Shipping studies were performed for finished product and raise no concerns.

Taking the results of the validation studies provided by the MAH together it can be concluded that the manufacturing process for Isatuximab SC finished product is validated and is capable of consistently producing product of acceptable quality.

3.2.3. Product specification

3.2.3.1. Specifications

The finished product proposed specifications include relevant tests for appearance, identification, potency, purity, particulate matter, visible particles, osmolality, poloxamer 188, extractable volume and safety.

The specifications for finished product are generally aligned with the specifications for active substance and Ph. Eur. Monograph 2031 on monoclonal antibodies for human use, and are typical for a monoclonal antibody. The MAH reported that visible particles were found in finished product vials of the proposed SC formulation. Due to the formation of intrinsic particles, the end-of-shelf life acceptance criteria for visible particles are "Liquid may contain a few translucent to white particles", which is acceptable in line with the EMA Questions and answers for biological medicinal products on visible particles.

For each of the analytical methods mentioned in this specification it is indicated which are compendial with references to Ph. Eur. For non-compendial methods the type of method is stated.

The justification of the parameters and acceptance criteria of the specification for Isatuximab SC finished product have been provided. The principles applied for the selection of the acceptance criteria are generally identical to those applied for active substance and are supported. The acceptance criteria are mostly aligned between active substance and finished product, with exception of some parameters that are evaluated specifically for finished product (e.g. poloxamer 188 and osmolality).

Acceptance criteria for sterility, bacterial endotoxins, particulate matter, extractable volume, protein content and pH, are acceptable.

For the tests common with active substance, the acceptance criteria were set in parallel for active substance and finished product by taking into account the process capabilities of both processes. For determining the process capabilities of finished product, a set of 11 batches were taken into consideration, which also include multiple clinical batches.

The characterization and control strategy of impurities in Isatuximab SC finished product has been described. The nitrosamine risk assessment reports for Isatuximab SC active substance and finished product indicate no risk of formation of nitrosamines. This is acceptable.

Elemental impurities were assessed in accordance with ICH Q3D. The safety risk associated with the presence of elemental impurities was considered negligible.

The assessment of extractables and leachables from the manufacturing process and container closure system raised no concerns.

Bacterial endotoxins were evaluated and concluded the absence of pyrogens.

Isatuximab SC FP may contain trace amounts of translucent to white particles after storage at the long-term storage condition. The identity of the particles was confirmed as Isatuximab protein with silicone oil. The MAH has assessed the potential medical impact of the presence of the silicone-protein particles. The MAH's position towards the safety and efficacy evaluation of the visible particles in Sarclisa SC is endorsed. Impact of the visible particles and the silicon-oil on the quality attributes of Isatuximab SC were assessed and are considered negligible. Nonetheless, the CHMP recommended some points for further investigation.

There are no potential product related impurities other than those described and characterized for the active substance. The control strategy for each of the potential product-related impurities is described, including an overview of the evolution of the levels of the impurities from active substance to finished product. No significant difference between the levels was observed. A slight increase in aggregates and acidic isoforms is observed during storage at the long-term storage conditions.

The control strategy for impurities of Isatuximab SC finished product is adequate and raises no concerns.

3.2.3.2. Analytical procedures and reference standards

The analytical procedures for a set of the methods from the Isatuximab finished product specification are provided. For methods that are common between Isatuximab SC active substance and Isatuximab SC finished product there is no analytical procedure provided by the MAH. For compendial methods, there is no separate analytical procedure provided except for some parameters. The non-compendial methods which are not common between Isatuximab SC active substance and Isatuximab SC finished product are clearly written and contain adequate system suitability test requirements.

The analytical procedure for visible particles references Ph. Eur. 2.9.20 and Ph. Eur. 5.17.2 and has specific evaluation instructions for stability testing to determine the identity and number of any present particles.

The MAH has verified compendial methods and validated (according to ICH Q2 guideline) non-compendial methods, which showed they are suitable for testing Isatuximab SC finished product. For methods in common with active substance, the validation was not repeated as it applies to finished product as well.

The validation, transfer and verification reports are clearly written and raise no concerns. In general, the analytical procedures are considered suitable for their intended purpose.

A study was perform which confirmed the absence of the Low endotoxin recovery (LER) effect, in accordance with EMA questions and answers for biological medicinal products.

An overview of the changes to analytical procedures over development is provided. Mostly, these changes were done in parallel for AS and FP. Overall, the information provided regarding the changes to analytical methods raises no concerns.

Reference Standards are described in the Active Substance Section.

3.2.3.3. Batch analysis

Batch analysis data is presented of all Isatuximab SC FP batches manufactured up until and including the PPQ batches. This includes the early development phase I batches and the phase III, pre-PPQ and PPQ batches that are representative of the intended commercial process.

All results complied with the specification limits effective at the time of release and indicate consistent manufacturing of the Isatuximab SC finished product.

3.2.3.4. Container closure

The finished product is packaged in 20 mL (ISO 20R) tubular type I colorless clear glass vials closed with bromobutyl stoppers. The stoppers are coated on the product contact side with an ETFE (copolymer of ethylene and tetrafluoroethylene) film and a silicone oil based coating on the non-product contact side.

The stoppered vials are crimped with an aluminum seal (non-product contact) covered with a green flip-off cap. The container closure system is described in sufficient detail, including specifications and drawings. Example certificates of analysis are provided. The vials and rubber stoppers are in compliance with the Ph.Eur. requirements.

Suppliers of the container closure system that come into contact with the product (vial, rubber closure) are included in the dossier.

3.2.4. Stability of the product

A shelf life of 36 months is claimed for the finished product when stored between 2 °C and 8 °C, protected from light.

The design, results and status of the set of stability studies to support the shelf-life and storage conditions of Isatuximab SC finished product are described and were performed in line with relevant ICH GL. The following studies were included: primary stability studies, confirmatory stability studies, time out of Refrigeration (TOR) stability studies, stress temperature studies, photostability studies.

A primary stability study was conducted in accordance with ICH guidelines, with finished product stored in the same container closure system as the intended commercial finished product. The design of the described stability studies is acceptable. The selected test items are appropriate and testing is performed with the analytical procedures listed in P.5.2. with the exception of CCIT, see below.

At the long-term storage condition, the three primary (full scale) stability batches met the acceptance criteria for all tested attributes.

At the accelerated conditions, the finished product batches remained within the acceptance criteria for 6 months.

Taken together, the presented primary stability studies at the long term storage and accelerated conditions raise no concerns.

Data is also presented for confirmatory stability studies at the long term storage, accelerated and temperature stress conditions. At the long term storage condition, the currently available data raise no concerns. At the accelerated storage condition, results are in-line with the results obtained during the primary stability studies. Result obtained for the temperature stress study (40 °C) are comparable with similar studies performed for active substance (CTD section 3.2.S.7.1) with respect to the degradation pathways.

The available results of the confirmatory stability studies raise no concerns.

Additonal storage was adequately studied and all the tested quality attributes were within the shelf life acceptance criteria, including sterility and CCIT.

The MAH therefore claims that additional storage of isatuximab finished product for 24 hours at room temperature before administration is allowable. This is reflected in section 6.4 of the SmPC which states that "Unpunctured vials may be stored at room temperature (≤ 30 °C) for a single period of up to 24 hours" and is considered acceptable.

The MAH has performed photostability studies of isatuximab SC finished product according to ICH Q1B (option 2). These are reported in CTD section 3.2.S.7.1. Based on the results, it was concluded that finished product is light sensitive and that it is recommended to protect it from light. This recommendation is reflected by section 6.4 of the SmPC, "store in the original package in order to protect from light".

Day-light exposure studies showed that protection from light during manufacturing is not required.

Freeze-thaw and shaking stress studies were performed on active substance and showed no significant evolution for any attributes.

Formation of visible particles during storage

During storage at the long-term storage conditions, visible particles may be formed. As a result, the shelf-life specifications for visible particles were adjusted to allow "a few translucent to white particles". Based on the stability data collected and provided, the proposed shelf life of 36 months when stored between 2 °C and 8 °C, protected from light for the finished product is acceptable. The available real-time stability data (36 months for all three batches) are all within the specifications and the trends observed in the data do not raise any concerns.

3.2.5. Medical Device aspects

Compatibility

The MAH describes the compatibility of the Isatuximab SC finished product solution with the administration devices described in the SmPC and to propose an in use storage condition.

Compatibility with the OBDS was studied by filling the OBDS and letting the finished product solution remain in contact with the fluid path for 4 hours or by dispensing it immediately. The design and acceptance criteria of the study are generally acceptable.

Quality attributes of Isatuximab were assessed to be within the acceptance criteria at both T0 and T4h time points. Moreover, the results were very consistent with each other. In the SmPC, section 6.3 Shelf life and 6.6 Special precautions for disposal and other handling, it is stated that "After insertion of the vial in CirCLIQ OBDS device. Once the vial is punctured, the injection with CirCLIQ OBDS On-Body Injector should be performed as soon as possible. CirCLIQ On-Body Injector should be used at temperature 18°C to 28°C and ambient light. If the injection is not completed within 4 hours, discard the vial and the On-Body Delivery System." The performed studies support this statement.

Compatibility with the syringe and infusion set was studied with a similar approach. Two combinations of syringe and infusion set were tested. The materials chosen for the compatibility studies are sufficiently representative of the range of materials used in clinical practice for administration of the finished product.

All results met the acceptance criteria. In the SmPC, section 6.3 Shelf life, it is stated that "After transfer of the solution to the syringe for manual administration. Store it for up to 4 hours at 15 °C to 25°C and ambient light, including the administration time. Discard after 4 hours, if not used.

In section 6.6 Special precautions for disposal and other handling, it is stated that "if the syringe containing SARCLISA subcutaneous is not used immediately, store it for up to 4 hours at room temperature (15 to 25 °C) and ambient light, including the administration time. Discard after 4 hours, if not used." The performed studies support these claims.

In line with EMA/CHMP/QWP/BWP/259165/2019 Guideline on quality documentation for medicinal products when used with a medical device, the MAH provided an assessment of the compatibility of the components of the device that contact the finished product solution, with respect to any leachables that may form during use of the device, taking into account the contact time. As part of this assessment (according to ISO 10993), data was generated for chemical characterization and toxicological risk assessment, which included extractable studies. Based on the results of these studies, it was concluded that the extracted compounds are not expected to cause systemic toxicity during the use of the OBDS.

Conformity, functional aspects and performance verification

The quality aspects of the OBDS medical devices that can be used for the administration of Isatuximab SC are described. The commercial name of the device is CirCLIQ and it is referenced as "CirCLIQ OBDS" or "CirCLIQ on-body injector" in the product information.

The OBDS is packaged separately from Isatuximab SC finished product and is considered a referenced medical device in the context of regulatory guidelines (Quality documentation for medicinal products when used with a medical device, EMA/CHMP/QWP/BWP/259165/2019). The MAH has submitted a declaration of conformity to the Medical Device Regulation of the CirCliq On-Body delivery system. Compliance of the referenced medical device to the Medical Device Regulation is considered sufficiently substantiated.

The functional design of the delivery device is described. Picture and schemes of the OBDS are included. Narrative descriptions provide sufficient understanding of the working mechanism of the device.

The MAH describes the principles of operation, illustrations are included. The principles of operation raise no concern. The product information refers to the CirCliQ OBDS Instructions for use, which are considered to provide a sufficiently detailed instruction for the administration of Sarclisa SC finished product.

The MAH indicates that the intended users of the OBDS are healthcare professionals (HCPs) for use in the treatment of adult patients. Human factors validation data is included in the device CE marking review.

3.2.6. Post-approval change management protocol(s)

No Post approval change management protocols have been submitted as part of the line extension application.

3.2.7. Adventitious agents

Aspects related to adventitious agents are not impacted by the line extension. Isatuximab is manufactured in Chinese Hamster Ovary cells without the direct use of animal derived materials. Indirect use of animal derived materials is adequately described and controlled. Viral clearance by the Isatuximab manufacturing process is considered validated.

The totality of data presented provides sufficient assurance of safety regarding adventitious agents.

3.3. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The MAH has presented a line extension for Sarclisa, to include a presentation of a solution for subcutaneous (SC) injection in addition to the previously approved concentrate for solution for intravenous (IV) injection.

The active substance of Sarclisa is Isatuximab, a monoclonal antibody that selectively binds human CD38 membrane protein. To support the change in the route of administration, a new SC formulation has been developed. The isatuximab SC finished product solution is intended for administration using an on-body delivery system (OBDS) or by manual administration (using commercially available syringe and infusion set).

Active substance

In this line extension application, the MAH presents the P3F3 active substance manufacturing process for Isatuximab SC, which is an evolution of previously approved P2F2 and P3F2 manufacturing processes of Isatuximab IV, adjusted for the subcutaneous formulation. A comparability study in line with the requirements put forward in ICH Q5E is presented which shows that the Isatuximab SC and Isatuximab IV active substances are comparable. The control strategy for Isatuximab SC active substance is considered acceptable to guarantee the quality of the material. Sufficient stability data is present to support the proposed shelf life of the active substance. The presented information on the development and manufacture of the Isatuximab SC active substance is satisfactory.

Finished product

Isatuximab SC finished product is a sterile solution of 1400 mg/mL, formulated specifically for subcutaneous injection. The finished product is intended to be administered with commercially available syringe and infusion sets or the CirCLIQ OBDS. The OBDS is a referenced medical device that is packaged and marketed separately. Several aspects of the OBDS were evaluated that may impact the quality, safety and efficacy of the finished product, including the compatibility with the Isatuximab solution, dose accuracy and in-use stability. The presented information on these medical device aspects was acceptable and a certificate of compliance of the OBDS device with the General safety and performance requirements (GSPR) of the Medical Device Regulation is provided. The control strategy for Isatuximab SC finished product is considered acceptable to guarantee the quality of the finished product. Sufficient stability data is present to support the proposed shelf life claim. The presented information on the development and manufacture of the Isatuximab SC finished product is satisfactory.

Recommendations are made regarding the control of visible particles in vials of Sarclisa SC finished product.

1.3.1. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Sarclisa SC 1400 mg is considered acceptable when used in accordance with the conditions as defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated.

The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

In conclusion this line extension application for Sarclisa SC 1400 mg is approvable from the quality point of view.

1.3.2. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

4. Non-clinical aspects

Introduction

One new non-clinical study has been submitted. The study combines local toxicity assessment and comparative pharmacokinetics in minipigs. This study has been conducted according to GLP.

4.1. Pharmacology

4.1.1. Pharmacodynamics

No new studies on pharmacodynamics were submitted.

4.1.2. Pharmacokinetics

The MAH directly compared pharmacokinetics of the IV administration route (20 mg/mL) and the SC administration route (140 mg/ML) for isatuximab in a GLP study in 20 minipigs. The minipig was not a toxicological species used in the original MAA as it is not pharmacologically active. Exposure in minipigs after IV administration appears to be higher (1.7-fold) than the exposure measured in monkeys at a similar dose.

A summary of the mean exposure pharmacokinetic (PK) parameters after a single IV or SC injection is presented in Table 3.

Table 3: Summary of the mean (CV%) plasma pharmacokinetic parameters of isatuximab in female minipigs (n=5/group) after a single IV or SC administration

Route / Injection rate (mL/min)	t_{max} (h)	C_{max} (µg/mL)	t_{last} (h)	C_{last} (µg/mL)	AUC_{last} (h*ug/mL)	AUC_{0-24} (h*ug/mL)	AUC_{0-72} (h*ug/mL)	AUC_{0-168} (h*ug/mL)	F[a]
IV	EOI[c]	1540	672[c]	366	364 000	28 400	69 800	136 000	-
3	(0)	(8)	(0)	(22)	(11)	(11)	(10)	(10)	
SC	96 [72-192] [b]	678	672[c]	349	325 000	5450	31 500	92 200	0.89
0.5	(50)	(8)	(0)	(24)	(13)	(48)	(20)	(11)	
SC	192 [48-264] [b]	1130	672[c]	677	565 000	8330	45 900	129 000	1.55[d]
1	(54)	(23)	(0)	(34)	(25)	(37)	(14)	(5)	
SC	168 [72-192] [b]	847	672[c]	440	369 000	6610	38 500	106 000	1.01
2	(45)	(12)	(0)	(36)	(23)	(19)	(10)	(10)	

Abbreviations: AUC_{0-t}: Area under plasma concentration versus time curve from 0 h to 24 h/72 h/168 h; AUC_{last}: Area under plasma concentration versus time curve from time 0 to the last measurable concentration; C_{last}: Last measurable concentration; C_{max}: Maximum plasma concentration; CV%: coefficient of variation in percent; EOI: End of infusion; F: Bioavailability; IV: Intravenous; SC: Subcutaneous; t_{last}: Time of the last measurable concentration; t_{max}: First time to reach C_{max}

a calculated using AUC_{last}

b median [min-max]

c same value for median, min and max

d high F value related to higher variability noted for this group, and specifically the contribution of 2/5 animals which showed an apparent higher exposure

Bioavailability of the SC administration compared to the IV administration was 89% in the SC 0.5 mL/min group, 155% in the SC 1 mL/min group (probably because of the large variability and high values in 2/5 animals) and 101% in the SC 2 mL/min group.

In the original MAA for Sarclisa, TK parameters were collected in non-human primates. At a comparable dose of 100 mg/kg (the minipigs weight was approx. 22 kg per animal, with a dose of 1800 mg/animal), the AUC_{0-168h} was 79740 h/ug*mL after a single IV administration in non-human primates. In the current study, an AUC_{0-168h} of 136000 h/ug*mL was measured in the minipigs.

4.2. Toxicology

4.2.1. Local tolerance

Local tolerance of the SC formulation was assessed in minipigs in a study combined with the pharmacokinetic assessment of the SC formulation compared to the IV formulation. The SC formulation was administered in the left flank at a fixed dose of 1800 mg/animal, but with three different infusion speeds (0.5 mL/min, 1 mL/min and 2 mL/min). Each animal also received a single dose of saline in the right flank as a control on Day 8.

No test item related clinical signs were observed in any of the animals in the IV group and SC groups. Body weight gain was also similar in all groups . Minimal to moderate injection site reactions (including swelling) were observed in all groups at the day of administration. These appeared to be more marked after isatuximab compared to 0.9% NaCl and more pronounced at higher flow rates, but remained minimal-moderate in severity.

4.2.2. Ecotoxicity/environmental risk assessment

The active substance is a natural substance (monoclonal antibody), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Isatuximab is not expected to pose a risk to the environment and no environmental risk assessment studies were submitted which is acceptable.

4.3. Overall discussion and conclusions on non-clinical aspects

4.3.1. Discussion

The MAH directly compared pharmacokinetics of the IV administration route and the SC administration route for isatuximab in a GLP study in 20 minipigs. SC administration of 1800 mg isatuximab/animal at 0.5 and 2 mL/min resulted in very similar AUC_{last} at 672 hours (the full cycle of 28 days as per the approved posology of isatuximab) compared to IV administration at 3 mL/min of the same dose. However, a clear absorption phase from the injection site is evident in the PK of the SC administration C_{max} after SC administration was approx. 50% lower than after IV administration and the $AUC_{0\text{-}24h}$ is also only about 20-25% of the $AUC_{0\text{-}24h}$ after IV administration. At 168h after administration this difference in exposure disappears and all are approximately equal. The SC 1mL/min group shows overall a higher exposure than IV, but according to the MAH there was more variability in this group of animals, which is agreed. However, even if the high-exposure animals are not included, the exposure at AUC_{last} is still slightly higher than after IV administration (116% of IV exposure with three animals excluded and 129% of IV exposure with 2 animals excluded). Bioavailability of the SC administration compared to the IV administration was 89% in the SC 0.5 mL/min group, 155% in the SC 1 mL/min group (probably because of the large variability and high values in 2/5 animals) and 101% in the SC 2 mL/min group.

To summarise, the SC administration of isatuximab did not result in a decreased overall exposure and had a high bioavailability compared to the IV administration. Absorption was slow (t_{max} between 96-168 hours), resulting in lower C_{max} compared to IV administration.

Local tolerance was assessed in the same study but did not reveal any significant findings.

4.3.2. Conclusions

From a NC point of view, the pharmacokinetics of the IV formulation and SC formulation are similar, except for the absorption phase, resulting in a lower Cmax. However, this is to be expected in a comparison between these two administration routes.

There are no toxicological concerns for the line-extension from the intravenous to subcutaneous administration route from a non-clinical point of view.

5. Clinical aspects

Introduction

Isatuximab is currently administered using the intravenous (IV) formulation at a dose of 10 mg/kg. In this procedure, the MAH is requesting authorisation for a newly developed SC formulation, which upon approval will be applicable to all current and future IV indications.

The SC administration of isatuximab is intended to:

- shorten the duration of administration.
- decrease the incidence of systemic infusion reactions
- reduce the administration volume (10 mL with Isa-SC versus 250 mL with Isa-IV), which may be clinically relevant in participants with cardiac or renal impairment

To this end, the MAH has submitted the result of pivotal study EFC15951 to demonstrate non-inferiority of Isa-SC versus Isa-IV in combination with pomalidomide and dexamethasone (IPd), and the data from the SC studies ACT17453 (IKd combination), IIT17041 (IVRd combination), IIT17756 (IVRd combination), and TCD15484 (IPd combination). An overview of the clinical studies can be found in Section 5.1.2.

5.1.1. GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1b TCD15484	First in human randomized Phase 1b study to assess the safety, PK and efficacy of Isa-SC in combination with pomalidomide and dexamethasone	Dose escalation: Isa-SC 1000 mg or 1400 mg Q1W Dose expansion: Isa-SC 1400 mg or Isa-IV 10 mg/kg Q1W	Adult RRMM patients who have received at least 2 previous therapies including lenalidomide and a PI	**Primary objective**: To evaluate safety and PK of isatuximab SC Endpoints: Safety, dose limiting toxicity **Secondary objective**: To evaluate the efficacy of isatuximab SC/IV administration Endpoints: ORR a.o.	56 randomised and treated 10 mg/kg IV N = 12 1000 mg SC infusion pump N = 12 1400 mg SC infusion pump N = 10 1400 mg SC OBDS N = 22
Phase 2 ACT17453 (IZALCO)	A randomized, Phase 2, open label study evaluating subcutaneous administration of isatuximab in combination with	Isa-SC 1400 mg Q1W in Cycle 1, then Q2W via manual administration or OBDS	Adult RRMM patients having received 1 to 3 prior lines of therapy.	**Primary objective**: Describe the efficacy of isatuximab SC Endpoints: ORR according to the 2016 IMWG criteria assessed by IRC **Key secondary objective**: To evaluate patient preference for the	74 randomised and treated Cohort 1 & 2: Manual administration for safety review N = 8 Cohort 3:

	carfilzomib and dexamethasone			OBDS versus manual administration of isatuximab SC. Endpoints*:* Patient preference for method of administration defined as the proportion of participants preferring OBDS over manual administration of isatuximab SC at Cycle 6/Day 15 using the PESQ Version 2.	1400 mg SC started with manual administration N = 42 1400 mg SC started with OBDS N =24
IIT17756 (IsaSoCut)	Multicentre, single-arm, Phase 2 study of subcutaneous isatuximab plus bortezomib, lenalidomide and dexamethasone Conducted across 23 sites in France DCO 8 months after LPI	Isa-SC 1400 mg Q1W in Cycle 1, then Q2W via OBDS	Adult Transplant ineligible NDMM	**Primary objective**: To describe the efficacy of isatuximab SC Endpoints: VGPR+ rate up to 8 months, assessed by Investigator based on 2016 IMWG criteria **Secondary Objective**: To evaluate the efficacy of Isatuximab SC in combination with VRd Endpoints: ORR a.o.	65 randomised and treated
Phase 3					
IIT17041 (GMMG-HD8)	A randomized Phase 3 non-inferiority trial assessing lenalidomide, bortezomib and dexamethasone induction therapy with either intravenous or subcutaneous isatuximab *Conducted across +/- 100 sites across Germany and Austria* Descriptive data, based on an interim safety analysis planned after 120 patients completed induction	Arm A: Isa-SC 1400 mg (OBDS) or Arm B: Isa-IV 10 mg/kg Q1W for 1 cycle, Q2W for cycles 2 and 3 followed by HDT-ASCT and consolidation/maintenance	Adult Transplant eligible NDMM up to 70 y/o	**Primary objective**: To describe the efficacy of isatuximab SC in combination with VRd after induction therapy Endpoints: VGPR+ at the end of induction, assessed by Investigator based on 2016 IMWG criteria **Secondary objective**: To describe SC isatuximab compared to IV isatuximab, both in combination with VRd, with respect to ORR after induction therapy Endpoints: ORR according to the 2016 IMWG criteria.	514 to be randomised and treated At DCO, 142 participants were enrolled Isa-SC: N = 69, of which N = 60 completed induction Isa-IV: N =73, of which N = 64 completed induction
Pivotal study: EFC15951 (IRAKLIA)	A randomized, Phase 3, open label study evaluating subcutaneous versus intravenous administration of isatuximab in combination with pomalidomide and dexamethasone	Arm A: Isa-SC 1400 mg (OBDS) or Arm B: Isa-IV 10 mg/kg Q1W in Cycle 1, then Q2W	Adult RRMM patients who have received at least 1 prior line of therapy including lenalidomide and a PI	**Primary objective**: Demonstrate the efficacy and PK non-inferiority between isatuximab SC and isatuximab IV in combination with Pd. Endpoint: ORR according to the 2016 IMWG criteria by IRC. Demonstrate the non-inferiority the geometric mean ratio of Ctrough at steady state Endpoints: Observed Ctrough concentration at steady state (pre-dose plasma concentration at Cycle 6 Day 1) **Key secondary objectives**: Assess efficacy of isatuximab SC compared to isatuximab IV in combination with Pd. Endpoint: VGPR+ rate according to the 2016 IMWG criteria assessed by IRC. Assess PK (Ctrough at 4 weeks) with isatuximab SC and IV. Endpoint: Observed concentration at 4 weeks (Cycle 2 Day 1 predose) Assess patient satisfaction with isatuximab SC and IV. Percentage of participants satisfied or very satisfied with the injection method used to administer study medication based on the PESQ questionnaire. Assess safety of isatuximab SC and IV in combination with Pd. Incidence rate IRs.	531 randomised and 527 treated Isa-SC N = 263 Isa-IV N = 268

a.o. = and others; DCO = data cut-off; IMWG = International Myeloma Working Group; IRs = infusion reactions; Isa = isatuximab; IRC = independent review committee; IV = intravenous; Kd = carfilzomib and dexamethasome; LPI = last patient in; NDMM = newly diagnosed multiple myeloma; OBDS = on-body delivery system; ORR = Overall Response Rate; Pd = pomalidomide and dexamethasone; PESQ = patient experience and satisfaction questionnaire; PI = proteasome inhibitor; PK = pharmacokinetic; RRMM = relapsed/refractory multiple myeloma; SC = sub-cutaneous; VGPR = very good partial response; VRd = lenalidomide, bortezomib and dexamethasone; Q1W = every week; Q2W = every 2 weeks; y/o = years old

5.2. Clinical pharmacology

5.2.1. Methods

The methods used for analysis of isatuximab (DOH1586), anti-isatuximab antibodies (DOH1517) and neutralising antibodies against isatuximab (DOH0718) were used in previous applications and the validation was assessed in these procedures.

The analysis of isatuximab showed consistent results in the 5 studies used for this application. Incurred sample reproducibility was performed in line with the requirements and was acceptable with 70.8% to 97.7% of the samples meeting the criteria. The samples were analysed within the stability period validated at the time of the analysis. Reasons for failed runs were provided.

For the measurement of PD markers in Study TCD15484, a new assay method was developed and validated. to quantify the CD38 receptor density (CD38RD) and its occupancy (CD38RO) on cancer cells (see Study FCM0028), in the presence of isatuximab. This method quantifying the receptor occupancy is specific to isatuximab as there is no interference with daratumumab with the use of a non-competitive antibody.

The method used for the assay of anti-isatuximab antibodies (DOH1517) was the same method as used in previous applications. A PandA assay using the Meso Scale Discovery platform was validated at Labcorp Drug Development (formerly Covance), Harrogate, United Kingdom, for the detection, confirmation, and titer determination of ADAs in human K3-EDTA plasma.

5.2.2. Pharmacokinetics

The pivotal study EFC15951 was a Phase 3 randomised, multicenter, open-label study evaluating SC versus IV administration of isatuximab in combination with Pd in adult participants with RRMM who received at least 1 prior line of therapy including lenalidomide and a PI. The study aimed to demonstrate the efficacy and PK non-inferiority of isatuximab SC+Pd compared with IV+Pd.

Isatuximab was administered as either 1400 mg SC or 10 mg/kg IV QW for 4 weeks (Cycle 1) and Day 1 and 15 of subsequent cycles.

Randomisation was stratified by MM isotype (immunoglobulin G [IgG] versus non-IgG), body weight (≤65 kg, >65 to ≤85 kg, and >85 kg), and number of prior lines (1-2 versus ≥3). A total of approximately 534 participants were planned, and eventually 531 participants were eligible and were randomized 1:1 into the SC arm, which received isatuximab SC at 1400 mg with a device injector (OBDS), and the IV arm, which received isatuximab IV at 10 mg/kg. Both forms were administered weekly for 4 weeks (Cycle 1) and on Day 1 and Day 15 of each subsequent cycle, in combination with Pd.

Plasma samples for analysis of isatuximab plasma concentrations after Isa-SC were collected at start of SC injection on dosing days from Cycle 1 Day 1 to Cycle 6 Day 1 and at 8, 24 and 96 hours after start of injection on Cycle 1 Day 1 and at 6, 24 and 96 hours after start of injection on Cycle 1 Day 22. Plasma samples for analysis of isatuximab plasma concentrations after Isa-IV were collected at start of IV infusion on dosing days from Cycle 1 Day 1 to Cycle 6 Day 1, at the end of infusion on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 4 and 5 Day 1, 1 hour after end of infusion on Cycle 1 Day 1 and 48 hours after start of injection on Cycle 1 Day 1.

The PK-related primary and secondary endpoints, based on observed concentration data, demonstrated non-inferiority of Isa-SC compared to Isa-IV: for both endpoints, the lower bound of the 90% CI of the

ratio of the geometric means (SC/IV) was greater than the non-inferiority margin of 0.80 as indicated in Table 4.

Table 4: Summary of C_{trough} at steady state (Cycle 6 Day 1) and after 1 cycle (CT4W) – Study EFC15951

C_{trough} (ug/mL)	Isa-IV + Pd	Isa-SC + Pd
Cycle 6 Day 1		
Number	121	121
Mean (SD)	340.45 (168.99)	499.07 (258.96)
SEM	15.362	23.542
Median	342.00	429.00
Q1 ; Q3	222.00 ; 450.00	329.00 ; 656.00
Min ; Max	5.0 ; 778.0	57.4 ; 1200.0
CV	49.636	51.888
Geometric Mean	278.15	426.16
Ratio of geometric mean of Isa-SC/Isa- IV		1.532
90% CI for ratio of geometric mean[a]		1.316 ; 1.784
Cycle 2 Day 1 (CT4W)		
Number	126	131
Mean (SD)	301.90 (117.13)	421.48 (214.89)
SEM	10.435	18.775
Median	298.00	388.00
Q1 ; Q3	225.00 ; 391.00	262.00 ; 524.00
Min ; Max	46.4 ; 809.0	5.0 ; 1460.0
CV	38.797	50.985
Geometric Mean	276.55	360.20
Ratio of geometric mean of Isa-SC/Isa- IV		1.302
90% CI for ratio of geometric mean[a]		1.158 ; 1.465

CI: confidence interval
a Two-sided 90% CI. Applied anti-log procedure to convert original scale. Statistically significance will meet if lower limit of 90% CI is greater or equal to 0.80.

5.2.2.1. Evaluation and qualification of models

5.2.2.1.1. Population Pharmacokinetics

POH0770: Population PK analysis of data from Study TCD15484 (Phase 1, IPd in RRMM)

The objectives of this analysis were to develop a population PK model for isatuximab to characterise its PK properties after SC administration in patients using plasma concentration-time data (functional isatuximab) from Phase 1 Study TCD15484, and to provide individual PK and exposure parameter estimates to be further used in the PK/PD analyses to support SC dose selection (DDM0040).

The analysis set contained isatuximab plasma concentrations from 56 patients for a total of 1576 individual observations. Of the 56 patients, 12 received Isa-SC 1000 mg (via infusion pump), 10 received Isa-SC 1400 mg (via infusion pump), 22 received Isa-SC 1400 mg (via OBDS), and 12 received Isa-IV. The structural PK model was built in two steps. First, the statistical PK model was developed with a combined residual error and log-normally distributed inter-individual variability (IIV) on PK parameters, except absolute bioavailability (F) and the concentration of isatuximab corresponding to half of maximum

binding capacity (Km) due to high precision on IIV. Then, the IIV on several parameters was tested for significance and meaningfulness. Inter-occasion variability was not implemented in the analysis. As an exploratory analysis, models with the time-varying clearance were tested referring to the isatuximab population PK model in RRMM patients (POH0503, included in the original Isa-IV [IPd] submission).

The analyses were performed using the non-linear mixed effects model with the MONOLIX software 2023 with the stochastic approximation expectation-maximization (SAEM) algorithm. Several structural PK models were evaluated.

Study POH0770 was based on a model used for earlier PK analysis of the IV administration (POH0458) that was used for the original Isa-IV submission. The POH0770 model was developed with the data from the phase 1b study with Isa-SC (TCD15484). Study POH0770 was primarily designed to determine the dose level used in the further phase 2 and 3 studies.

Population PK model (Study POH1117)

The pharmacokinetics of isatuximab was best described by a 2-compartment structural kinetic model with linear elimination from the central compartment, a combined residual error model and interindividual variability on all parameters.

Data from 769 MM patients (12928 plasma concentrations) from the IPd, IKd, and IVRd studies were used. EFC15951 data accounted for 68 and 71% of total number of patients and total number of observed plasma concentrations in POH1117, respectively. Overall, approximately 60 and 40% of total data were collected after SC and IV administrations, respectively.

Qualification of the population PK model was performed using standard goodness-of-fit plots, visual predictive checks and nonparametric bootstrap with resampling from the original dataset.

The analyses were performed using nonlinear mixed effects modeling methodology as implemented in Monolix 2024R1 with the SAEM algorithm. Pre- and post-processing of data from each modeling step was conducted using R software or SAS/JMP software.

Study POH1117 described the popPK of the 5 studies provided in this application. The structural PK model building was performed considering the previously identified population PK models in POH0503 and POH1230.

5.2.2.2. Absorption

In Phase 1 Study TCD15484, 1000 mg and 1400 mg doses of Isa-SC were selected using the same dosing schedule as Isa-IV 10 mg/kg. Based on population PK model-based simulations, the 1400 mg SC dose (with a bioavailability between 50 and 80%) was shown to achieve C_{trough} concentrations at 4 weeks (the best predictor for efficacy) comparable to the target C_{trough} from a 10 mg/kg IV dose. Assuming a bioavailability of 80%, the predicted C_{trough} and C_{max} after 1400 mg SC dose were below the C_{trough} and C_{max} values from the highest tested IV dose of 20 mg/kg, which is also a safe and efficacious dose.

In Study TCD15484, after completion of the first 2 cohorts at 1000 and 1400 mg, the SC dose of 1400 mg was selected for the SC-OBDS cohort based on trial simulations. Briefly, simulations were conducted to select a SC dose non-inferior to IV 10 mg/kg (ie, the lower bound of the 90% confidence interval [CI] for the SC/IV ratio for C_{trough} at 4 weeks [CT4W, the best PK predictor for efficacy] was to be at least 0.80). These simulations showed that a 1000 mg SC dose had a low probability of success (<50%) for achieving PK non-inferiority, while the probability of success was predicted to be at least 90% after a 1400 mg SC dose when considering a SC bioavailability in the range of 60-65%. This was later confirmed with simulations conducted per the EFC15951 study design, where C_{trough} at steady state

([$C_{trough,SS}$] C6D1, the co-primary endpoint in Study EFC15951) after a 1400 mg SC dose was predicted to have at least a 90% probability of success to be non-inferior to IV 10 mg/kg.

Isatuximab was slowly absorbed when administered SC as shown in Figure 1 and Figure 2 with a rate of absorption (Ka) of 0.00715 $hour^{-1}$ based on population pharmacokinetic evaluation (POH1117). The maximum plasma concentration of isatuximab was achieved at a median t_{max} generally between 83 and 165 hours (TCD15484 and ACT17453) over Cycle 1 (following the first or fourth administration), with no apparent dose effect or effect of SC delivery methods (infusion pump or manual administration vs OBDS) (Table 5 and Table 6).

Figure 1: Mean (SD) isatuximab plasma concentrations-time profiles after a single dose (Cycle 1) of isatuximab – linear and semilog scales (TCD15484)

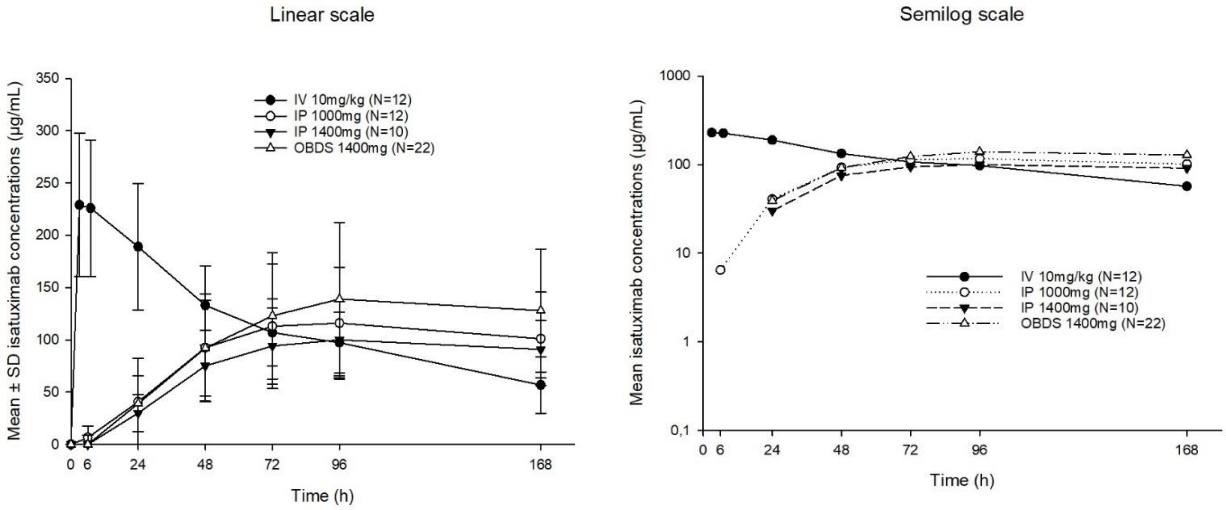


Figure 2: Mean (SD) isatuximab plasma concentrations-time profiles after repeated administrations (Cycle 3) of isatuximab – linear and semilog scales (TCD15484)

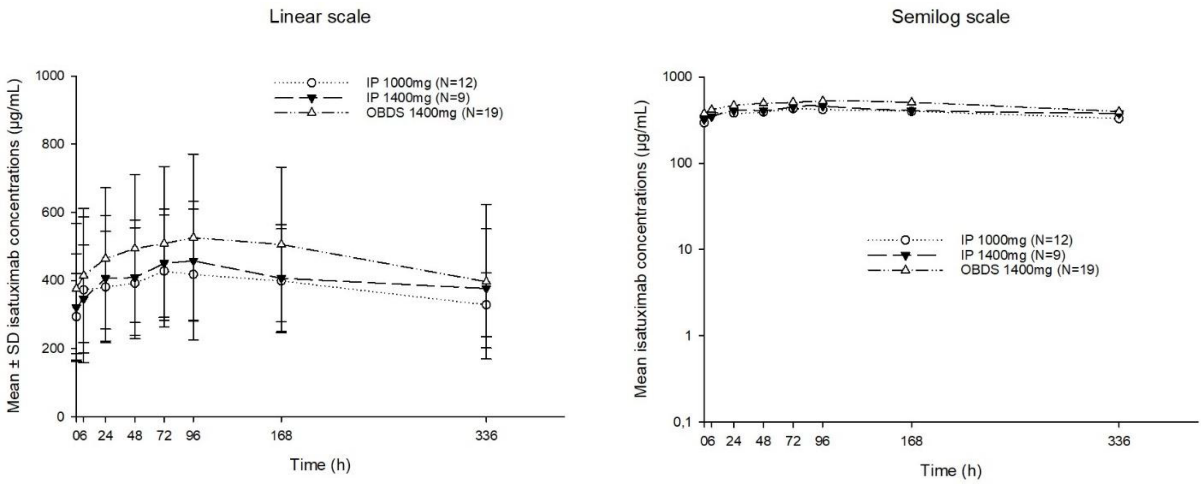


Table 5: Isatuximab PK parameters after the first administration at Cycle 1 by treatment cohort using NCA (TCD15484)

Mean ± SD (Geometric mean) [CV%]	IV 10 mg/kg (Cohorts 1b and 2b)	SC 1000 mg pump (Cohort 1a)	SC 1400 mg pump (Cohort 2a)[a]	SC 1400 mg OBDS (Cohort 3)[a]	SC 1400 mg pool (Cohorts 2a and 3)
N	12	12	10	22	32
C_{max} (µg/mL)	234 ± 66.7 (225) [29]	120 ± 56.1 (108) [47]	104 ± 34.8 (98.6) [33]	145 ± 71.4 (130) [49]	132 ± 64.6 (119) [49]
t_{max}[b] (h)	3.63 (3.33-11.3)	83.2 (44.4-168)	92.6 (68.4-168)	95.1 (46.9-192)	94.7 (46.9-192)
AUC_{0-168h} (µg•h/mL)	19300 ± 5320 (18500) [28]	18000 ± NC[c] (18000) [NC]	11300 ± 5240[d] (10500) [46]	16500 ± 8920[e] (13700) [54]	14100 ± 7640[f] (12100) [54]
AUC_{last} (µg•h/mL)	18700 ± 5460[g] (18000) [29]	15200 ± 7760[g] (13500) [51]	13100 ± 5080 (12300) [39]	18500 ± 8470[h] (16800) [46]	16700 ± 7880[i] (15200) [47]
C_{last} (µg/mL)	63.2 ± 34.1 (52.8) [54]	102 ± 42.6 (94.5) [42]	90.8 ± 27.5 (86.9) [30]	129 ± 56.0 (117) [43]	117 ± 51.7 (107) [44]
T_{last} [b] (h)	168 (95.9-170)	167 (93.7-168)	168 (164-187)	167 (94.1-192)	167 (94.1-192)

Table 6: Isatuximab PK parameters at Cycle 3 by treatment cohort using NCA (TCD15484)

Mean ± SD (Geometric mean) [CV%]	SC 1000mg pump	SC 1400mg pump	SC 1400mg OBDS	SC 1400mg pool
N	12	9	19	28
C_{max} (µg/mL)	446 ± 191 (416) [43]	470 ± 180 (437) [38]	541 ± 231 (503) [43]	518 ± 215 (480) [42]
t_{max} [a] (h)	93.1 (5.00-166)	95.0 (19.8-191)	93.7 (21.2-192)	94.2 (19.8-192)
AUC_{0-336h} (µg•h/mL)	131000 ± 53000[b] (123000) [41]	169000 ± 48600[c] (165000) [29]	128000 ± 36200[d] (123000) [28]	139000 ± 41500[e] (132000) [30]
AUC_{last} (µg•h/mL)	143000 ± 56100[d] (135000) [39]	141000 ± 58500 (129000) [42]	165000 ± 73700[f] (153000) [45]	157000 ± 68600[g] (144000) [44]
C_{last} (µg/mL)	316 ± 83.9 (304) [27]	377 ± 175 (336) [47]	408 ± 203 (370) [50]	398 ± 192 (358) [48]
t_{last} [a] (h)	336 (164-386)	336 (311-362)	336 (149-339)	336 (149-362)

Abbreviations: AUC_{0-336h}=area under the concentration-time curve from time zero to 336h; AUC_{last}=area under the concentration-time curve from time zero to tlast; C_{last}=last concentration observed above the lower limit of quantitation; C_{max}=maximum concentration observed; CV=coefficient of variation; SD=standard deviation; t_{max}=time to reach C_{max}; t_{last}=time of C_{last}

a Median (Min – Max)
b N=7
c N=3
d N=9
e N=12
f N=17
g N=26

5.2.2.2.1. Bioavailability

Absolute bioavailability of Isa-SC was estimated at 75.9% in the population PK analysis (POH1117).

Administration of Isa-SC with OBDS or manual administration resulted in comparable pharmacokinetics over 1 administration cycle, as is indicated in Table 7.

Table 7: Descriptive statistics of individual isatuximab exposure parameters at 1400 mg following manual administration or OBDS over Cycle 1 - NCA analysis (ACT17453)

	Cycle 1 1st administration		Cycle 1 4th administration		Over Cycle 1 (4 weekly administrations)	
Mean ± SD (Geometric mean) [CV%]	**OBDS**	**Manual administration**	**OBDS**	**Manual administration**	**OBDS**	**Manual administration**
N	13	16	9	8	6	6
C_{max} (µg/mL)	133 ± 70.7 (116) [53]	131 ± 40.6 (120) [31]	471 ± 138 (457) [29]	499 ± 148 (482) [30]	525 ± 150 (509) [29]	465 ± 120 (454) [26]
t_{max}[a] (h)	165 (91.2-170)	162 (91.3-169)	95.3 (21.9-167)	93.9 (0-168)	599 (527-671)	598 (482-672)
AUC_{last} (µg•h/mL)	14700 ± 9030 (12500) [62]	13600 ± 5000 (12200) [37]	72900 ± 28600 (68900) [39]	74000 ± 21200 (71700) [29]	203000 ± 79000 (193000) [39]	173000 ± 37600 (169000) [22]
Cl_{last} (µg/mL)	127 ± 66.4 (110) [52]	121 ± 37.4 (112) [31]	413 ± 113 (402) [27]	473 ± 139 (456) [29]	443 ± 127 (430) [29]	449 ± 142 (433) [32]
t_{last}[a] (h)	168 (146-189)	167 (145-169)	168 (166-191)	168 (143-191)	671 (670-696)	672 (649-693)

Abbreviations: AUC_{last}=area under the concentration-time curve from time zero to t_{last} with t_{last} corresponding to C1D8 (prior 2nd administration) for the AUC calculated after the 1st administration and corresponding to C2D1 (prior 5th administration) for AUC calculated over Cycle 1 (ie, cumulative AUC over 4 weeks); AUC last corresponds to partial AUC from C1D22 (prior 4th administration) to C2D1 (prior 5th administration) for AUC after 4th administration; C_{last}=last concentration observed above the lower limit of quantitation, corresponding to C1D8 for Clast after the 1st administration, to C2D1 for Clast after the 4th administration or over Cycle 1; C_{max}=maximum concentration observed; CV=coefficient of variation; SD=standard deviation; t_{max}=time to reach C_{max}; t_{last}=time of C_{last}, corresponds to C1D8 (168h after the 1st administration), to C2D1 after the 4th administration (ie, 168 hours after the 4th administration) or over Cycle 1 (ie, 671/672 after the first administration).
a Median (Min-Max)

5.2.2.2.2. Bioequivalence

One isatuximab SC formulation and one IV formulation was used for all studies in this application.

Based on NCA and on modeling, there is no impact on isatuximab PK due to the SC mode of administration (infusion pump, manual, or OBDS SC administration).

The administration methods applied for (manual and OBDS) are compared using the popPK model. Based on the geometric mean ratios and the 90% CI's of C_{trough}, C_{max}, and AUC after the first administration, the first administration cycle and Cycle 3 1st administration, Cycle 3 2nd administration, Cycle 6 1st administration, and Cycle 6 2nd administration there is no difference between the methods of administration geometric mean ratios (1.04 to 1.14).

5.2.2.3. Distribution

Based on the population PK analysis, the volume of distribution for the central compartment (V1) was 2.90 L and 2.78 L for the peripheral compartment (V2) resulting in a total volume of distribution of 5.68 L

(POH1117, Table 9). This suggests that isatuximab is primary distributed in the vascular systems with some limited extravascular tissue distribution, consistent with what is known for other IgG1 based mAbs.

5.2.2.4. Metabolism

Specific metabolism studies were not conducted with isatuximab. As a large protein, isatuximab is expected to be metabolized by non-saturable proteolytic catabolism processes.

5.2.2.5. Elimination

No specific elimination and excretion studies were conducted. As a large protein, isatuximab is expected to be eliminated by non-saturable proteolytic catabolism processes whichever the route of administration (IV or SC).

Isatuximab CL is governed by two parallel elimination pathways: a nonlinear, target mediated pathway prominent at low concentrations; and a nonspecific, linear pathway prominent at higher concentrations. This could be explained by 2 processes, a parallel linear and nonlinear saturable, target-mediated clearance in the population PK analysis. The contribution of nonlinear CL to the total CL is negligible following the therapeutic doses of either 1400 mg SC or 10 mg/kg IV QW/Q2W. The model estimated mean linear clearance is 4.45 mL/h and is associated with a time-dependent decrease described by a sigmoidal Emax function (data not shown). For a typical patient, the linear clearance decreases 50% from its initial value over the first 11 weeks of treatment. Based on a population PK analysis, the typical half - life at steady state associated with the linear CL is 40.2 days.

Consistent with the Isa-IV program, an association between time-varying linear CL and clinical response rate was confirmed with Isa-SC (Study EFC15951); the reduction in inflammation and IgG M-protein- leads to a greater proportion of isatuximab going through salvage pathways resulting in lower clearance.

5.2.2.6. Dose proportionality and time dependency

In Study TCD15484, following an increase in SC dose from 1000 mg and 1400 mg by an infusion pump, isatuximab C_{max} and AUC_{1week} after the first dose were comparable (Table 10). This is likely due to imbalances in patient characteristics in the small cohort of patients who received 1400 mg Isa-SC via the infusion pump compared to the other groups. Of note, there was a 20% to 24% higher exposure (Table 11) when 1400 mg was administered by OBDS compared to 1000 mg administered via the infusion pump.

In IRAKLIA pivotal study, isatuximab was administered subcutaneously as a flat dose of 1400 mg with the same schedule of administration as isatuximab 10 mg/kg administered intravenously, every week for 4 weeks followed by every 2 weeks. The median time to reach steady state was 22 weeks (Cycle 6) with 4.87-fold accumulation for C_{trough}. The mean predicted C_{max} (CV%) and AUC2weeks at steady state (Cycle◦6) were 594◦µg/mL (45.7%) and 188,000◦µg.h/mL, respectively.

The typical half-life at steady state associated with the linear CL is 40.2 days.

5.2.2.7. Pharmacokinetics in the target population

All studies were performed in the target population.

5.2.2.8. Special populations

The PK data from SC studies were used to conduct a comprehensive population model-based covariate analysis (POH1117). This analysis showed a moderate to large interindividual variability (CV%) in isatuximab parameters, Ka, linear CL at steady state, CLm, KCL, V1, and V2 (46.9%, 32.9%, 39.4%, 210%, 27.2%, and 51.0%, respectively). Of note, the interindividual variability in F was low (18.3%). The residual variability (CV%) was estimated to be 20.2% (Table 9).

Population PK analysis identified body weight as a significant covariate impacting linear CL at steady state; β2 microglobulin, MM type (IgG versus non-IgG), and serum M-protein level as significant covariates impacting CLm; MM type impacting KCL, body weight, and gender impacting V1; and body weight impacting V2 (Table 9). In addition, a study effect was identified, impacting linear CL at steady state. The presence of ADA had no impact on the PK of isatuximab, consistent with previous observations in RRMM, acknowledging that RRMM patients represent 85% of the MM population dataset.

Table 8: Final popPK parameters (Study POH1117)

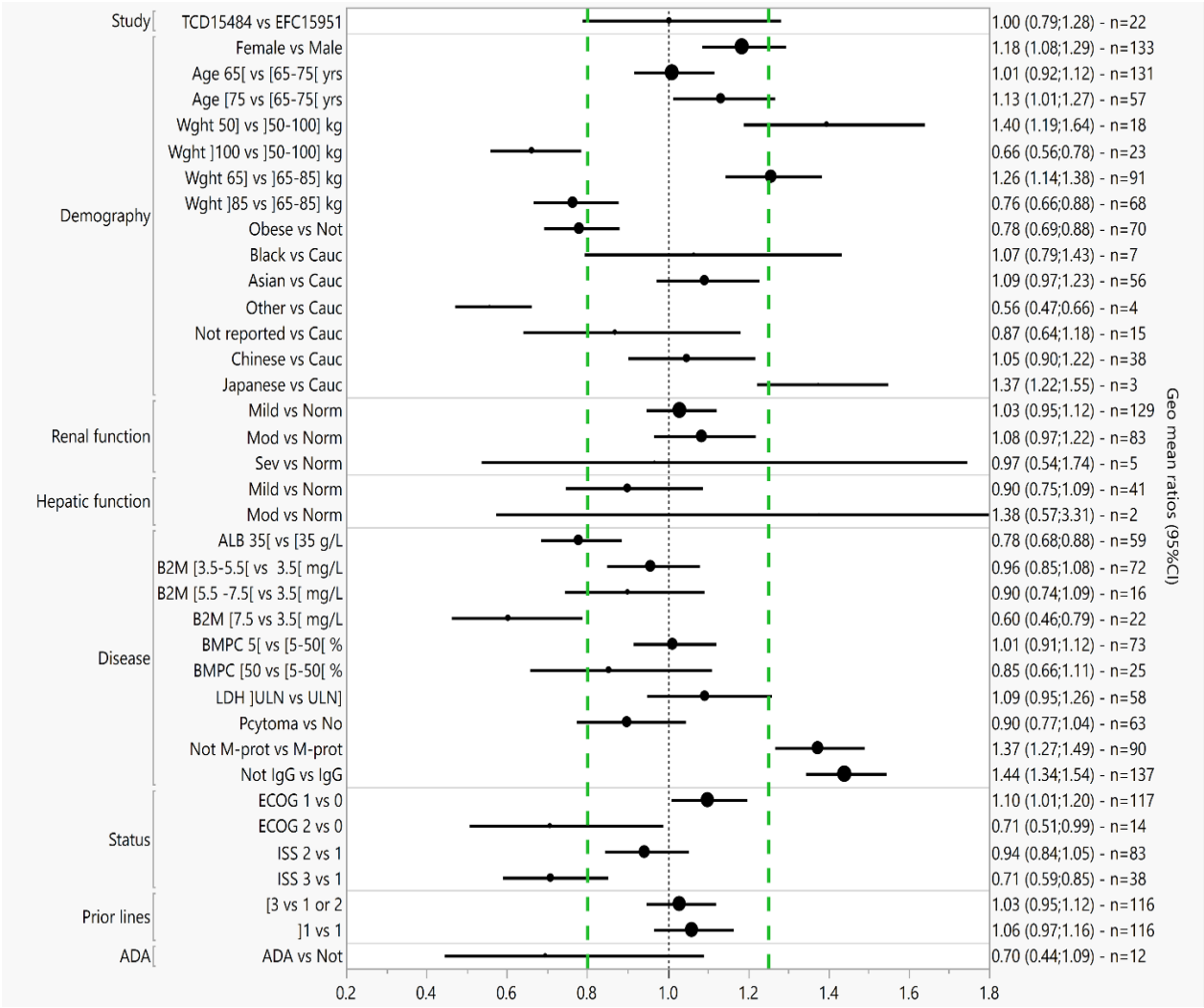
	Parameter	Estimate	RSE (%)
Ka (1/h)		0.00715	3.11
F		0.759	1.55
CLinf (L/h)		0.00445	1.80
	β_{CLinf} ~ Weight	0.925	7.35
	β_{CLinf} ~ ACT17453	-0.359	15.2
	β_{CLinf} ~ IIT17041/IIT17756	-0.165	30.7
CLm		0.909	3.31
	β_{CLm} ~ Non IgG	0.331	20.1
	β_{CLm} ~ B2M	0.385	6.64
	β_{CLm} ~ MPROT	0.134	12.3
KCL (h)		1885	9.38
	β_{KCL} ~ Non IgG	-2.41	7.18
Gamma		4.02	9.38
V1 (L)		2.90	2.14
	β_{V1} ~ Weight	0.500	14.8
	β_{V1} ~ Female	-0.0919	36.2
Q (L/h)		0.0129	5.87
	β_{Q} ~ Weight	0.819	28.7
V2 (L)		2.78	3.80
	β_{V2} ~ Weight	0.453	33.5
ω(Ka) (CV %)		46.9	5.99
ω(F) (CV %)		18.3	7.09
ω(CLinf) (CV %)		32.9	3.75
ω(CLm) (CV %)		39.4	6.16
ω(KCL) (CV %)		210	5.50
ω(Gamma) (CV %)		154	6.51
ω(V1) (CV %)		27.2	5.06
ω(Q) (CV %)		91.7	8.00
ω(V2) (CV %)		51.0	6.64
σ_{add} (mg/L)		6.74	5.78
σ_{prop} (%)		20.2	1.13

CLinf = 0.00445 * (Wght/72.8)^0.925 * exp(-0.165*IIT) * exp(-0.359*ACT) with IIT=1 for IIT17041 & IIT17756, else IIT=0, ACT=1 for ACT17453, else ACT=0.
CLm = 0.909 * (B2M/3.00)^0.385 * (MPROT/1.20)^0.134 + (0.331*Non IgG) with Non IgG=1 for Non IgG, else Non IgG=0.
KCL = 1885 * exp(-2.41*Non IgG)
V1 = 2.90 * (Wght/72.8)^0.500 * exp(-0.0919*Female) with Female=1 for Female, else Female=0.
Q = 0.0129 * (Wght/72.8)^0.819
V2 = 2.78 * (Wght/72.8)^0.453

Baseline covariates identified as sources of variability with Isa-SC are consistent with those identified previously in Isa-IV program; the main influential covariates remained the same. Ig MM Type and body weigh being by far the most impactful covariates on exposure (Figure 3).

It is to be noted that serum albumin, MM disease type (serum or urine M-protein or free light chain), ECOG, and ISS stage were not identified as significant covariates in population PK analysis but show an apparent impact on simulated post-hoc exposure of isatuximab (Figure 3), mainly due to the fact that they are correlated to β2 microglobulin or Ig MM type (IgG versus non-IgG), all reflecting the severity or the type of the disease.

Figure 3: Simulated post-hoc isatuximab exposure (C_{trough} at the end of 4 weeks) by covariates (geometric mean ratios of covariate value versus reference [95% CI]) after 1400 mg SC/OBDS in RRMM patients treated with IPd (POH1117)



Impaired renal function

The population PK analysis (POH1117) did not identify the estimated glomerular filtration rate (eGFR) as a significant covariate influencing isatuximab PK. Among the 769 patients included in the analysis, 380 patients were identified with mild renal impairment (60 mL/min/1.73 m^2 ≤ eGFR <90 mL/min/1.73 m^2), 187 patients with moderate renal impairment (30 mL/min/1.73 m^2 ≤ eGFR <60 mL/min/1.73 m^2), and 8 patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2).

Post-hoc exposure after 1400 mg Isa-SC/OBDS QW/Q2W in combination with Pd were similar in patients regardless of renal function (Figure 3).

Impaired hepatic function

The population PK analyses (POH1117) did not identify bilirubin or transaminases as significant covariates influencing isatuximab PK. Among the 769 patients included in the population PK analysis, 95 patients were identified with mild hepatic impairment (total bilirubin 1.0× to 1.5× upper limit of normal [ULN] or AST >ULN), and only 7 patient with moderate hepatic impairment (total bilirubin >1.5× to 3× ULN and any AST). Post-hoc exposure after 1400 mg Isa-SC/OBDS QW/Q2W in combination with Pd was similar in patients with mild hepatic impairment compared to those with normal hepatic function (Figure 3).

Gender

Among the 769 patients in the population PK dataset (POH1117), 345 (44.9%) were female and 424 (55.1%) were male. The population PK analysis identified gender as a significant covariate influencing isatuximab V1 following SC administration (ie, V1 was 8.78% lower in a typical female patient relative to a typical male patient). However, as the impact was limited to V1, it did not translate to a meaningful impact on exposure (ie, the maximal increase in exposure was 23% in females relative to males when assessed on mean $C_{trough,SS}$ after 1400 mg Isa-SC/OBDS QW/Q2W in combination with Pd. The slightly higher exposure in females observed can be explained by confounding effects with body weight.

Ethnic factors

Population PK analysis with data from 511 Caucasian (66.5% of the population PK data set), 117 Asian (15.2%), 20 Black (2.6%), and 13 patients of other races (1.7%) did not identify race as a significant covariate influencing isatuximab PK following SC administration (POH1117). This translated into no meaningful difference in exposure across Caucasian, Asian, and Black patients in studies TCD15484 and EFC15951 while there was a noticeable lower exposure in 'Other' races after 1400 mg Isa-SC /OBDS QW/Q2W in combination with Pd. Furthermore, within the Asian patients (N=56), post-hoc exposure in Chinese patients (N=38) and Japanese patients (N=3) over Cycle 1 and at steady state were found similar to the overall population after 1400 mg Isa-SC/OBDS QW/Q2W in combination with Pd.

Weight

There is variability in isatuximab exposure based on body weight associated with the SC flat dose. Treatment effect on efficacy endpoints was comparable across body weight groups in Study EFC15951, and no relationship between any safety endpoints of interest (including Grade ≥3 neutropenia, Grade 4 neutropenia, and neutropenic complications) was evident with PK exposure at Cycle 1 (after the first administration or over the 4-weekly administrations).

Body weight was identified as a significant covariate influencing isatuximab PK following SC administration (POH1117).

At a body weight of 105 kg (95th percentile in the population PK dataset), there were increases of 40.3% in linear CL at steady state, 20.1% in V1 and 18.1% in V2 relative to 72.8 kg (median body weight); at a body weight of 49.8 kg (5th percentile), there were 29.6%, 17.3%, and 15.8% decreases in linear CL at

steady state, V1, and in V2 , respectively, relative to a body weight of 72.8 kg (median body weight). As isatuximab is given as a flat dose subcutaneously, it is expected that exposure is inversely correlated with body weight. This translated to an increase in steady-state exposure of 36.8-38.9% for a typical patient weight of 49.8 kg (5th percentile) and a decreased exposure of 26.3-27.5% for a typical patient weighing 105 kg (95th percentile), compared to a typical patient weighing 72.8 kg (median weight). Table 10 shows a similar pattern based on post-hoc exposure in patients across the body weight group (≤50 kg, >50-100 kg, and >100 kg body weight groups).

Table 9: Simulated mean (%CV) post-hoc isatuximab 1400 mg SC/OBDS exposure at Cycle 1 and at steady-state by body weight in RRMM patients treated with IPd (POH1117)

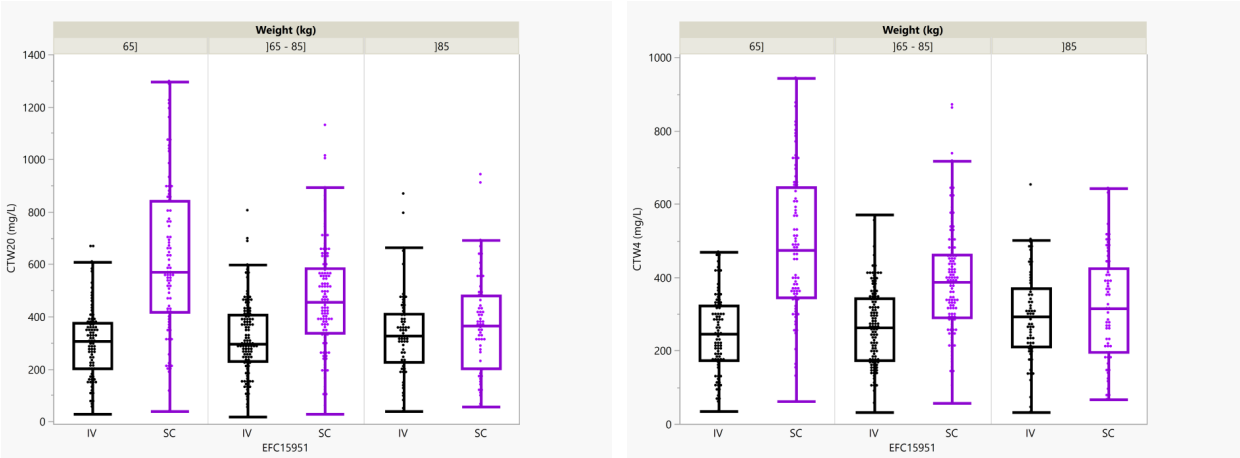
Body weight (kg) (N)	Cycle 1						Steady State[a]		
	1st administration			Over Cycle 1 (4 weekly administrations)					
	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{1week} (µg•h/mL)	C_{max} (µg/mL)	CT4W (µg/mL)	AUC4W (µg•h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{2weeks} (µg•h/mL)
Isa-SC									
≤65 (91)	163 (40.2)	157 (38.3)	20400 (42.8)	519 (38.5)	493 (39.7)	214000 (37.7)	747 (41.3)	628 (46.4)	237000 (42.9)
>65 – ≤85 (124)	130 (41.6)	124 (36.8)	16400 (42.7)	411 (36.6)	387 (37.9)	169000 (35.3)	561 (38.5)	462 (42.9)	177000 (39.4)
>85 (68)	107 (41.7)	102 (40.7)	13600 (41.4)	334 (42.5)	314 (45.9)	138000 (40.9)	443 (44.8)	362 (51.5)	139000 (46.8)
≤50 (18)	190 (38.1)	178 (29.7)	23900 (43.1)	580 (31.7)	538 (31.8)	242000 (30.8)	764 (31.2)	621 (37.6)	240000 (33.0)
>50 - ≤100 (242)	135 (42.7)	129 (40.7)	16900 (43.9)	429 (40.8)	407 (42.6)	176000 (39.7)	602 (44.7)	501 (49.8)	190000 (46.3)
>100 (23)	94.4 (35.2)	90.1 (37.7)	12300 (35.5)	284 (38.1)	262 (41.4)	121000 (37.0)	359 (42.7)	281 (50.2)	112000 (44.7)
Isa-IV (from PopPK study POH0503)									
<50 (14)	130 (21.3)	21.2 (85.6)	8140 (39.6)	-	92.8 (62.6)	57500 (43.8)	255 (38.7)	122 (75.1)	54900 (59.4)
50-99 (418)	170 (30.0)	48.1 (49.2)	13900 (31.7)	-	157 (49.9)	97100 (36.4)	345 (41.1)	173 (72.0)	76500 (57.7)
≥100 (44)	200 (33.3)	56.4 (44.4)	16400 (27.9)	-	186 (49.5)	115000 (33.9)	393 (41.2)	191 (68.9)	85700 (54.3)

AUC_{1week} and AUC_{2weeks} = area under the plasma concentration time curve over the dosing interval of 1 or 2 weeks, respectively; AUC4W = Cumulative area under the plasma concentration-time curve over 4 weeks; C_{max} = maximum concentration; C_{trough} = predose concentration during repeated dosing; CT4W = C_{trough} at 4 weeks; N = number of patients
The body weight groups ≤65 kg, >65 to ≤85 kg, and >85 kg correspond to the EFC15951 protocol randomization stratification categories. The body weight groups ≤50 kg, >50 to ≤100 kg, >100 kg correspond to the extreme body weight categories at EFC15951 baseline (per eCRF).
a Steady state corresponds to C6D1; C_{max} is the first administration of Cycle 6; C_{trough} corresponds to the C_{trough} pre-dose at C6D1; AUC_{2weeks} corresponds to AUC from Week 20 to 22.

Boxplots of exposure by body weight subgroups and route of administration are presented in Figure 4 (≤65, >65-85, and >85 kg) and Figure 5 (≤50, >50-100, and >100 kg). The isatuximab SC flat dose showed acceptable exposure across body weight subgroups; the CT4W following Isa-SC were higher than

(but overlapping with) those following Isa-IV in each body weight subgroup (Figure 4). The same trend was seen at steady state (CT20W).While C_{max} at steady state after 1400 mg SC administration appeared to be slightly higher in the lower BW group (≤65 kg) than those after 10 mg/kg IV administration in the higher BW group (>85 kg), it remained overall lower than the mean C_{max} (CV%) at Cycle 4 for the 20 mg/kg IV dose (1026 µg/mL [73%] administered as monotherapy and in combination with dexamethasone [BAY0063; previously submitted]).

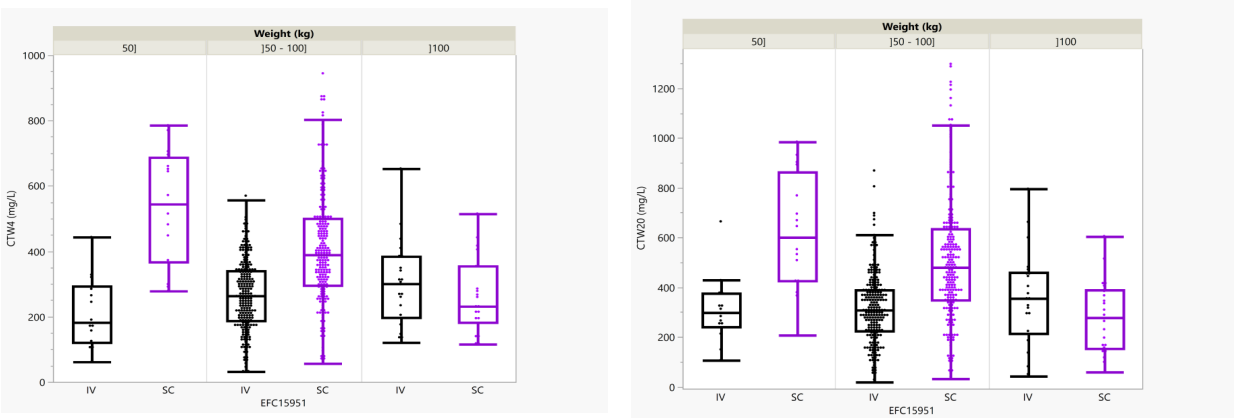
Figure 4: Boxplots of simulated CT4W (C_{trough} at 4 weeks) and CT20W (C_{trough} at 20 weeks) by body weight (per protocol stratification categories) following isatuximab 1400 mg SC/OBDS administration and isatuximab 10mg IV administration in EFC15951 patients with RRMM who received IPd (POH1117)



a) CT4W b) CT20W

For the box plot presentation, the upper and the lower horizontal line corresponds to the 75th and 25th percentiles while the horizontal line in between represents the median; the whiskers represent the furthest values from the median that did not exceed 1.5 × IQR. Dots represent individual values.

Figure 5: Boxplots of simulated CT4W and CT20W by body weight (per extreme body weight categories at EFC15951 baseline) following isatuximab 1400 mg SC/OBDS administration and isatuximab 10mg IV administration in EFC15951 patients with RRMM who received IPd (POH1117)



a) CT4W b) CT20W

For the box plot presentation, the upper and the lower horizontal line corresponds to the 75th and 25th percentiles while the horizontal line in between represents the median; the whiskers represent the furthest values from the median that did not exceed 1.5 × IQR. Dots represent individual values.

Elderly

Population PK analysis using data from the 5 SC studies with 769 patients aged 31 to 86 years (17.8% and 0.9% of patients in the dataset were ≥75 years and ≥85 years of age, respectively) (POH1117) did not identify age as a significant covariate influencing isatuximab PK following SC administration. There were similar post-hoc exposures over Cycle 1 and at steady across the age groups (<65, 65-<75 and ≥75 years old) after 1400 mg Isa-SC/OBDS QW/Q2W in combination with Pd (Table 10).

Table 10: Simulated mean (%CV) post-hoc isatuximab 1400 mg SC/OBDS exposure at Cycle 1 and at steady-state by age in RRMM patients treated with IPd (POH1117)

Age (years) (N)	Cycle 1						Steady State[a]		
	1st administration			Over Cycle 1 (4 weekly administrations)					
	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{1week} (µg•h/mL)	C_{max} (µg/mL)	CT4W (µg/mL)	AUC4W (µg•h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{2weeks} (µg•h/mL)
<65	138	132	17400	430	405	179000	573	470	180000
(131)	(43.5)	(42.5)	(44.0)	(44.5)	(46.8)	(42.8)	(45.5)	(51.9)	(47.5)
65 - <75	131	124	16400	408	385	169000	602	502	191000
(95)	(39.7)	(40.2)	(40.7)	(39.5)	(41.4)	(38.4)	(46.0)	(49.9)	(47.1)
≥75	137	131	17000	452	432	182000	620	520	196000
(57)	(52.1)	(42.4)	(55.5)	(40.2)	(39.8)	(40.6)	(46.2)	(51.2)	(47.5)

AUC_{1week} and AUC_{2weeks} = area under the plasma concentration time curve over the dosing interval of 1 or 2 weeks, respectively; AUC4W = Cumulative area under the plasma concentration-time curve over 4 weeks; C_{max} = maximum concentration; C_{trough} = predose concentration during repeated dosing; CT4W = C_{trough} at 4 weeks; N = number of patients
a Steady state corresponds to C6D1; C_{max} is the first administration of Cycle 6; C_{trough} corresponds to the C_{trough} pre-dose at C6D1; AUC_{2weeks} corresponds to AUC from Week 20 to 22.

The number of patients per age group, i.e., <65 years, 65-74 years, 75-84 years and ≥85 years, presented per study, can be found in Table 11.

Table 11. The number of patients in the different age groups, presented per study

	Age (yrs) - n (% of total)			
Study	65[	[65 - 75[	[75-85[	[85
EFC15951	236 (45.2%)	194 (37.2%)	86 (16.5%)	6 (1.15%)
TCD15484	22 (39.3%)	23 (41.1%)	11 (19.6%)	0 (0%)
IIT17041	42 (80.8%)	10 (19.2%)	0 (0%)	0 (0%)
IIT17756	0 (0%)	41 (63.1%)	24 (36.9%)	0 (0%)
ACT17453	35 (47.3%)	29 (39.2%)	9 (12.2%)	1 (1.35%)
POH1117	335 (43.6%)	297 (38.6%)	130 (16.9%)	7 (0.91%)

Anti-drug antibody

After SC administration, the incidence of treatment emergent ADAs was low in RRMM patients (4.9%), while it was higher in the NDMM patients (15.9%). The majority of patients with ADA positivity had a transient treatment induced ADA (88.9% of RRMM and 92.9% of NDMM patients). The incidence of treatment-emergent NAbs was low (0.5% and 2.3% among RRMM and NDMM patients, respectively).

The median time to first onset of treatment-induced ADA was 0.49 months (approximately 2 weeks, ie at Cycle 1, Day 15) for both RRMM and NDMM.

Based on visual inspection of PK profiles and comparison of PK parameters of the ADA-positive and ADA-negative patients in the population PK analysis, there appeared to be no to minimal effect on isatuximab PK observed following SC administration.

5.2.2.9. Pharmacokinetic interaction studies

No new in-vitro, in-silico or in-vivo interaction studies were performed for this application.

5.2.2.9.1. Dose proportionality

In Study TCD15484, following an increase in SC dose from 1000 mg and 1400 mg by an infusion pump, isatuximab C_{max} and AUC_{1week} after the first dose were comparable (Table 10). This is attributed to imbalances in patient characteristics in the small cohort of patients who received 1400 mg Isa-SC via the infusion pump compared to the other groups. Of note, there was a 20% to 24% higher exposure (Table 11) when 1400 mg was administered by OBDS compared to 1000 mg administered via the infusion pump.

5.2.2.9.2. Time independence

In IRAKLIA pivotal study, isatuximab was administered subcutaneously as a flat dose of 1400 mg with the same schedule of administration as isatuximab 10 mg/kg administered intravenously, every week for 4 weeks followed by every 2 weeks. The median time to reach steady state was 22 weeks (Cycle 6) with 4.87-fold accumulation for C_{trough}. The mean predicted C_{max} (CV%) and AUC_{2weeks} at steady state (Cycle◦6) were 594◦µg/mL (45.7%) and 188,000◦µg.h/mL, respectively.

The typical half-life at steady state associated with the linear CL is 40.2 days.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Isatuximab (SAR650984, hu38SB19) is an immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to a specific extracellular epitope of the human cell surface antigen molecule classified as cluster of differentiation (CD)38.

CD38 is a transmembrane glycoprotein with ectoenzymatic activity, which is highly expressed on plasma cells, with particularly high surface density on MM cells. However, B cell, T cells and natural killer (NK) cells can also upregulate CD38 surface expression to similar levels upon activation.

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

5.2.3.2. Primary and secondary pharmacology

CD38 Receptor Density (RD): Similar levels of CD38 RD were observed at baseline in all cohorts in study TCD15484, with a median RD of 136 180 specific antibody binding capacity (sABC) on bone marrow plasma cells and 16 660 sABC on NK cells following Isa-SC administration. CD38 RD at baseline was 136

736 sABC in responders and 131 686 sABC in non-responders. Similar levels of CD38 RD were observed at C2D1 in all cohorts with a median RD of 17 702.5 sABC on bone marrow plasma cells and 3 760 sABC on NK cells. Median decreases of approximately 85% of CD38 RD on bone marrow plasma cells and approximately 73% on bone marrow NK cells were observed after treatment with isatuximab compared to the baseline. A similar decrease was observed in all cohorts as well as in responders and non-responders.

CD38 Receptor Occupancy (RO): There was high CD38 RO on bone marrow plasma cells by isatuximab observed at C2D1 in all cohorts (median RO ranging between 73% and 81%) and in responders and non-responders (median RO was approximately 79% for each group). Median CD38 RO values were Isa IV 10mg/kg + Pd: 73.9% vs. All Isa 1400mg + Pd: 79.1%.

CD38 RO by isatuximab on NK cells was observed at C2D1 in all cohorts (median RO ranging between approximately 65% and 70%) and in responders and non-responders (median RO was approximately 68% and 63%, respectively).

Immune cell analysis: In all the participant samples, the bone marrow plasma cells expressed CD38. A median decrease of 49.4% of CD38+ bone marrow plasma cells was observed at C2D1 compared to the baseline. A higher median decrease of CD38+ bone marrow plasma cells was observed in responders (55.4%) compared to non-responders (29.9%).

The median CD38 expression in total bone marrow NK cells was 97.3% at baseline and 97.1% at C2D1. A median decrease of 75.3% of CD38+ NK cells as a percentage of bone marrow leukocytes was observed after treatment with isatuximab compared to the baseline. A similar median decrease was observed in responders (69.8%) and non-responders (87.7%).

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

N/A

5.2.3.4. Genetic differences in PD response

N/A

5.2.3.5. Immunological events

The presence of anti-isatuximab antibodies (ADA) was measured in all participants treated with isatuximab, either IV or SC. All participants were evaluable for immunogenicity in study in TCD15484 (N=56). In the all Isa-SC + Pd pool (N=44), 95.5% of participants were ADA negative at baseline, and 9.1% of participants developed ADA during isatuximab treatment vs. 8.3% in the Isa-IV cohort. The incidence of treatment-emergent NAbs was low (0.5% and 2.3% among RRMM and NDMM patients, respectively).

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

PK/PD relationship for efficacy

Among the different PK exposure parameters tested, C_{trough} at 4 weeks (CT4W) was found to be the best predictor of ORR ($p < 0.0001$). The probability of an ORR was found to increase with a log-linear increase of CT4W (log-linear form of logit function CT4W link; Figure 6 and Figure 7). Besides CT4W, the final logistic regression model included weight (as a log function), presence of plasmacytoma (yes/no), age (≥75 years versus <75 years), prior line of therapy (≥3 versus <3), and refractory to IMiD (yes/no). For

the same CT4W value, the model predicted a higher ORR in patients aged <75 years, with less than 3 prior lines, not refractory to IMiD, and without plasmacytoma disease. In addition, ORR increased with increased body weight (log).

Based on the final model, the overall model-predicted ORR rate was 76.5% when the CT4W was above the median and was 66.9% when the CT4W was below or equal to the median. Moreover, when focusing on the lowest part of the E-R curve, the model-predicted ORR was 59.4% for the 1st exposure quartile (Q1) (Figure 7). Additional analysis of the lowest exposure quartile suggests that results in this quartile were confounded by the patients' baseline disease characteristics (more patients with higher disease burden or poor prognosis characteristics in MM), and by high incidence in dose modifications both for isatuximab and pomalidomide.

The subgroup analysis showed similar efficacy in terms of ORR across the body weight range evaluated (≤65, 65-85, and >85 kg) after the flat Isa-SC dose regimen compared to IV weight-based dose regimen in Study EFC15951. It is to be noted that body weight was significantly associated with ORR after adjusting for exposure in the E-R analysis for efficacy for Isa-SC but not for Isa-IV (CTS0153); ORR increased with body weight (log function). As such the ORR was predicted to be lower for lower extreme body weight (≤50 kg) compared to higher body weight (>50-100 kg) for a given CT4W. However, the weight effect was confounded by the patients' disease characteristics as there was a higher proportion of patients in the lowest extreme body weight group with high-risk cytogenetics, albumin levels (<35 g/L), and higher percentage of bone marrow plasma cells, and all are refractory to PI or IMiDs at any regimens. These disease characteristics are well-known prognostic factors of lower probability of response to treatment.

Figure 6: Typical patient and mean of individual model-predicted ORR versus CT4W based on the final model - Isa SC in PK/PD Efficacy population (N=261) (CTS0153)

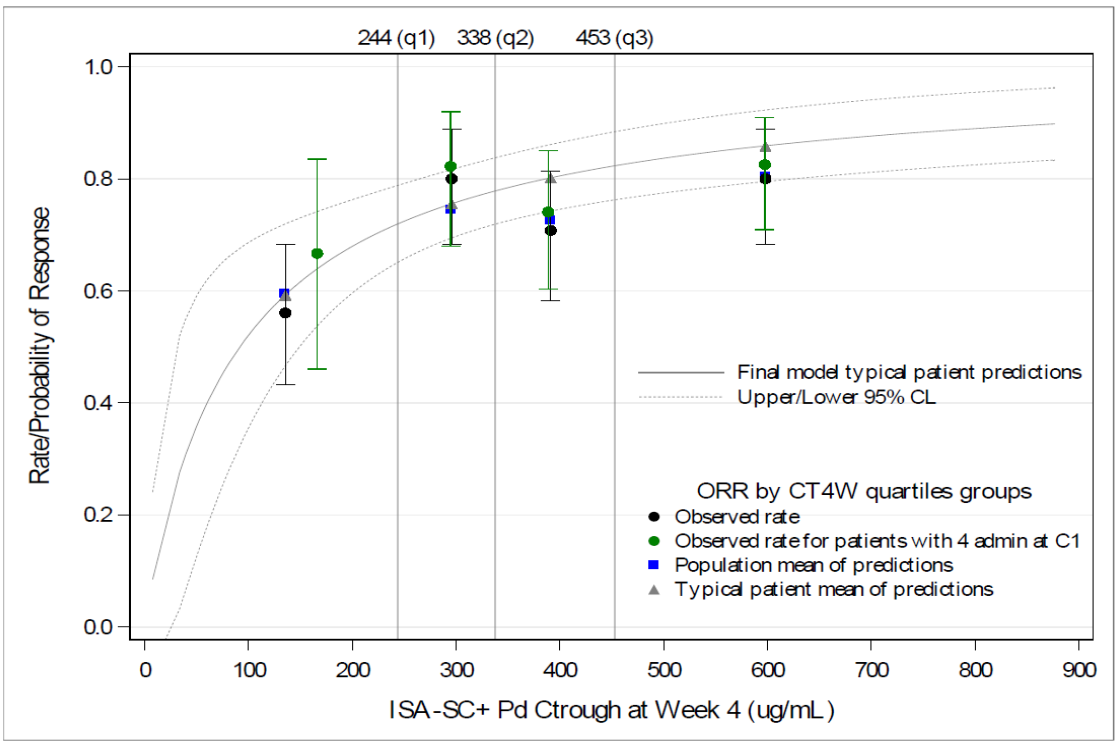
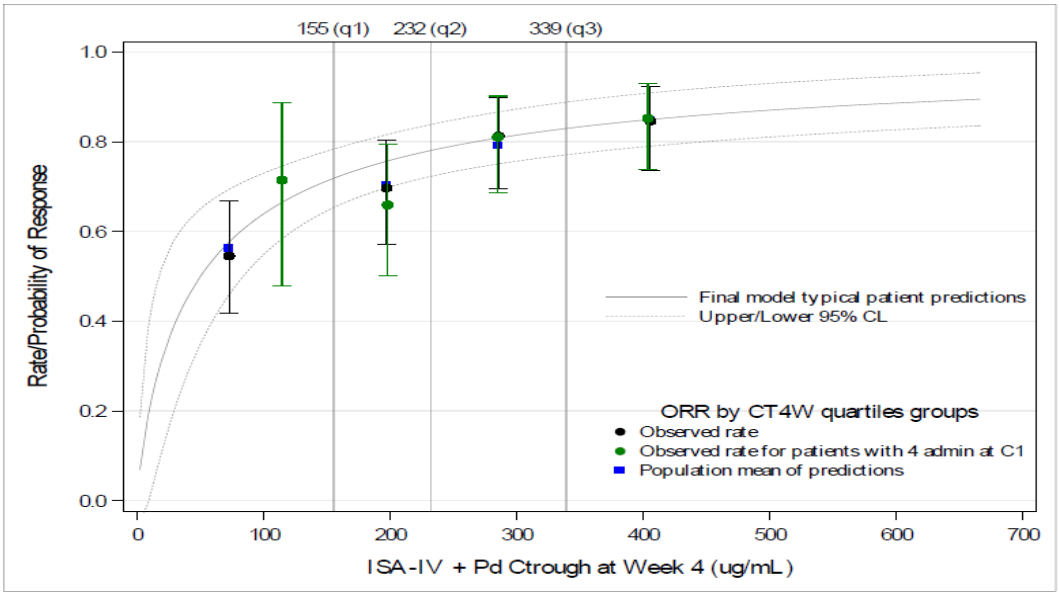
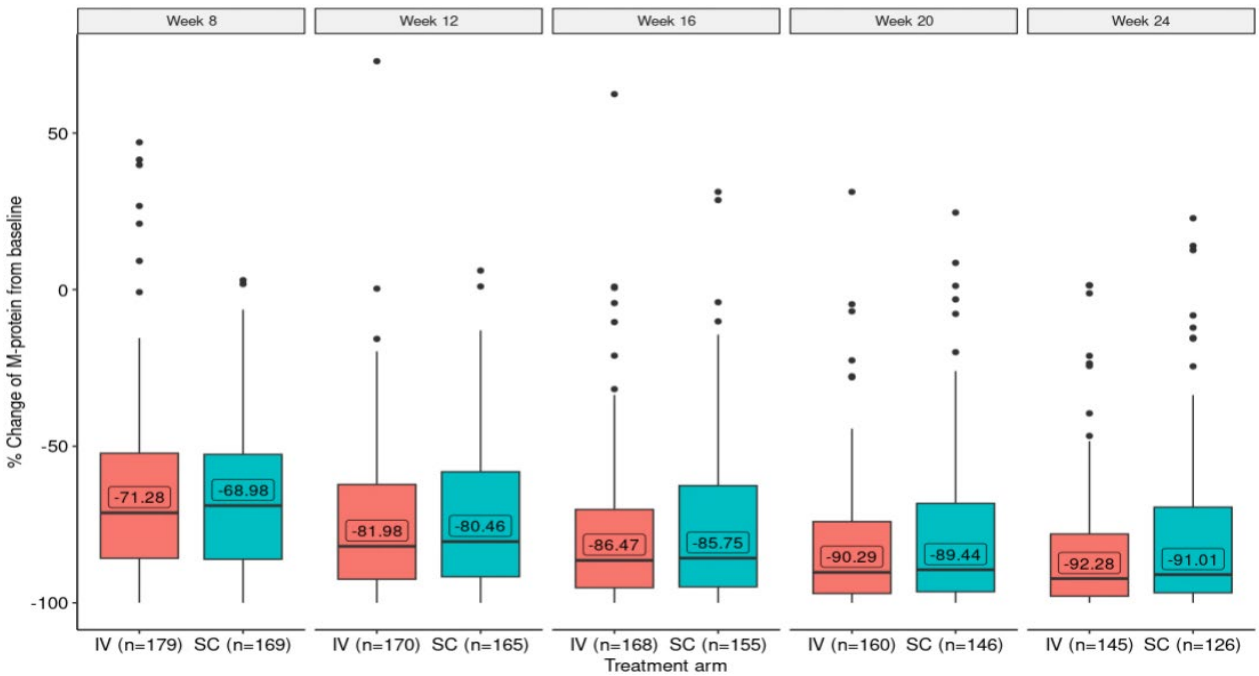


Figure 7: Typical patient and mean of individual model-predicted ORR versus CT4W based on the final model - Isa-IV in PK/PD Efficacy population (CTS0153)



Furthermore, in the PK/PD analysis with longitudinal serum M-protein data from study EFC15951 (DDM0051), there was no impact of the route of administration (ie, comparable distribution of the individual model parameters following IV or SC administration; Figure 8) nor of body weight. Simulations demonstrate that patients with body weight ≥100 kg from the SC arm of the study would have responded the same if they would have received 10 mg/kg IV dose, suggesting that these patients with high body weight were not underdosed with 1400 mg SC dose.

Figure 8: Predicted percent change of serum M-protein from baseline for 357 patients in IRAKLIA study



PK/PD relationship for safety

The exploratory E-R analyses defined quartiles of exposure with pooled data from studies EFC15951 and TCD15484. These analyses did not show an apparent relationship between an increase in the isatuximab maximum concentration after the first administration (C_{max}, C1D1), or between other metrics after the first administration (CT1W or AUC1W), and the incidence of the safety outcomes of interest (Grade ≥3 neutropenia, Grade 4 neutropenia, neutropenic complications, Grade ≥3 infections and infestations, pneumonia and Grade ≥3 thrombocytopenia) based on the safety PK/PD population or on data from subgroup analysis. The exception was the incidence of Grade ≥3 lymphopenia in Q1 of C_{max} C1D1 which was lower (44.2%) compared to the remaining quartiles, where the incidence appeared to plateau between Q2, Q3, and Q4 (52.6%, 52.7%, and 53.9%), with an overlap of confidence intervals across the quartiles. A similar trend was observed for CT1W and AUC1W. However, the univariate analyses showed that Grade ≥3 lymphopenia was not significantly correlated with any of the PK exposure parameters, confirming a lack of relationship between isatuximab exposure and lymphopenia. Overall, comparable results were observed for the other PK metrics (AUC, C_{max} and C_{trough}) after repeated administrations and for the subgroup analysis (IgG and non-IgG MM type patients), or for study EFC15951 only. Nevertheless, when comparing to the IV arm, there was a trend of higher incidence of neutropenia Grade ≥3, Grade 4 neutropenia, and neutropenic complications, which was slightly more marked for the non-IgG subpopulation but with no clear trend toward more events in the highest exposure quartile (C_{max},C1D1, CT1W, or AUC1W). When looking at the exposure at Cycle 1, there was a trend toward more neutropenia Grade ≥3 in the three highest exposure quartiles compared to the first quartile for CT4W, but the 95% CI were overlapping and this was not observed for Grade 4 neutropenia and neutropenic complications. Of note, a slightly higher incidence of neutropenia Grade ≥3 was observed in the extreme low body weight quartile (Q1), for which higher exposure was observed due to the flat dose. However, the univariate analyses showed that neutropenia Grade ≥3 was not significantly correlated with any of the PK exposure tested, nor to body weight or BMI.

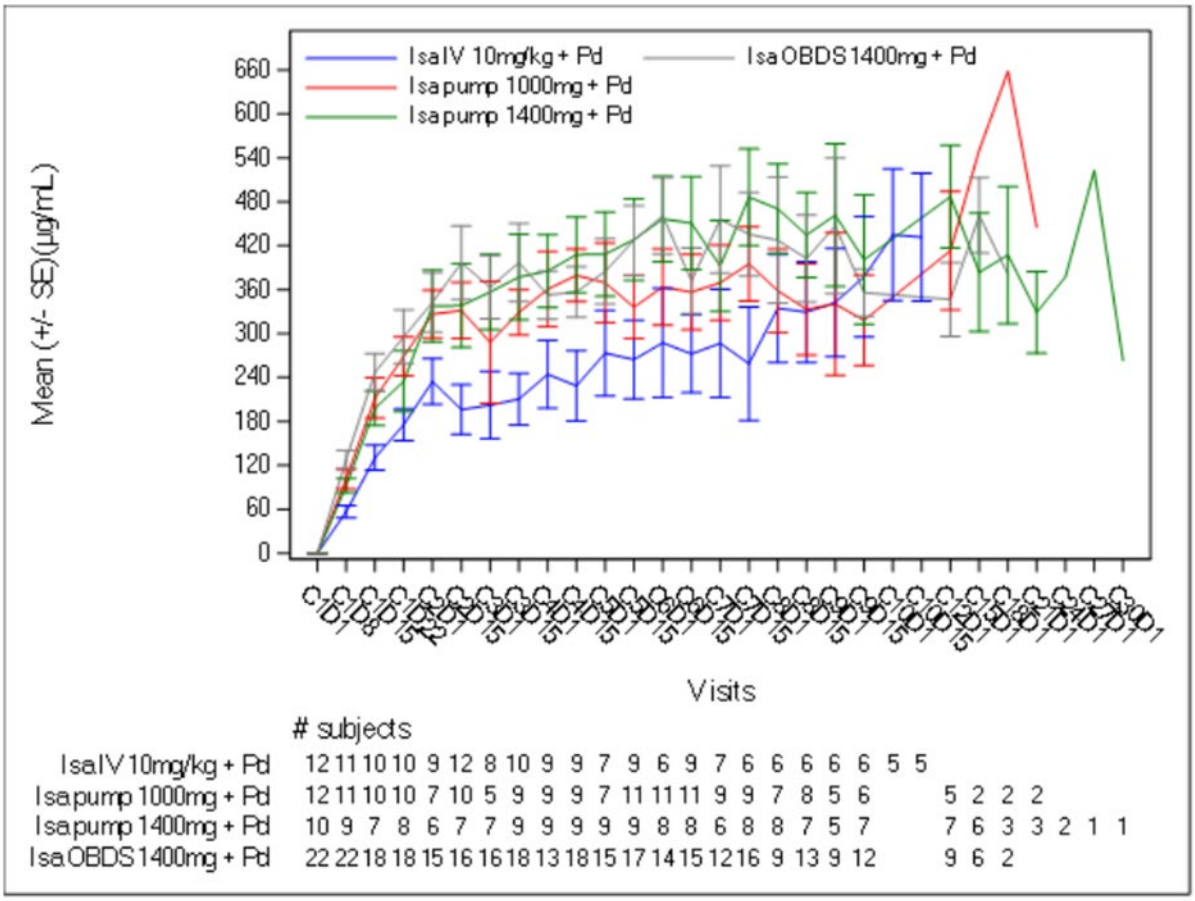
5.2.5. Dose selection and therapeutic window

Previous analyses demonstrated a strong relationship between C_{trough} at 4 weeks (CT4W) and efficacy.

In the Phase 1 Study TCD15484, 1000 mg and 1400 mg doses of Isa-SC were selected using the same dosing schedule as Isa-IV 10 mg/kg. Based on population PK model-based simulations, which accounted for imbalances in baseline patient and disease characteristics between cohorts, the 1400 mg SC dose (with a bioavailability between 50 and 80%) was shown to achieve C_{trough} concentrations at 4 weeks (the best predictor for efficacy) comparable to the target C_{trough} from a 10 mg/kg IV dose . Assuming a bioavailability of 80%, the predicted Ctrough and Cmax after 1400 mg SC dose were below the C_{trough} and C_{max} values from the highest tested IV dose of 20 mg/kg, which is also a safe and efficacious dose.

A steep increase of trough concentrations was observed regardless of the route, dose, and SC delivery mode of administration during weekly dosing up to Cycle 2 Day 1. During bi-weekly dosing, a slight increase is still observed up to Cycle 5-6. Comparable trough levels were observed for SC administrations regardless of dose and SC delivery mode of administration while slightly lower when isatuximab is administered using Isa-IV route (**Figure 9**).

Figure 9: Isatuximab mean C_{trough} (+/- SE) over time



A steep increase of trough concentrations was observed regardless of the route, dose, and SC delivery mode of administration during weekly dosing up to Cycle 2 Day 1. During bi-weekly dosing, a slight increase is still observed up to Cycle 5-6. Comparable trough levels were observed for SC administrations regardless of dose and SC delivery mode of administration while slightly lower when isatuximab is administered using Isa-IV route.

In Study TCD15484, after completion of the first 2 cohorts at 1000 and 1400 mg, the SC dose of 1400 mg was selected for the SC-OBDS cohort based on trial simulations. Briefly, simulations were conducted to select a SC dose non-inferior to IV 10 mg/kg (ie, the lower bound of the 90% confidence interval [CI] for the SC/IV ratio for C_{trough} at 4 weeks [CT4W, the best PK predictor for efficacy] was to be at least 0.80). These simulations showed that a 1000 mg SC dose had a low probability of success (<50%) for achieving PK non-inferiority, while the probability of success was predicted to be at least 90% after a 1400 mg SC dose when considering a SC bioavailability in the range of 60-65%. This was later confirmed with simulations conducted per the EFC15951 study design, where C_{trough} at steady state ([$C_{trough,SS}$] C6D1, the co-primary endpoint in Study EFC15951) after a 1400 mg SC dose was predicted to have at least a 90% probability of success to be non-inferior to IV 10 mg/kg.

PK/PD model-based simulations of serum M-protein and PFS using data from Study TCD15484 suggest that Isa-SC 1400 mg would be at least as efficacious as the approved Isa-IV dose of 10 mg/kg, with a slightly greater decrease in serum M-protein and a prolonged median PFS predicted in 90% of the simulated trials compared to Isa-IV 10 mg/kg. Therefore, based on the PK and PK/PD simulations, 1400 mg Isa-SC was selected for the pivotal Phase 3 Study EFC15951 with IPd as well as for the other combination studies.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Pharmacokinetics

For this application, isatuximab PK has been investigated in multiple myeloma patients treated with isatuximab SC in combination with pomalidomide and dexamethasone, pomalidomide and carfilzomib, or bortezomib, lenalidomide and dexamethasone. The proposed posology is 1400 mg SC in combination with pomalidomide and dexamethasone (Isa-SC + Pd) or in combination with carfilzomib and dexamethasone (Isa-SC + Kd) once weekly for the first 4 weeks (one cycle), followed by every 2 weeks for the following cycles, or in combination with bortezomib, lenalidomide, and dexamethasone (Isa-SC + VRd) once weekly for the first 4 weeks (one cycle), followed by every 2 weeks for the following 11 cycles and by every 4 weeks after that.

In the dose finding study (**TCD15484**), 1000 mg isatuximab SC and 1400 mg isatuximab SC were compared with 10 mg/kg isatuximab IV. Based on the PK data from this study and a popPK analysis, the 1400 mg isatuximab SC was chosen for further development. There were no indications that the higher dose would have a negative effect on the safety and the popPK model indicated that the 1000 mg SC dose could have a negative effect on the efficacy in the highest body weight group (>85 kg). Isatuximab was slowly absorbed with a median T_{max} ranging from 65 to 95 hours after the first administration in the first cycle. Mean C_{max} after the first administration in cycle 1 was comparable between the 1000 mg and 1400 mg isatuximab sc administration and lower than the mean C_{max} after 10 mg/kg isatuximab IV as is expected from SC administration. In the 3rd cycle, the mean C_{max} for 1000 mg isatuximab SC was lower than for 1400 mg isatuximab SC. Mean C_{max} values increased with each treatment cycle.

Based on the results from the studies provided for this application, an absolute bioavailability of 75.9% was estimated for SC isatuximab in the popPK study POH1117. This value was derived from the comparison with IV administration.

In the pivotal study (**EFC15951**) 1400 mg SC was compared with 10 mg/kg IV in combination with pomalidomide and dexamethasone (Isa-SC + Pd/Isa-IV + Pd). Study EFC15951 had a combined efficacy and PK primary endpoint.

Seven to nine blood samples for PK/ADA were collected during Cycle 1 for the measurement of isatuximab concentration. During C2 – C5, blood samples were collected bi-weekly, followed by monthly samples in C6 – C9, then every 3 months for the remainder of the study. This is considered adequate for therapeutics with a long half-life, such as monoclonal antibodies.

After multiple administrations of 1400 mg isatuximab SC using manual administration or the OBDS device there was no relevant difference between the administration methods as assessed in the popPK analysis.

The estimated volume of distribution of 5.68 L suggests that isatuximab is primary distributed in the vascular systems with some limited extravascular tissue distribution, consistent with what is known for other IgG1 based mAbs.

The median time to reach steady state was 22 weeks with a 4.87- to 5.44-fold accumulation (based on C_{trough} and C_{max}, respectively).

In study EFC15951, non-inferiority of isatuximab 1400 mg SC vs. isatuximab 10 mg/kg IV was demonstrated for both C_{trough} at steady state and CT4W. The lower limits of the 90% CI of the geometric mean ratio was 1.316 for C_{trough} at steady state and 1.158 for CT4W. The non-inferiority margin for the PK-endpoint CT4W is acceptable.

Subgroup analyses showed consistency between MM isotype (IgG versus non-IgG) and body weight groups. Of note, the geometric mean ratio of C_{trough} (Isa-SC/Isa-IV) was similar for the non-IgG subgroup at C6D1 and C2D1 (1.32 and 1.27 for C_{trough} at C6D1 and C2D1, respectively), while it tended to increase in the IgG subgroup (1.68 and 1.34 for C_{trough} at C6D1 and C2D1, respectively).

The isatuximab OBDS dose showed acceptable exposure across body weight subgroups; CT4W (predose C2D1) with isatuximab OBDS (flat dose) were similar to, or higher than those with isatuximab IV in each body weight subgroup). The mean observed C_{trough} was 67% higher after Isa-SC versus Isa-IV in participants ≤65 kg and was 9% higher after Isa-SC versus Isa-IV in participants >85 kg at the end of weekly dosing (acknowledging an overlap in C_{trough} for the two administration routes for each body weight subgroup). The trend was similar at steady state.

PK variations in special populations were primarily based on popPK simulations (study **POH1117**). PopPK analysis identified body weight as a significant covariate impacting linear CL at steady state; β2 microglobulin, MM type (IgG versus non-IgG), and serum M-protein level as significant covariates impacting CLm; MM type impacting KCL, body weight, and gender impacting V1; and body weight impacting V2.

Overall the exposure of isatuximab 1400 mg sc was comparable with the exposure of isatuximab 10 mg/kg iv.

Given the flat dose administered, a potential effect of weight could be expected. Even though exposure in the lowest body weight group (<50 kg) was higher than in the highest body weight group (>100 kg) it was still overlapping with the exposure in the middle body weight group (50 – 100 kg). The effect of gender may also be the result of a weight effect. Distribution of SC exposure across body weight groups was shown acceptable considering the overall inter-individual variability of the compound. Only a limited number of patients with a body weight >120 kg have been studied using a flat-dose (1400 mg) Isa-SC. This information is included in SmPC section 5.2, and a warning about potential reduced efficacy in this population is issued in section 4.4.

The effect of β2 microglobulin, MM type (IgG versus non-IgG), and serum M-protein level was also observed in the original application and is, therefore, not further discussed here.

Based on the popPK analysis, there are no indications that dose adjustments are required for any specific populations.

No new interaction studies were performed for this application. As the application concerns the addition of Isa-SC to the approved Isa-IV, no additional interactions would be expected. The absence of new interaction studies is, therefore, acceptable.

Exposure to Isa-SC assessed after the first administration or over Cycle 1 (4 weekly administrations) was consistent across indications (RRMM versus NDMM) and combinations (IPd, IKd, IVRd), while at steady state there were higher exposures among those with NDMM/IVRd (studies IIT17756 and IIT17041) and RRMM/IKd (study ACT17453) compared to RRMM/IPd (studies EFC15951 and TCD15484). As observed previously with the isatuximab IV program, the increase in the exposure difference over time in the RRMM/IKd and NDMM/IVRd populations compared to RRMM/IPd may be attributed to a higher proportion of responders, especially patients with a very good response rate or better (VGPR+) (ie, VGPR+: 62.2% [RRMM/IKd, study ACT17453], 73.9% [NDMM/IVRd, during induction in study IIT17041], and 87.8% [NDMM/IVRd, study IIT17756], versus 46.4% [RRMM/IPd, study EFC15951]), acknowledging that the data are still maturing.

Pharmacodynamics

The mechanism of action has been adequately described in the registrational studies that were submitted for the already approved IV formulation of the product.

With regard to CD38 RD, the CD38 receptor was abundantly expressed on bone marrow plasma cells of MM patients at baseline (median 136 180 sABC), as expected. Data were also comparable to the CD38 RD data that were generated in the original FIH studies of the Isa-IV formulation, which was 150 068 sABC for the single-agent 10 mg/kg QW treatment. CD38 RD decreases in all patients after treatment with isatuximab, as expected.

Receptor occupancy on bone marrow plasma cells (i.e. the population of interest) was comparable between Isa-IV and Isa-SC (73.9% vs. 79.1%, respectively). Data were also comparable to the CD38 RO data generated in the original FIH studies of the Isa-IV formulation, which was 79.4% for the single-agent 10 mg/kg QW treatment.

The CD38 RO and RD data show that the target of isatuximab is expressed on the tumour cells, and that the drug can bind to the target. The immune cell analysis shows that bone marrow plasma cells were cleared. A higher median decrease of CD38+ bone marrow plasma cells was observed in responders compared to non-responders, showing that the proposed MoA correlated with the observed clinical response.

On-target off-tumour effects were assessed in NK cells. NK cells have a lower CD38 RD than tumour cells. Nonetheless, CD38 RO after treatment with isatuximab on NK cells is comparable to CD38 RO on tumour cells, and bone marrow NK cells are cleared by isatuximab, regardless of whether the patient is a responder or a non-responder. This was already known and is described in the SmPC.

5.2.6.2. Conclusions

Overall, Isa-SC PK was similar to Isa-IV PK taking into consideration that Isa-SC was administered as a flat dose of 1400 mg and Isa-IV as a body weight dependent dose of 10 mg/kg. Non-inferiority of Isa-SC vs. Isa-IV was confirmed. The PopPK analysis, indicated body weight as a significant covariate, however, additional analyses indicated that the effect of body weight on exposure should not have an effect on efficacy or safety.-SC vs. Isa-IV was confirmed. The PopPK analysis, indicated body weight as a significant covariate

The pharmacodynamic effects of isatuximab in multiple myeloma patients support its immunomodulatory mechanism of action.

ADA formation for the SC formulation is in line with what was already known for Isa-IV.

5.3. Clinical efficacy

5.3.1. Main study

The main results regarding the PK endpoints are also discussed in the Clinical Pharmacology section when relevant.

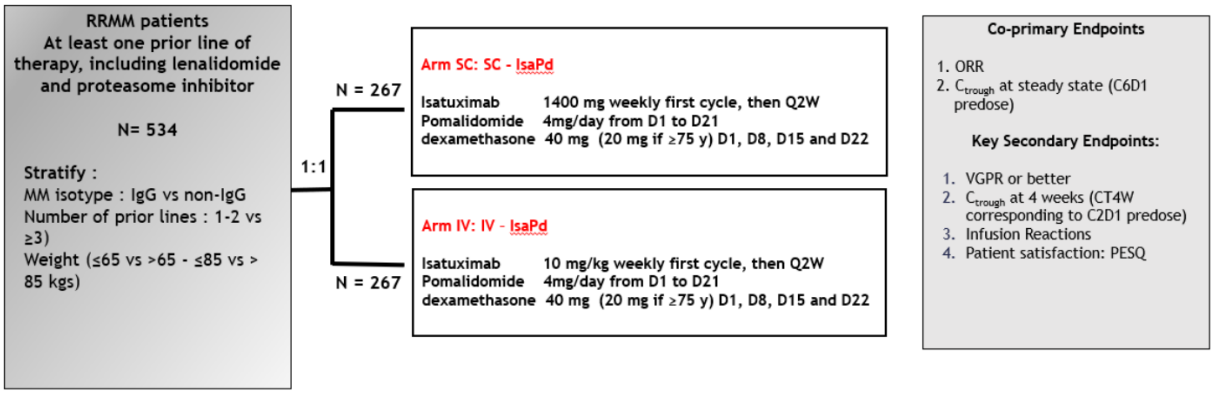
5.3.1.1. EFC15951 (IRAKLIA)

5.3.1.1.1. Study design

EFC15951(IRAKLIA) is a Phase 3 randomized, multicentre, open-label study evaluating SC versus IV administration of isatuximab in combination with Pd in adult participants with RRMM who have received at least 1 prior line of therapy, including lenalidomide and a PI. The study aimed to demonstrate the efficacy and PK non-inferiority of Isa-SC+Pd compared to Isa-IV+Pd.

A total of 534 participants were planned to be included, and eventually 531 participants were randomized 1:1 into the SC arm (1400 mg isatuximab with a device injector [OBDS]), or the IV arm (10 mg/kg isatuximab). A graphical representation of the study design is provided in Figure 10.

Figure 10: Study EFC15951 schema



C_{trough} = trough concentration; CT4W = C_{trough} at 4 weeks; IsaPd = Isatuximab + Pomalidomide + dexamethasone; IV = intravenous; ORR = overall response rate; PESQ = patient experience and satisfaction questionnaire; RRMM = relapsed and/or refractory multiple myeloma; SC= subcutaneous; VGPR = very good partial response

5.3.1.1.1.1. Treatment

One treatment cycle consisted of 28 days, and patients received the following treatments:

Isatuximab

IV formulation (Arm IV only)

Isatuximab was administered weekly at the dose of 10 mg/kg for the first 4 weeks (Cycle 1) and every other week on Day 1 and 15 of subsequent cycles. The calculation of the Isatuximab IV dose was based on the most recent weight available.

SC formulation (Arm SC only)

Isatuximab was administered weekly at the nominal dose of 1400 mg for the first 4 weeks (Cycle 1) and every other week on Day 1 and 15 of subsequent cycles. Isatuximab was administered in the periumbilical region at a single site, using an investigational device injector (the OBDS). From Cycle 6 onwards, at home administration on Cycle Day 15 by a Health Care Professional (HCP) was proposed to participants in the SC arm. All visits on Cycle Day 1 remained outpatient visits at the clinic. The decision for at home administration on Day 15 was based on the absence of an IR at Cycle 4 and Cycle 5, the haematology test at Day 1 of each corresponding cycle and the Investigator's judgement.

Dexamethasone (both arms)

Dexamethasone was taken orally at a dose of 40 mg (or 20 mg for participant ≥75 years) on Day 1, 8, 15, and 22 of each cycle. If a dose of dexamethasone was missed, it should be taken as soon as possible within the next 2 days. The dose per cycle could not exceed 160 mg (80 mg if the participant was ≥75 years old). When administered on the same day as other investigational medicinal products (IMP)s, dexamethasone was administered before all other IMPs.

Pomalidomide (both arms)

Pomalidomide was taken orally at a dose of 4 mg on Days 1 to 21 of each Cycle. If a dose of pomalidomide was missed, it should be taken as soon as possible on the same day.

Premedication (both arms)

All participants received premedication to prevent or reduce the incidence or severity of isatuximab-related IRs, at least 15 to 30 minutes (but no longer than 60 minutes) prior to isatuximab infusion (regardless of route). Participants who did not experience IRs after 4 consecutive administrations of isatuximab had their need for subsequent premedication reconsidered at the Investigator's discretion, except for montelukast which was administered only in Cycle 1.

The standard premedication regimen included, in this order:

- Montelukast (ATC code: R03DC03) 10 mg PO (or equivalent; to be administered during Cycle 1 only).
- Dexamethasone (ATC code: H02AB02) 40 mg PO
    - Methylprednisolone (ATC code: H02AB04) (or equivalent):100 mg IV if dexamethasone is discontinued earlier than isatuximab and premedication is still needed.
- Acetaminophen (paracetamol ATC code: N02BE01) 650 to 1000 mg orally.
- Diphenhydramine (ATC code: R06AA02) 50 mg PO (or equivalent: e.g., cetirizine, promethazine, dexchlorpheniramine, according to the approval availability) or Diphenhydramine 25 to 50 mg IV (or equivalent). Intravenous route is preferred for at least the first 4 IV isatuximab infusions.

Concurrent treatment with any other anti-myeloma therapy as well as any other investigational drug was prohibited. However, palliative radiotherapy could be given to control pain.

Participants were allowed to continue therapy until disease progression (PD), unacceptable adverse events (AEs) or participant request to discontinue treatment.

5.3.1.1.1.2. Randomisation and blinding

Randomisation

All eligible participants were randomly assigned to a treatment group (SC or IV arm) in a 1:1 ratio using an interactive response technology (IRT). Participant assignment to a treatment group was performed according to a stratified randomization list as follows:

- MM isotype (IgG versus non-IgG).
- Body weight (≤65 kg, >65- ≤85 kg, and >85 kg).
- Number of prior lines (1-2 versus ≥3).

Study treatment was initiated within 3 working days after randomization.

Blinding

During the trial, administration of isatuximab SC or IV was open-label, and no attempts were made to blind administration. An IRT centralized randomization system was used, so the investigators did not know the study intervention assignment in advance. Despite the open-label administration of treatments, assessment of efficacy outcomes was based on collected data (radiological assessments for tumour response and central laboratory assessment) that were reviewed by a blinded IRC. During the course of the study, an external independent statistician performed unblinded safety and efficacy analyses for the data review of the Data Monitoring Committee (DMC). Access to these data and analyses was restricted to the DMC members.

5.3.1.1.1.3. Patient population

Participants were randomized at 120 sites in 21 countries. The countries with the largest enrolment were China (82 participants), Australia (61 participants), Chile (50 participants), Spain (35 participants), Hungary (32 participants), and Turkey (30 participants).

Main inclusion criteria

- ≥18 years of age
- documented diagnosis of multiple myeloma with measurable disease based on presence of M-protein in serum/urine and/or an abnormal sFLC ratio
- at least 1 prior line of anti-myeloma therapy, which must include lenalidomide and a PI given alone or in combination. Participants who received only one prior line of therapy must be lenalidomide refractory.
- documented evidence of progressive disease on or after the last regimen.
- Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- Capable of giving signed informed consent.

Main exclusion criteria

- Primary refractory multiple, concomitant plasma cell leukaemia.
- Inability to tolerate thromboprophylaxis or excess risk of bleeding.
- Prior anti-CD38 treatment administered less than 9 months before randomisation or intolerant to the anti-CD38 previously received.
- Prior therapy with pomalidomide.
- Prior allogenic HSC transplant with active graft versus host disease (GvHD)
- ECOG status >2.
- Platelets <50000 cells/µL; ANC <1000 µL (1 x 10^9/L).
- Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m^2
- Total bilirubin >1.5 × upper limit of normal (ULN); serum calcium (corrected for albumin) level above the ULN range; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN.

- Ongoing toxicity from any prior anti-myeloma therapy >Grade 1.
- Hypersensitivity to IMiDs (thalidomide or lenalidomide), defined as any hypersensitivity reaction leading to stop IMiDs within the 2 first cycles or reaction which does meet intolerance definition.
- ≥Grade 2 peripheral neuropathy.
- Significant cardiac dysfunction
- Diagnosed or treated for another malignancy within 3 years prior to randomization
- Known infection with HIV, hepatitis A, B or C infection requiring treatment.
- Malabsorption syndrome or any condition that can significantly impact the absorption of pomalidomide.
- Active primary amyloid light-chain amyloidosis.
- Daily requirement for corticosteroids.

5.3.1.1.2. Objectives and estimands

5.3.1.1.2.1. Primary objective

There were two co-primary objectives:

1) To demonstrate non-inferiority of efficacy between isatuximab SC and isatuximab IV in combination with Pd through based on central laboratory M protein analysis and central radiology review response assessment according to the 2016 IMWG criteria assessed by an IRC
2) To demonstrate non-inferiority of PK between isatuximab SC and isatuximab IV in combination with Pd through comparing observed concentration before dosing (C_{trough}) at steady state (corresponding to pre-dose at C6D1).

The non-inferiority of ISA- SC+ Pd relative to Isa- IV + Pd was concluded if both the efficacy and PK endpoints achieved non-inferiority.

5.3.1.1.2.2. Estimands for the primary objective

The estimand for the efficacy objective is to establish non-inferiority of isatuximab subcutaneous (SC) compared with isatuximab intravenous (IV) in adult RRMM patients who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor (PI) based on the relative risk of best objective response to be determined without the need for new anti-MM therapy but allowing for treatment. The intercurrent event "use of new anti-MM therapy", as handled under the "while-on-treatment" strategy, was defined as response to treatment prior to the occurrence of this intercurrent event. Specifically, only the data before the use of new anti-MM therapy was included for the response endpoint analysis (i.e. ORR, VGPR+ rate, PFS). However, inherent to this definition, the use of new anti-MM therapy before PD is a reason for stopping the follow up of patients for response.

The estimand for the PK objective is to establish non-inferiority of isatuximab subcutaneous (SC) compared with isatuximab intravenous (IV) in adult RRMM patients who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor (PI) in terms of geometric means of Ctrough at steady state, based on the analysis sample of patients who would be able to meet criteria for the PK evaluation in terms of the number of doses and collection of samples.

5.3.1.1.2.3. Secondary objectives

The key secondary objectives were:

- To assess efficacy of isatuximab SC compared to isatuximab IV in combination with Pd through determining the Very Good Partial Response or better rate, defined as the proportion of participants with sCR, CR, and VGPR according to the 2016 IMWG criteria judged by an IRC. The lower limit of the 95% CI of the relative risk will be compared with the pre-defined non-inferiority margin of 0.6312.
- To demonstrate the PK non-inferiority between isatuximab SC and isatuximab IV in combination with Pd through determining the Observed concentration before dosing (C_{trough}) at 4 weeks (i.e., CT4W corresponding to pre-dose at C2D1).
- To assess safety of isatuximab SC and IV in combination with Pd through determining incidence rate of infusion-reactions (IRs).
- To assess patient satisfaction with isatuximab SC and IV by reporting the percentage of participants satisfied or very satisfied with the injection method used to administer study medication based on the PESQ questionnaire.

Other secondary objectives included time-to-event endpoints, such as DOR, TT1R, TTBR, PFS, OS and PFS2.

5.3.1.1.2.4. Estimands for the key secondary objectives

VGPR or better rate per IRC assessment: The estimand for the first key secondary objective has similar attributes to the primary estimand, with the exception of the variable of interest, with the interest being a Very Good Partial Response or better rate, defined as the proportion of participants with sCR, CR, and VGPR according to the 2016 IMWG criteria judged by an IRC.

C_{trough} at 4 weeks: The estimand for the secondary key objective is similar to the co-primary PK estimand, with the C_{trough} measured at 4 weeks and the requirement to have had all 4 isatuximab doses for Cycle 1 administered in order to be included in the analysis sample.

Incidence rate of infusion reactions: The estimand for the third key secondary objective evaluates the relative risk of experiencing an infusion reaction isatuximab subcutaneous (SC) compared with isatuximab intravenous (IV) in adult RRMM patients who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor (PI), regardless of any dose reduction or omissions and within 30 days of full treatment discontinuation.

Patient satisfaction: The estimand for the fourth key secondary objective evaluates the rate of patients who are satisfied or very satisfied with the injection method of isatuximab subcutaneous (SC) compared with isatuximab intravenous (IV) in adult RRMM patients who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor (PI), participants who discontinued study treatment before Cycle 5, Day 15 will be considered to be non-satisfied.

Statistical methods for estimation and sensitivity analysis

The following analysis sets were defined:

Intent-to-treat (ITT) analysis set

The ITT analysis set includes all participants who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the IRT. Participants were analysed

according to the treatment group allocated by IRT, regardless of whether the participants received any study treatment or received a different study treatment from that to which they were randomized. The ITT analysis set was used for the analysis of all response-based analyses, including the co-primary efficacy endpoint.

Safety analysis set

The safety analysis set includes randomised participants who have received at least 1 dose or a part of a dose of the study intervention and was based on the treatment actually received. All safety analysis used the safety analysis set.

PP-PK analysis set

The PP-PK set includes all randomized participants which have received at least eleven isatuximab doses out of twelve up to C5D15 (one dose omission permitted during Cycle 1), with isatuximab C6D1 (predose) concentration results from PK sample collected within the defined per protocol time window and adequate documentation of dosing and sampling dates and times. This analysis set was used for the co-primary PK endpoint.

CT4W-PK population

The CT4W-PK analysis set for CT4W endpoint includes all randomized participants having completed administration of all the first 4 weekly isatuximab doses at Cycle 1, with isatuximab C2D1 (predose) concentration results from PK sample collected within the defined per protocol time window and adequate documentation of dosing and sampling dates and times. This analysis set was used for the analysis of the CT4W PK endpoint.

Primary endpoints analyses

The number and proportion of participants who achieve ORR per IRC assessment was to be calculated for each treatment group. The relative risk of Isa-SC + Pd relative to Isa-IV + Pd and its two-sided 95% CI using Farrington and Manning method was to be estimated. If the lower bound of the 95% CI was not less than a non-inferiority margin of 0.839, non-inferiority of efficacy Isa- SC + Pd relative to Isa- IV + Pd would be concluded. The odds ratio of Isa-SC+ Pd relative to Isa- IV + Pd with their 95% CI was also to be estimated. Assuming an ORR ratio (SC/IV) of 1.02, an effect retention of 40% resulted in a workable sample size (n = 534), while still resulting in a clinically acceptable maximum difference in ORR between the arms of 1.6%.

For the co-primary PK endpoint of Ctrough at steady state (corresponding to pre-dose at C6D1), summary statistics including the geometric means, coefficient of variation, median and range were to be estimated for each treatment group. The ratio of the geometric means of Isa-SC+ Pd relative to Isa- IV + Pd and corresponding two-sided 90% CI was to be estimated by calculating the 90% CI under the logarithm scale then converting back to its original scale. The non-inferiority of PK Isa- SC + Pd relative to Isa- IV + Pd was to be concluded if the lower bound of the 90% CI for the geometric mean ratio of Ctrough at steady state was at least 80% (a non-inferiority margin of 80%).

The non-inferiority of Isa-SC+ Pd relative to Isa- IV + Pd was concluded if both the efficacy and PK endpoints achieved non-inferiority.

Secondary endpoints analyses

VGPR or better rate per IRC assessment was to be summarized for the ITT analysis set in the same way as for the primary ORR endpoint. The non-inferiority test for non-unity null according to Farrington and Manning (1990) was performed for VGPR or better rate. The non-inferiority margin is 0.6312, which was calculated as 40% retention of the observed historical clinical benefit of VGPR or better ratio 0.478 (upper

bound of the 95% CI of rate ratio for Pd over CD38+ Pd as demonstrated in ICARIA-MM trial) under the logarithm scale then converting back to its original scale. If the lower bound of the 95% CI was not less than a non-inferiority margin of 0.6312, the non-inferiority of Isa-SC + Pd relative to Isa- IV + Pd on the VGPR or better rate could be concluded.

The PK endpoint of CT4W was to be summarized for the CT4W-PK population in the same way as for the Ctrough at steady state endpoint. The non-inferiority of Isa- SC + Pd relative to Isa-IV + Pd on CT4W corresponding to pre-dose at C2D1 could be concluded if the lower bound of the 90% CI for the geometric mean ratio of CT4W was at least 80% (a non-inferiority margin of 80%).

Incidence rate of IRs was to be compared between treatment arms on the safety population using the Fisher's exact test. The relative risk, odds ratio of ISA- SC+ Pd relative to Isa- IV + Pd with their 95% CI were to be provided.

The percentage of participants who reported satisfied or very satisfied with the injection method used to administer the study medication based on the PESQ questionnaire at C5D15 visit were to be compared between treatment arms on the ITT analysis set using the stratified Cochran–Mantel–Haenszel method.

Pre-specified subgroup analyses

Subgroup analyses for ORR and VGPR+ rate were planned to be performed when at least 10 participants were included in each treatment arm within a subgroup. Subgroup analyses were to be estimated based on demographic and baseline characteristics (Age, Race, Gender, Region, Body weight, ECOG and eGFR) and disease characteristics (MM isotype, ISS at study entry, At least one R-ISS chromosomal abnormality, At least one chromosomal abnormality, Number of prior lines of MM therapy per IRT, Number of prior lines of MM therapy per eCRF, Refractory to lenalidomide during any regimen, Refractory to lenalidomide during last regimen, R-ISS staging at study entry, R2-ISS staging at study entry).

For TEAEs, subgroup analyses were to be performed by age, gender, race, MM isotype, (extreme) body weight, number of prior treatment lines, baseline eGFR and hepatic status.

Post-hoc subgroup analyses

The following subgroup analyses were added after study unblinding/database lock:

A subgroup analysis of TEAEs and neutropenia and neutropenic complications was added to evaluate alternative body weight categories (≤50 kg, >50 to ≤100 kg, >100 kg).

For C_{trough} at steady state and at 4 weeks, a subgroup analysis based on body weight was added.

Other Secondary Endpoints

The CR rate was to be summarized in the same way as for the ORR endpoint.

The median PFS per IRC assessment and probabilities of being progression free at different time points calculated using the Kaplan-Meier methods as well as corresponding 95% CI were to be estimated by treatment arm. The Kaplan-Meier PFS curves were to be provided, along with the HR estimated from the Cox proportional hazards model as well as its associated 95% CI.

The analysis for PFS2, OS, DOR, and TTR (TT1R and TTBR) were to be estimated in a similar way as for the PFS per IRC assessment.

Sample size determination

A total sample size of 534 participants (randomization ratio 1:1, i.e., 267 randomisd participants in the SC arm, and 267 randomized participants in the IV arm) was determined to demonstrate non-inferiority

of SC arm versus IV arm on the proportion ratio of participants who achieved ORR, and the geometric mean ratio of Ctrough at steady state (corresponding to pre-dose at C6D1).

For the co-primary efficacy endpoint of ORR, the non-inferiority test for non-unity null according to Farrington and Manning was implemented. With 2.5% one sided Type I error rate, and a non-inferiority margin of 0.839, which was calculated as 40% retention of the observed historical clinical benefit of ORR ratio 0.7463 (upper bound of the 95% CI of rate ratio for Pd over CD38+Pd as demonstrated in ICARIA-MM trial) under the logarithm scale then converting back to its original scale, 534 randomized participants provide approximately 80% power for this efficacy co-primary endpoint, assuming that ORR for IV arm is 60.4% and the true response rate ratio is 1.02 for SC arm over IV arm.

For the PK co-primary endpoint of Ctrough at steady state, assuming Ctrough at steady state follows log normal distribution with a true geometric mean ratio of 1 and a CV of 75%, and an assumed drop-out rate of no more than 50% to the PK per-protocol analysis sample, 534 randomized participants will provide at least an 86% power to show the lower bound of the 90% CI of the geometric mean ratio of Ctrough at steady state is at least 80% (a non-inferiority margin of 80%).

Error probabilities, adjustment for multiplicity and interim analyses

No interim analysis with alpha spending were planned for this study.

Both co-primary endpoints are needed to achieve non-inferiority in order to claim the non-inferiority of Isa SC+ PomDex relative to Isa IV + PomDex.

Hypothesis testing of key secondary endpoints (VGPR or better rate per IRC assessment and CT4W) for non-inferiority, and key secondary endpoints (incidence of IRs and percentage of participants satisfied or very satisfied based on the PESQ questionnaire) for superiority was carried out. A hierarchical test procedure was used to control the familywise Type I error rate at one-sided significance level of 0.025, meaning that testing of key secondary endpoints was performed only if the non-inferiority for both co-primary endpoints was established and testing on subsequent endpoints continued only if the null hypothesis for the previously tested endpoint was rejected. The hierarchical procedure for testing the key secondary endpoints comparing SC arm with IV arm was performed according to the following order:

- VGPR or better rate for non-inferiority.
- CT4W for non-inferiority.
- Incidence of IRs for superiority.
- Percentage of participants who reported satisfied or very satisfied with the injection method used to administer the study medication at C5D15 visit for superiority.

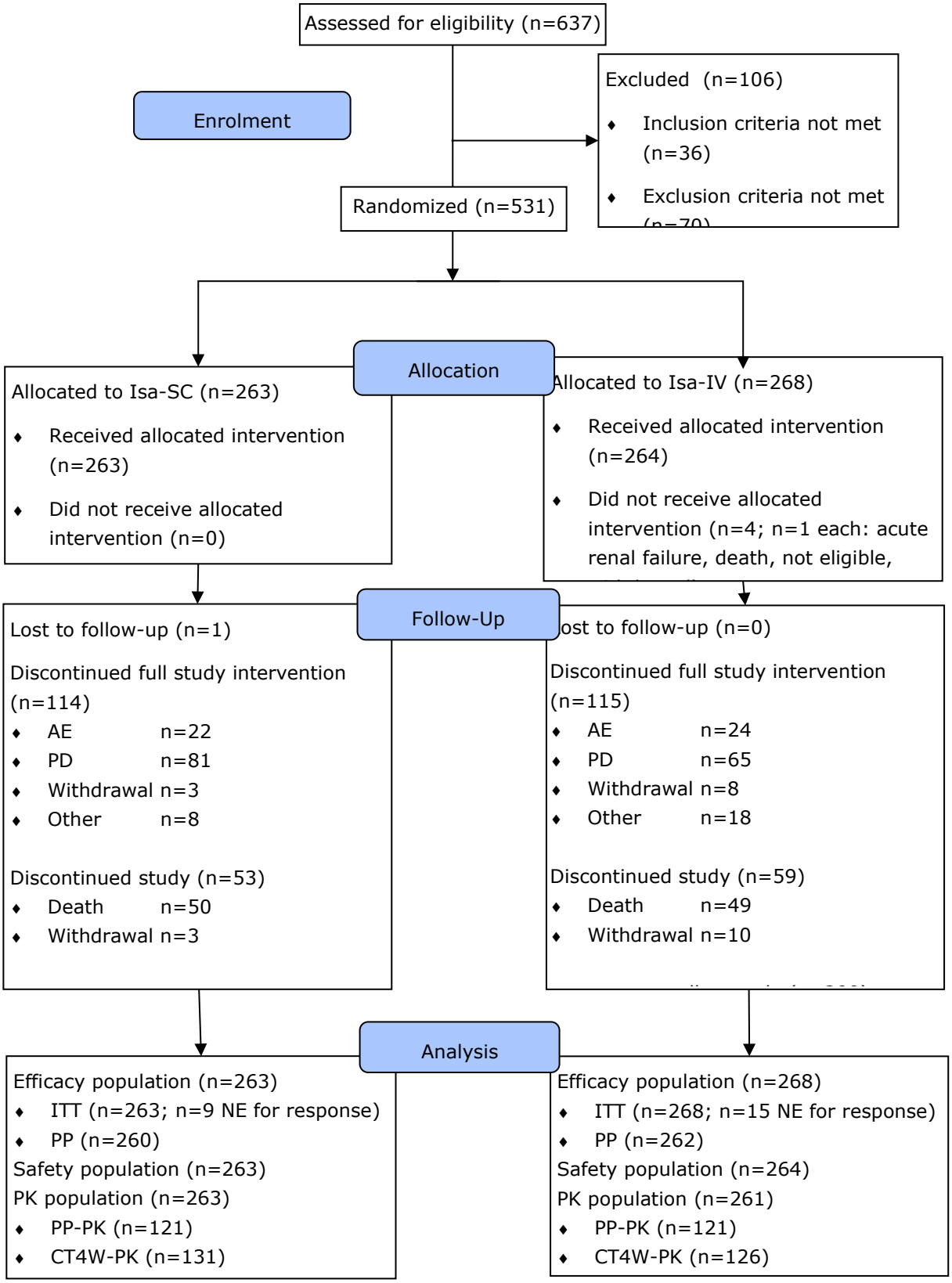
5.3.1.1.3. Results

First patient included:	06 July 2022
Last patient included:	13 May 2024
Primary completion date:	06 November 2024
Final PFS analysis and OS data update:	29 August 2025
Planned final OS analysis:	November 2026

5.3.1.1.3.1. Participant flow and numbers analysed

The flow of the progress of study participants through all the phases of the trial is depicted in Figure 11.

Figure 11: Participant flow in study EFC15951



Among the 8 patients treated with Isa-SC having discontinued treatment due to "Other" reasons, treatment discontinuations were due to:

- progressions not meeting IMWG criteria n = 6
- poor responses n = 2

Among the 18 patients treated with Isa-IV having discontinued treatment due to "Other" reasons, treatment discontinuations were due to:

- progressions not meeting IMWG criteria n = 12
- poor responses n = 4
- other reasons n = 2

For the co-primary endpoint of ORR, the ITT population was used. Nine (3.4%) participants in the Isa-SC arm and fifteen (5.6%) of participants in the Isa-IV arm were not evaluable for response rate.

The co-primary endpoint of C_{trough} at steady state (corresponding to pre-dose at C6D1) was determined in the PP-PK population. There were 121 participants in each arm evaluable for the pre-dose C6D1.

5.3.1.1.3.2. Deviations from study plan

Participants were enrolled from 06 July 2022 to 13 May 2024. Changes in the conduct of the study that were implemented by 4 protocol amendments, of which the first three were implemented while enrolment was still ongoing. The protocol amendments are summarized in Table 12.

Table 12: Summary of protocol amendments in study EFC15951

Amendment	Date	Purpose of amendment
1	11 Oct 2022	To incorporate feedback received from health authorities and ethics committees, to ensure consistency across sections and across program documents, and to provide clarifications in several sections.
2	15 Mar 2023	To allow MRI for bone lytic disease assessment according to feedback from sites in Germany where MRI is used for annual assessment as per local recommendations.
		To remove reference to bone plasmacytoma and to clarify definition and follow-up of extramedullary disease and paramedullary disease.
		To allow switching of participants to long-term follow-up study after the final OS analysis cut-off; to clarify guidelines for urine 24-hour M-protein.
		To define overdose for non-IMPs and to clarify overdose for IMPs.
3	03 Oct 2023	To simplify wording for Inclusion criterion I04 and exclusion criterion E03.
		To introduce a 14-day timeframe following granulocyte-colony stimulating factor use in exclusion criterion E11.
		To modify recommendations regarding antithrombotic prophylaxis to allow for oral anticoagulants in participants with at least one risk factor for thromboembolism.
		To allow semi-quantitative urinalysis at baseline as several countries faced operational issues performing quantitative analysis.
4	10 Jul 2024	To implement language related to new CTA European regulation.

Major protocol deviations were mostly related to in- and exclusion criteria, randomization and assessment/procedure. Deviations for in- and exclusion criteria concerned 3 (1.1%) participants in the Isa-SC arm and 3 (1.1%) participants in the Isa-IV arm. Deviations concerning randomization occurred in 26 [9.9%] and 28 [10.4%] participants in the Isa-SC and Isa-IV arms, respectively, and were all due to wrong stratum of randomization. The stratification error was primarily due to incorrect allocation on the MM isotype (n = 13 [4.9%]) and number of prior lines in the Isa-SC arm (n = 13 [4.9%]), and due to incorrect number of prior lines (n = 23 [8.6%]) in the Isa-IV arm. Other major or critical were most frequently related to Assessment/Procedures (44 [16.7%] and 51 [19.0%]) in the Isa-SC and Isa-IV arms, respectively), in particular PESQ assessment not performed (18 [6.8%] participants and 11 [4.1%] participants, respectively) and planned PK sample on Cycle 2 Day 1 and/or Cycle 6 Day 1 not performed (16 [6.1%] participants and 18 [6.7%] participants, respectively). No participant in either treatment arm received IMP via the wrong mode of administration.

5.3.1.1.3.3. Baseline data

Table 13: Demographic characteristics and other baseline characteristics - Randomised population (Study EFC15951)

	Isa-IV + Pd (N=268)	**Isa-SC + Pd (N=263)**	**All (N=531)**
Age (years)			
Number	268	263	531
Mean (SD)	64.7 (9.7)	65.7 (9.4)	65.2 (9.6)
Median	66.0	66.0	66.0
Q1 ; Q3	58.0 ; 72.0	59.0 ; 74.0	58.0 ; 73.0
Min ; Max	31 ; 85	36 ; 86	31 ; 86
Age group (years) [n (%)]			
Number	268	263	531
<65	118 (44.0)	121 (46.0)	239 (45.0)
65 to <75	109 (40.7)	88 (33.5)	197 (37.1)
>=75	41 (15.3)	54 (20.5)	95 (17.9)
Sex [n(%)]			
Number	268	263	531
Male	156 (58.2)	137 (52.1)	293 (55.2)
Female	112 (41.8)	126 (47.9)	238 (44.8)
Race [n(%)]			
Number	267	263	530
American Indian or Alaska Native	1 (0.4)	0	1 (0.2)
Asian	58 (21.7)	53 (20.2)	111 (20.9)
Black or African American	14 (5.2)	8 (3.0)	22 (4.2)

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
Native Hawaiian/Other Pacific Islander	0	1 (0.4)	1 (0.2)
White	184 (68.9)	184 (70.0)	368 (69.4)
Multiple	0	3 (1.1)	3 (0.6)
American Indian or Alaska Native/ White	0	1 (33.3)	1 (33.3)
Black or African American/ White	0	2 (66.7)	2 (66.7)
Not reported/unknown	10 (3.7)	14 (5.3)	24 (4.5)
Ethnicity [n(%)]			
Number	268	263	531
Hispanic or Latino	67 (25.0)	52 (19.8)	119 (22.4)
Not Hispanic or Latino	191 (71.3)	196 (74.5)	387 (72.9)
Not reported/unknown	10 (3.7)	15 (5.7)	25 (4.7)
Geographical region [n(%)]			
Number	268	263	531
America	76 (28.4)	59 (22.4)	135 (25.4)
Asia	55 (20.5)	50 (19.0)	105 (19.8)
Europe	98 (36.6)	102 (38.8)	200 (37.7)
Other[0]	39 (14.6)	52 (19.8)	91 (17.1)
Baseline weight (kg)			
Number	268	263	531
Mean (SD)	74.94 (17.40)	74.62 (17.42)	74.78 (17.39)
Median	72.00	73.00	72.00
Q1 ; Q3	62.25 ; 85.00	63.00 ; 84.90	62.80 ; 85.00
Min ; Max	36.4 ; 160.5	36.6 ; 139.0	36.4 ; 160.5
Baseline weight by category (kg) [n(%)]			
Number	268	263	531
<=65 kg	87 (32.5)	83 (31.6)	170 (32.0)
>65 kg to <=85 kg	116 (43.3)	118 (44.9)	234 (44.1)
>85 kg	65 (24.3)	62 (23.6)	127 (23.9)
Extreme baseline weight (kg) [n(%)]			
Number	268	263	531
<=50 kg	15 (5.6)	16 (6.1)	31 (5.8)
>50 kg to <=100 kg	231 (86.2)	225 (85.6)	456 (85.9)

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
>100 kg	22 (8.2)	22 (8.4)	44 (8.3)
Body surface area (m^2)			
Number	267	263	530
Mean (SD)	1.82 (0.24)	1.81 (0.24)	1.82 (0.24)
Median	1.80	1.81	1.80
Q1 ; Q3	1.64 ; 2.00	1.65 ; 1.98	1.64 ; 1.98
Min ; Max	1.2 ; 2.7	1.3 ; 2.4	1.2 ; 2.7
Body mass index (kg/m^2)			
Number	267	263	530
Mean (SD)	27.03 (4.71)	27.26 (5.21)	27.14 (4.96)
Median	26.29	26.62	26.56
Q1 ; Q3	23.83 ; 29.45	23.67 ; 30.12	23.73 ; 29.80
Min ; Max	17.9 ; 50.1	13.9 ; 53.4	13.9 ; 53.4
Baseline BMI by category (kg/m^2) [n(%)]			
Number	267	263	530
<18.5	2 (0.7)	3 (1.1)	5 (0.9)
18.5 to <25	93 (34.8)	92 (35.0)	185 (34.9)
25 to <30	112 (41.9)	101 (38.4)	213 (40.2)
≥30	60 (22.5)	67 (25.5)	127 (24.0)
ECOG performance status [n(%)]			
Number	268	263	531
0	155 (57.8)	140 (53.2)	295 (55.6)
1	101 (37.7)	109 (41.4)	210 (39.5)
2	12 (4.5)	14 (5.3)	26 (4.9)

Other = Australia, Turkey

On overview of disease characteristics, prior anti-myeloma treatment and refractory status from those treatments at study entry is presented in Table 14, Table 15 and Table 16.

Table 14. Summary of disease characteristics at study entry - Randomised population (Study EFC15951)

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
MM subtype at study entry[a] [n(%)]			
Number	268	263	531

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
Ig G	162 (60.4)	156 (59.3)	318 (59.9)
Ig A	60 (22.4)	52 (19.8)	112 (21.1)
Ig M	1 (0.4)	1 (0.4)	2 (0.4)
Ig D	1 (0.4)	4 (1.5)	5 (0.9)
Ig E	0	0	0
Kappa light chain only	26 (9.7)	33 (12.5)	59 (11.1)
Lambda light chain only	17 (6.3)	16 (6.1)	33 (6.2)
Unknown/undetectable	1 (0.4)	1 (0.4)	2 (0.4)
Biclonal status at study entry[a] [n(%)]			
Number	268	263	531
Yes	9 (3.4)	8 (3.0)	17 (3.2)
No	259 (96.6)	255 (97.0)	514 (96.8)
Beta-2 Microglobulin (mg/L)			
Number	263	258	521
Mean (SD)	3.50 (2.44)	3.92 (2.74)	3.71 (2.60)
Median	2.80	3.10	2.90
Q1 ; Q3	2.20 ; 4.00	2.30 ; 4.40	2.20 ; 4.20
Min ; Max	1.2 ; 22.6	1.3 ; 21.6	1.2 ; 22.6
Beta-2 Microglobulin (mg/L) [n(%)]			
Number	263	258	521
< 3.5	175 (66.5)	153 (59.3)	328 (63.0)
≥ 3.5 and < 5.5	61 (23.2)	68 (26.4)	129 (24.8)
≥ 5.5	27 (10.3)	37 (14.3)	64 (12.3)
Albumin (g/L)			
Number	267	261	528
Mean (SD)	41.48 (5.24)	41.56 (5.49)	41.52 (5.36)
Median	42.00	42.00	42.00
Q1 ; Q3	39.00 ; 45.00	39.00 ; 45.00	39.00 ; 45.00
Min ; Max	23.0 ; 52.0	19.0 ; 57.0	19.0 ; 57.0
Albumin (g/L) [n(%)]			
Number	267	261	528
<35	26 (9.7)	24 (9.2)	50 (9.5)
≥35	241 (90.3)	237 (90.8)	478 (90.5)
Serum LDH (IU/L)			
Number	267	261	528
Mean (SD)	207.86 (222.79)	213.10 (115.19)	210.45 (177.78)
Median	182.00	187.16	184.00
Q1 ; Q3	151.00 ; 221.96	150.00 ; 234.00	151.00 ; 227.98
Min ; Max	54.0 ; 3680.0	79.0 ; 1265.0	54.0 ; 3680.0
Serum LDH (IU/L) [n(%)]			
Number	267	261	528
≤ULN	222 (83.1)	207 (79.3)	429 (81.3)
>ULN	45 (16.9)	54 (20.7)	99 (18.8)
ISS stage at study entry [n(%)]			
Number	268	263	531
Stage I	169 (63.1)	146 (55.5)	315 (59.3)
Stage II	67 (25.0)	74 (28.1)	141 (26.6)
Stage III	27 (10.1)	37 (14.1)	64 (12.1)
Unknown	5 (1.9)	6 (2.3)	11 (2.1)

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
R-ISS stage at study entry [n(%)]			
Number	268	263	531
Stage I	82 (30.6)	67 (25.5)	149 (28.1)
Stage II	125 (46.6)	142 (54.0)	267 (50.3)
Stage III	12 (4.5)	11 (4.2)	23 (4.3)
Not classified[b]	49 (18.3)	43 (16.3)	92 (17.3)
Fish done but risk not classified	24 (49.0)	9 (20.9)	33 (35.9)
Fish assessment missing	17 (34.7)	24 (55.8)	41 (44.6)
At least one biological assessment missing	10 (20.4)	14 (32.6)	24 (26.1)
R2-ISS stage at study entry [n(%)]			
Number	268	263	531
Stage I	51 (19.0)	42 (16.0)	93 (17.5)
Stage II	62 (23.1)	65 (24.7)	127 (23.9)
Stage III	64 (23.9)	72 (27.4)	136 (25.6)
Stage IV	13 (4.9)	11 (4.2)	24 (4.5)
Not classified[b]	78 (29.1)	73 (27.8)	151 (28.4)

Ig: immunoglobin, MM: multiple myeloma, ISS: international staging system, R-ISS: revised international staging system, eCRF: electronic case report form, LDH: lactate dehydrogenase, ULN: upper limit of normal, R2-ISS: revised international staging system 2

a As per central laboratory results

b A participant can have more than one reason to have R-ISS stage not classified.

The proportion of patients with renal impairment (eGFR <60 mL/min/1.73 m^2) was 32% in the Isa-SC+ Pd arm and 23% in the Isa-IV+ Pd arm.

Overall, 20.5% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14), t(14;16), and chromosomal 1q21 abnormality were present in 10%, 9.6%, 2.1% and 35.6% of patients, respectively.

Table 15: Prior antimyeloma treatments - Randomised population (Study EFC15951)

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
No. prior lines by participant			
Number	268	263	531
Mean (SD)	2.3 (1.3)	2.3 (1.3)	2.3 (1.3)
Median	2.0	2.0	2.0
Q1 ; Q3	1.0 ; 3.0	1.0 ; 3.0	1.0 ; 3.0
Min ; Max	1 ; 8	1 ; 8	1 ; 8
No. prior lines by category per eCRF [n(%)]			
Number	268	263	531
1-2	168 (62.7)	168 (63.9)	336 (63.3)
≥ 3	100 (37.3)	95 (36.1)	195 (36.7)
No. prior lines			
Number	268	263	531
1	84 (31.3)	76 (28.9)	160 (30.1)
2	84 (31.3)	92 (35.0)	176 (33.1)
3	56 (20.9)	52 (19.8)	108 (20.3)
4	23 (8.6)	23 (8.7)	46 (8.7)
5	13 (4.9)	13 (4.9)	26 (4.9)
6	7 (2.6)	6 (2.3)	13 (2.4)
≥ 8	1 (0.4)	1 (0.4)	2 (0.4)

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
Participants with ≥1 transplant [n(%)]	151 (56.3)	147 (55.9)	298 (56.1)
Autologous Stem Cell Transplant	147 (54.9)	143 (54.4)	290 (54.6)
Allogeneic Stem Cell Transplant	5 (1.9)	4 (1.5)	9 (1.7)

eCRF: electronic case report form, IMiD: immunomodulators, HDAC: histone deacetylase

Table 16: Refractory status to prior antimyeloma treatments - Randomised population (Study EFC15951)

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)	All (N=531)
Refractory to IMiD [n(%)]	222 (82.8)	228 (86.7)	450 (84.7)
Refractory to lenalidomide	220 (82.1)	224 (85.2)	444 (83.6)
Refractory to pomalidomide	0	0	0
Refractory to thalidomide	26 (9.7)	34 (12.9)	60 (11.3)
Refractory to PI [n(%)]	132 (49.3)	132 (50.2)	264 (49.7)
Refractory to bortezomib	100 (37.3)	105 (39.9)	205 (38.6)
Refractory to ixazomib	28 (10.4)	23 (8.7)	51 (9.6)
Refractory to carfilzomib	26 (9.7)	27 (10.3)	53 (10.0)
Refractory to IMiD and PI [n(%)]	116 (43.3)	120 (45.6)	236 (44.4)
Refractory to lenalidomide and bortezomib	84 (31.3)	90 (34.2)	174 (32.8)
Refractory to lenalidomide and ixazomib	27 (10.1)	19 (7.2)	46 (8.7)
Refractory to lenalidomide and carfilzomib	26 (9.7)	26 (9.9)	52 (9.8)
Refractory to lenalidomide, bortezomib, ixazomib and carfilzomib	1 (0.4)	0	1 (0.2)
Refractory to last regimen [n(%)]	218 (81.3)	223 (84.8)	441 (83.1)
Lenalidomide	171 (63.8)	183 (69.6)	354 (66.7)
Bortezomib	46 (17.2)	37 (14.1)	83 (15.6)
Pomalidomide	0	0	0
Thalidomide	4 (1.5)	5 (1.9)	9 (1.7)
Carfilzomib	16 (6.0)	20 (7.6)	36 (6.8)
Lenalidomide and bortezomib	29 (10.8)	26 (9.9)	55 (10.4)
Lenalidomide and carfilzomib	7 (2.6)	6 (2.3)	13 (2.4)

lMiD: immunomodulators, PI: proteasome inhibitors

5.3.1.1.3.4. Outcomes and estimation

Co-primary endpoint: Overall response rate

Overall response rate (ORR) was defined as the proportion of participants who have a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) according to the 2016 IMWG criteria. Efficacy data demonstrated that Isa-SC was non-inferior to Isa-IV in terms of ORR (Table 17),

Table 17: ORR - Primary analysis - Summary of overall response rate per IRC - ITT population in study EFC15951

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)
Best overall response [n(%)]		
Stringent complete response (sCR)	12 (4.5)	11 (4.2)
Complete response (CR)	43 (16.0)	36 (13.7)
Very good partial response (VGPR)	68 (25.4)	75 (28.5)
Partial response (PR)	66 (24.6)	65 (24.7)
Minimal response (MR)	10 (3.7)	13 (4.9)
Stable disease (SD)	46 (17.2)	50 (19.0)
Progressive disease (PD)	6 (2.2)	3 (1.1)
Non progressive disease (NON-PD)	1 (0.4)	0
Unconfirmed progressive disease (uPD)	1 (0.4)	1 (0.4)
Not evaluable/Not assessed (NE)	15 (5.6)	9 (3.4)
Overall response rate (sCR, CR, VGPR or PR) [n(%)]	189 (70.5)	187 (71.1)
95% CI[a]	0.6467 to 0.7591	0.6522 to 0.7651
Relative risk (95% CI)[b]		
vs Isa-IV+Pd		1.008 (0.903 to 1.126)
P-value using Farrington-Manning method[c]		
vs Isa-IV+Pd		0.0006
Odds ratio (95% CI)[d]		
vs Isa-IV+Pd		1.028 (0.708 to 1.495)

CI: confidence interval, sCR: stringent complete response, CR: complete response, VGPR: very good partial response, PR: partial response, IRC: independent review committee.

[a]Two-sided 95% CI estimated using the Clopper-Pearson method.

[b]Two-sided 95% CI estimated using Farrington-Manning method. Statistically significance will be met if lower limit of 95% CI is greater or equal to 0.839.

[c]One-sided significance level is 0.025.

[d]Two-sided 95% CI estimated using Miettinen-Nurminen Score method.

Co-primary endpoint: C_{trough} at steady state

The observed concentration before dosing (C_{trough}) of isatuximab at steady state was assessed based on the observed concentrations before dosing at Cycle 6 Day 1 in the per-protocol PK (PP-PK) population.

The mean±SD $C_{trough,SS}$ (Cycle 6 Day 1 pre-dose) was higher for Isa-SC than for Isa-IV and the corresponding geometric mean ratio for C_{trough} was 1.532 (90% CI: 1.316-1.784) (Table 18 nd Figure 12 respectively).

Table 18: Summary of Ctrough at steady state - Per protocol pharmacokinetic population in study EFC15951

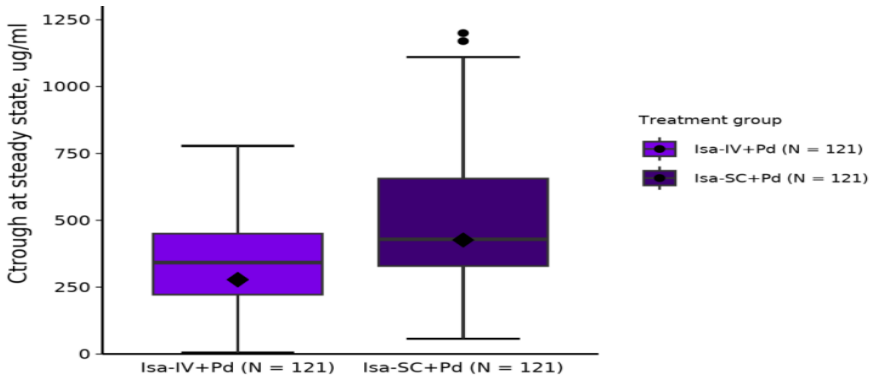
C_{trough} (ug/mL)	Isa-IV + Pd (N=121)	Isa-SC + Pd (N=121)
Cycle 6 Day 1		
Number	121	121
Mean (SD)	340.45 (168.99)	499.07 (258.96)
SEM	15.362	23.542
Median	342.00	429.00
Q1 ; Q3	222.00 ; 450.00	329.00 ; 656.00
Min ; Max	5.0 ; 778.0	57.4 ; 1200.0

C_{trough} (ug/mL)	Isa-IV + Pd (N=121)	Isa-SC + Pd (N=121)
CV	49.636	51.888
Geometric Mean	278.15	426.16
Ratio of geometric mean of Isa-SC/Isa-IV		1.532
90% CI for ratio of geometric mean[a]		1.316 ; 1.784

CI: confidence interval

a Two-sided 90% CI. Applied anti-log procedure to convert original scale. Statistically significance will meet if lower limit of 90% CI is greater or equal to 0.80.

Figure 12: Boxplot of Ctrough at steady state - Per protocol



The diamond symbol represents the geometric mean.

Key secondary endpoints

Very Good Partial Response or better rate

Efficacy data demonstrated also that Isa-SC is non-inferior to Isa-IV in terms of VGPR+ rate (Table 19),

Table 19: Summary of VGPR or better response rate per Investigator and response-related secondary endpoints - ITT population in study EFC15951

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)
VGPR or better Response [n(%)]		
Stringent complete response (sCR)	12 (4.5)	11 (4.2)
Complete response (CR)	43 (16.0)	36 (13.7)
Very good partial response (VGPR)	68 (25.4)	75 (28.5)
VGPR or better		
Response rate (sCR, CR, VGPR) [n(%)]	123 (45.9)	122 (46.4)
95% CI[a]	0.3982 to 0.5207	0.4024 to 0.5262
Relative risk (95% CI)[b] vs Isa-IV+Pd		1.011 (0.841 to 1.215)
P-value using Farrington-Manning method[c] vs Isa-IV+Pd		<0.0001
Odds ratio (95% CI)[d] vs Isa-IV+Pd		1.020 (0.725 to 1.435)
Complete response		
Complete response (sCR, CR) [n(%)]	55 (20.5)	47 (17.9)
95% CI[a]	0.1585 to 0.2586	0.1344 to 0.2305
Odds ratio (95% CI)[d] vs Isa-IV+Pd		0.843 (0.547 to 1.297)

CI: confidence interval, sCR: stringent complete response, CR: complete response, VGPR: very good partial response, IRC: independent review committee.

[a]Two-sided 95% CI estimated using the Clopper-Pearson method.

[b]Two-sided 95% CI estimated using Farrington-Manning method. Statistically significance will be met if lower limit of 95% CI is greater or equal to 0.6312.

[c]One-sided significance level is 0.025.

[d]Two-sided 95% CI estimated using Miettinen-Nurminen Score method.

Observed concentration before dosing (C_{trough}) at 4 weeks

The mean±SD of the C_{trough} of isatuximab at 4 weeks was 421±215 µg/mL in the Isa-SC arm compared to 302±117 µg/mL in the Isa-IV arm. The ratio of geometric means (90% CI) of Isa-SC/Isa-IV was 1.302 (1.158 to 1.465). Non-inferiority of Isa-SC over Isa-IV was confirmed, as the lower limit of the 90% CI was greater than the non-inferiority margin of 0.80).

Incidence rate of infusion-reactions

A statistically significant lower incidence of systemic IRs induced by isatuximab were observed in the Isa-SC arm (4 [1.5%]) compared to the Isa-IV arm (66 [25.0%]), with a relative risk (95% CI) of Isa-SC versus Isa-IV of 0.061 (0.022 to 0.164), p<0.0001.

Dose interruptions occurred in 7 of 5145 (0.1%) injections in the Isa-SC arm, and interruptions occurred in 76 of 5274 (1.4%) infusions in the Isa-IV arm. The median duration of first infusion/injection in the Isa-SC arm was 13 minutes (range 5 to 37) and 208.5 minutes (range 30 to 1112) the Isa-IV arm. Isa-SC was administered at a constant duration throughout the study (median of 13.0 minutes [range 1 to 83] for males and 13.0 minutes [range 0 to 41] for females). The median duration of Isa-IV infusion was 209.0 minutes (range 60 to 1112) for males and 208.0 minutes (range 30 to 742) for females at the first infusion. A total of 110 (2.1%) of 5117 Isa-SC injections had duration >20 minutes, including 25 (0.5%) injections lasting more than 30 minutes.

Patient satisfaction

The number (%) of participants who responded as satisfied or as very satisfied with the injection method used to administer study medication (item-8 of the PESQ) at Cycle 5 Day 15 is shown in Table 20).

Table 20. Patient experience and satisfaction questionnaire (PESQ-FU) - Key secondary endpoint - Summary of participant satisfaction rate based on PESQ-FU questionnaire at cycle 5 day 15 - ITT population - EFC15951

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)
Number of questionnaires not completed at cycle 5 day 15	66 (24.6)	73 (27.8)
Number of participants who discontinued the study treatment before cycle 5 day 15	50 (18.7)	45 (17.1)
Number of questionnaires completed at cycle 5 day 15	202 (75.4)	190 (72.2)
Satisfaction with injection method		
Very Satisfied	37 (13.8)	93 (35.4)
Satisfied	106 (39.6)	91 (34.6)
Neither Satisfied nor Dissatisfied	52 (19.4)	5 (1.9)
Dissatisfied	5 (1.9)	1 (0.4)
Very Dissatisfied	2 (0.7)	0
Participant satisfaction rate[a] [n(%)]	143 (53.4)	184 (70.0)
95% CI[b]	0.4719 to 0.5945	0.6403 to 0.7544

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)
Relative risk (95% CI)[c] vs Isa-IV+Pd		1.311 (1.143 to 1.504)
Stratified[d] Relative risk (95% CI)[c] vs Isa-IV+Pd		1.304 (1.136 to 1.496)
Stratified[d] Cochran-Mantel-Haenszel test p-value[ef] vs Isa-IV+Pd		0.0001

CI: confidence interval, PESQ: patient expectation and satisfaction questionnaire, IRT: interactive response technology, CMH: cochran-mantel-haenszel

[a]Participants who have not responded as satisfied or as very satisfied with the injection method used to administer study medication will be counted as non-satisfied. Participants who discontinued study treatment before Cycle 5 Day 15 will be counted as non-satisfied.

[b]Two-sided 95% CI estimated using the Clopper-Pearson method

[c]Two-sided 95% CI estimated using the Wald method.

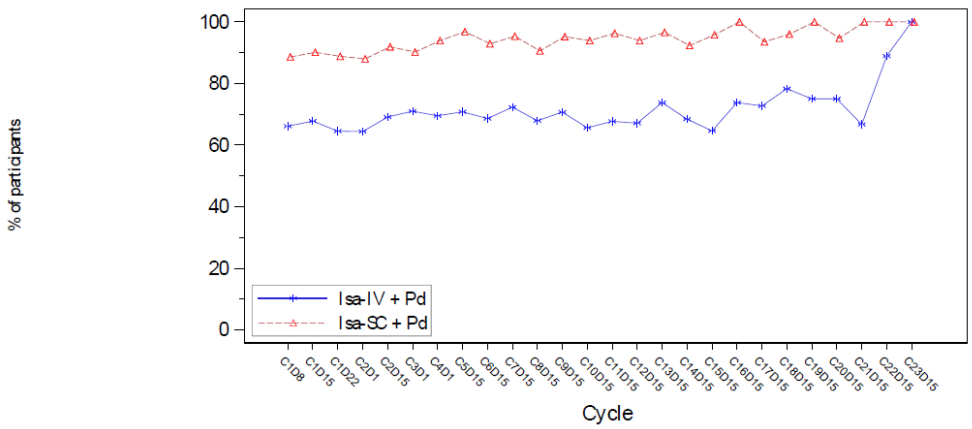
[d]Stratified on MM isotype (IgG versus non-IgG), body weight (<= 65 kg, >65 to <= 85 kg, and >85 kg), and number of prior lines (1-2 versus >= 3) according to IRT

[e]p-value is provided from a CMH test stratified according to the stratification factors.

[f]One-sided significance level is 0.025.

This result was consistent across most timepoints, with the exception of those with a very low number of respondents (see Figure 13).

Figure 13: Satisfaction with injection method over time (PESQ-FU)



Only cycles where at least 10 participants answered the question are included.

Y-axis represents the percentage of participants that are very satisfied and satisfied. Note the denominator is the number of participants who answered the question.

Other Secondary Endpoints

Duration of response (DOR)

Among 187 and 189 participants in the Isa-SC and Isa-IV arms who were responders based on IRC assessment (PR or better), the median (95% CI) duration of response was not reached in either treatment arm.

Time to first response (TT1R) by IRC

In the ITT population, the median time to first response was 2.04 months (95% CI: 1.906 to 2.793) and 1.91 months (95% CI: 1.216 to 1.971) in the Isa-SC and Isa-IV arms, respectively, with a stratified hazard ratio of 0.793 (95% CI: 0.644 to 0.977).

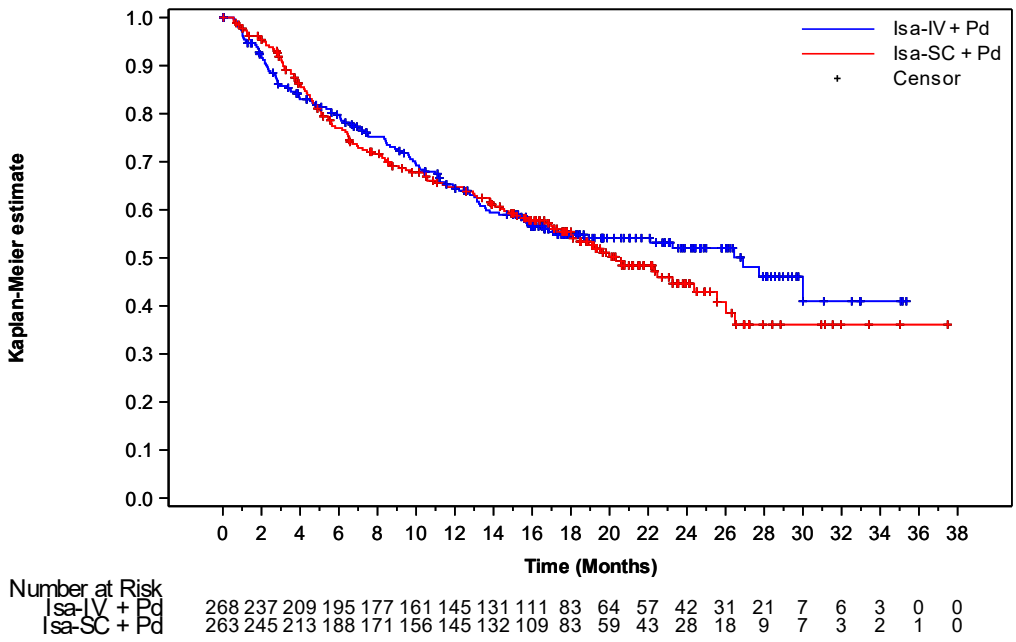
Time to best response (TTBR) by IRC

In the ITT population, the median time to best response was 4.60 months (95% CI: 3.811 to 5.125) and 3.94 months (95% CI: 3.548 to 4.862) in the Isa-SC and Isa-IV arms, respectively, with a stratified hazard ratio of 0.909 (95% CI: 0.737 to 1.120).

Progression free survival (PFS) by IRC

With a median follow-up duration of 21.75 months, 122 (46.4%) and 115 (42.9%) participants had PFS events in the Isa-SC+Pd and Isa-IV+Pd arms, respectively. The estimated median (95% CI) PFS time was 20.34 months (16.986 to 25.561) and 26.91 months (15.934 to NC), respectively. The stratified HR was 1.108 (95% CI: 0.856 to 1.434). At the time of the cut-off date, a total of 153 (57.1%) and 141 (53.6%) participants in the Isa-IV + Pd and Isa-SC+Pd groups, respectively, did not have a PFS event and were censored. The main reason for censoring was administrative censoring. The rates of censoring in other censoring categories were balanced between the arms.

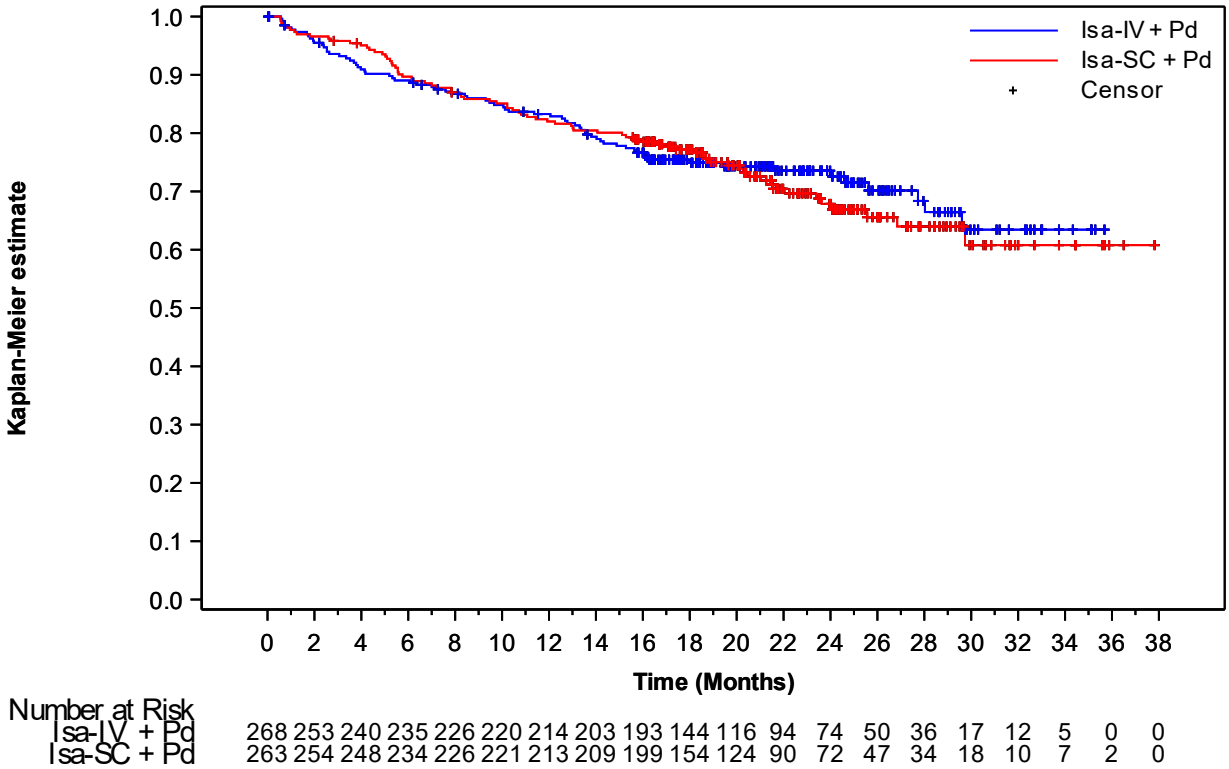
Figure 14. PFS analysis based on disease assessment by IRC - Kaplan-Meier curves by treatment group - ITT analysis set



Overall survival (OS)

With a median follow-up duration of 21.75 months, the incidence of participants who had a death event was 77 (29.3%) participants in the Isa-SC+Pd arm and 73 (27.2%) participants in the Isa-IV+Pd arm, with a stratified HR of 1.029 (95% CI: 0.746 to 1.420). At the time of the cut-off date, a total of 195 (72.8%) and 186 (70.7%) participants in the Isa-IV+Pd and Isa-SC+Pd groups, respectively, were alive and censored for the OS analysis. The main reason for censoring was administrative censoring (78.5% and 74.2% in the Isa-IV+Pd and Isa-SC+Pd groups, respectively). There were 13 (6.7%) participants in the Isa-IV+Pd group and 4 (2.2%) participants in the Isa-SC+Pd group classified as lost to follow-up.

Figure 15. Overall survival - Kaplan-Meier curves by treatment group - ITT analysis set



Progression free survival after first progression (PFS2) by IRC

Acknowledging the limited median follow-up duration of 12.06 months, the probability of PFS2 was similar between treatment arms, with 59 (22.4%) and 63 (23.5%) participants having a PFS2 event in the Isa-SC and Isa-IV arms, respectively (stratified HR = 0.887, 95% CI: 0.620 to 1.269).

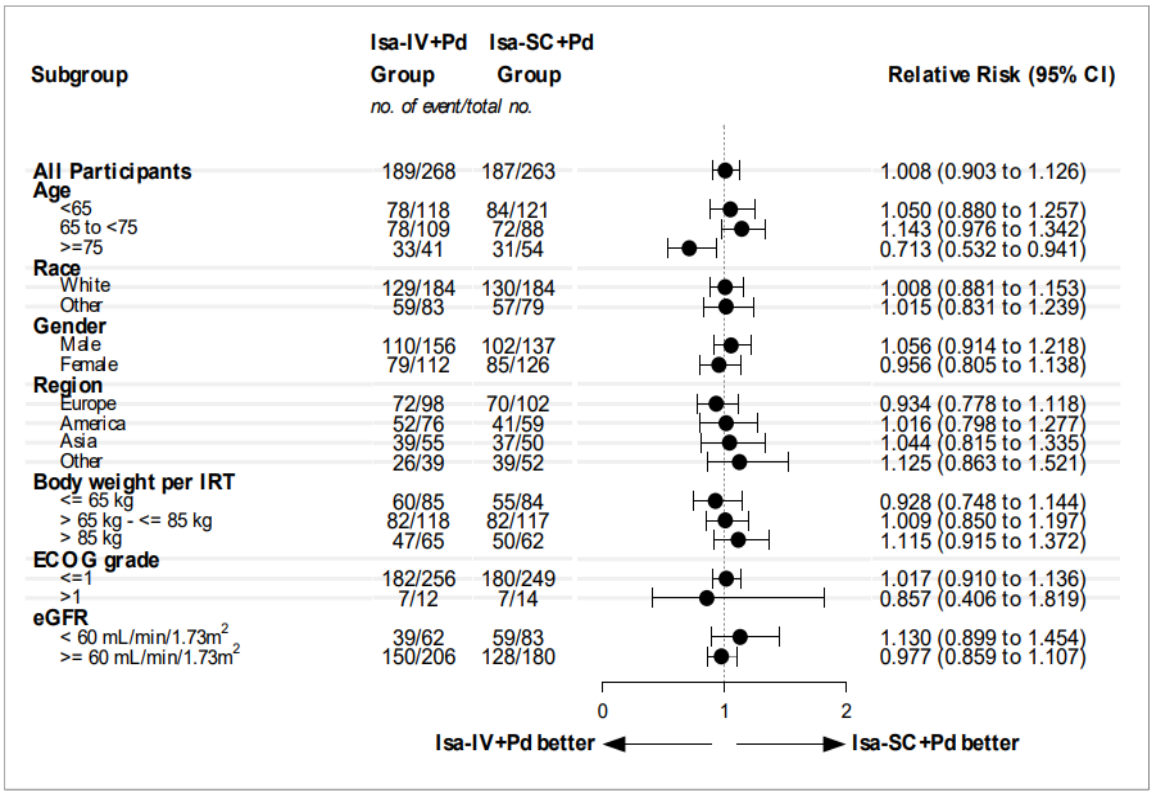
5.3.1.1.3.5. Pre-defined and post-hoc subgroup analyses

Co-primary endpoint ORR

The ORR with one prior line of therapy was 73.7% for Isa-SC versus 76.2% for Isa-IV, and in patients with at least 2 prior lines of therapy, the ORR was 70.1% versus 67.9%, respectively.

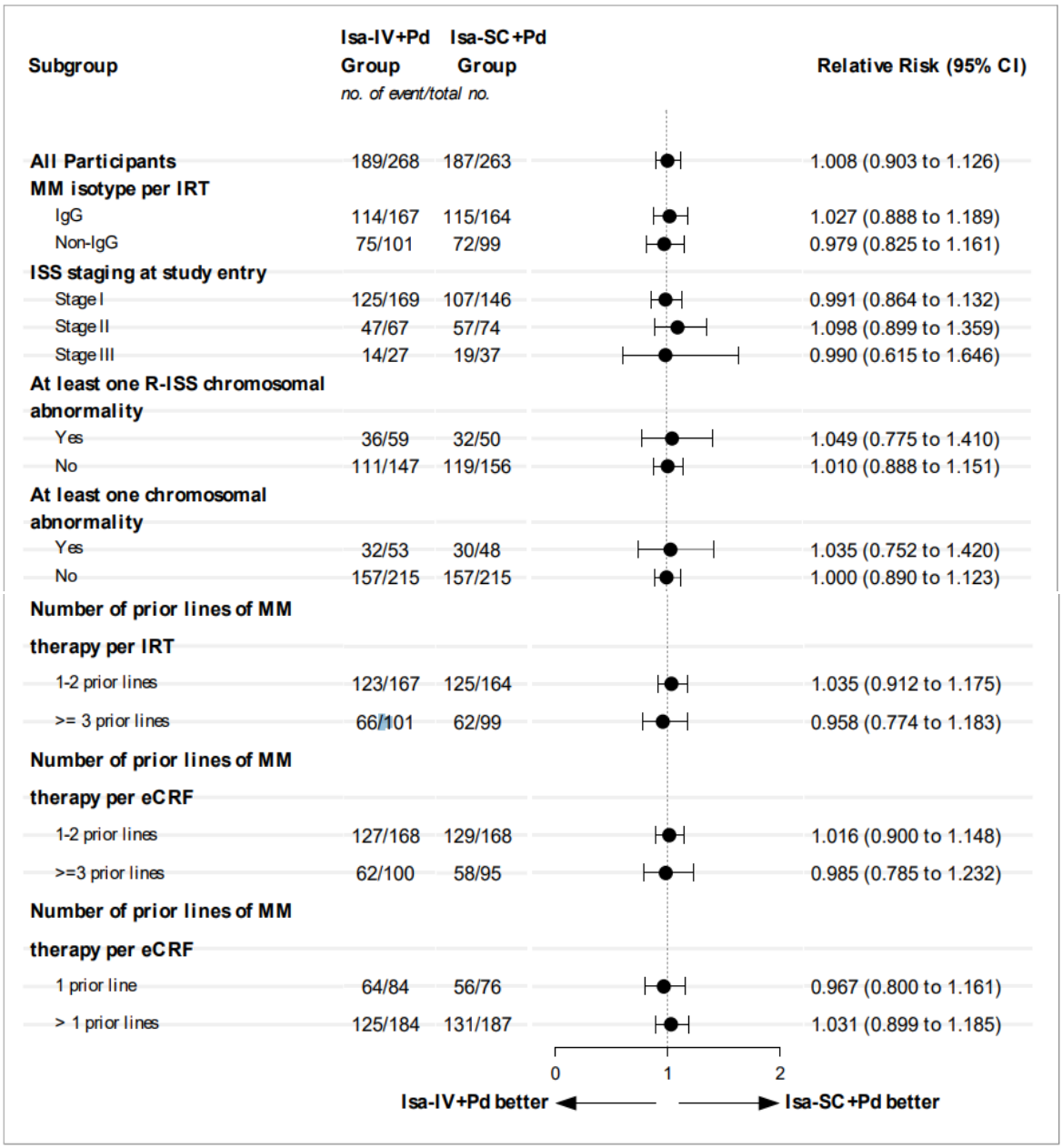
Subgroup analyses of ORR were conducted when at least 10 participants were included in each treatment arm within a subgroup. Subgroup analyses for the majority of the prespecified subgroups (Age, Body weight, Race, Gender, Region, ECOG grade, eGFR, MM isotype, ISS at study entry, R-ISS at study entry, at least one R-ISS chromosomal abnormality, at least one chromosomal abnormality, number of prior lines of therapy, refractory to lenalidomide) are shown in Figure 16- Figure 18 .

Figure 16: Subgroup analyses - ORR based on IRC assessment by demographics and baseline characteristics (forest plot) - ITT population



ORR: objective response rate, IRC: independent review committee, CI: confidence interval, ECOG: eastern cooperative oncology group, IRT: interactive response technology.

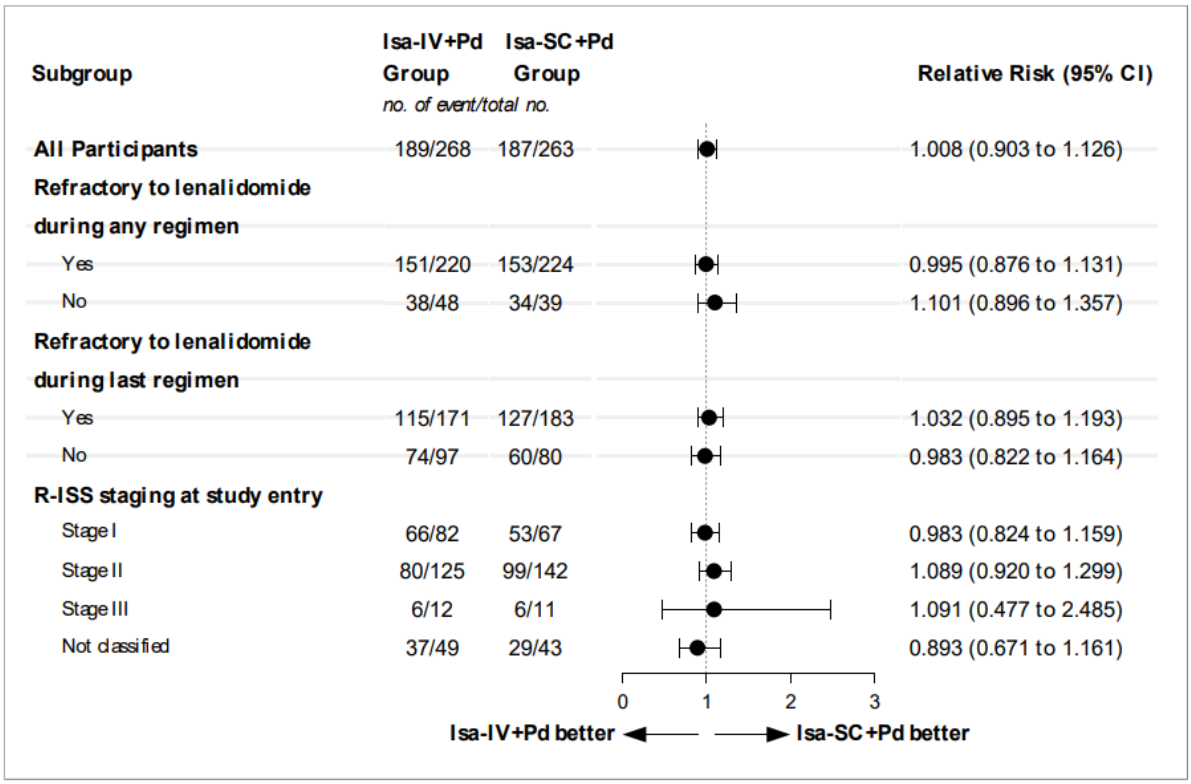
Figure 17: ORR - Subgroup analyses - ORR based on IRC assessment by disease characteristics (forest plot) (1/2) - ITT population



ORR: objective response rate, IRC: independent review committee, CI: confidence interval, MM: multiple myeloma, IRT: interactive response technology, eCRF: electronic case report form.

Relative risks are not calculated for subgroups will less than 10 participants in either Isa-IV arm or Isa-SC arm

Figure 18: ORR - Subgroup analyses - ORR based on IRC assessment by disease characteristics (forest plot) (2/2) - ITT population



ORR: objective response rate, IRC: independent review committee, CI: confidence interval, R-ISS: revised international staging system.
Relative risks are not calculated for subgroups will less than 10 participants in either Isa-IV arm or Isa-SC arm

ORR by age

The ORR based on IRC assessment in the Isa-SC arm was similar to Isa-IV arm for almost all subgroups, with the exception of participants 75 years of age and older, for which the ORR was lower in the Isa-SC arm compared with the Isa-IV arm (ORR [95% CI]: 57.4% [0.4321 to 0.7077] vs 80.5% [0.6513 to 0.9118]; relative risk [95% CI] 0.713 [0.532 to 0.941]). The p-value for the interaction of treatment by age was 0.0153. In the Isa-SC arm, more participants (+ 10 percentage points) had plasmacytoma at study entry compared with the Isa-IV arm (17/54 [31.5%] versus 9/41 [22.0%]), and more participants (+ 17 percentage points) in the Isa-SC arm had disease that was refractory to lenalidomide at last regimen compared with the Isa-IV arm (37/54 [68.5%] versus 21/41 [51.2%]).

ORR by body weight

ORR by body weight subgroups (≤65 kg, >65 to ≤85 kg, and >85 kg;(Figure 16) had relative risks of Isa-SC over Isa-IV of 0.928, 1.009, and 1.115, respectively (interaction p-value=0.4261), whereas for ORR by extreme body weight (≤50 kg, >50 to ≤100 kg, and >100 kg), in the heaviest body weight subgroup of >100 kg, the ORR was lower in the Isa-SC arm compared with the Isa-IV arm (68.2% versus 86.4%).

Among the 22 participants in each treatment arm with extreme high body weight (>100 kg), disease characteristics were as follows:

- ISS Stage II/III at study entry: 10 (45.0%) in Isa-SC vs. 5 (22.7%) in Isa-IV
- R-ISS II/III at study entry: 14 (63.6%) in Isa-SC vs. 8 (36.4%) in Isa-IV

- beta 2-micrglobulin level <3.5 mg/L: 12 (57.1%) in Isa-SC vs. 18 (81.8%) in Isa-IV
- eGFR <60 ml/min/1.73 m^2: 9 (40.9%) in Isa-SC vs. 3 (13.6%) in Isa-IV
- VGPR best overall response at last regimen: 4 (18.2%) in Isa-SC vs. 8 (36.4%) in Isa-IV
- median duration at last treatment: 10.12 months in Isa-SC vs. 20.70 months in Isa-IV

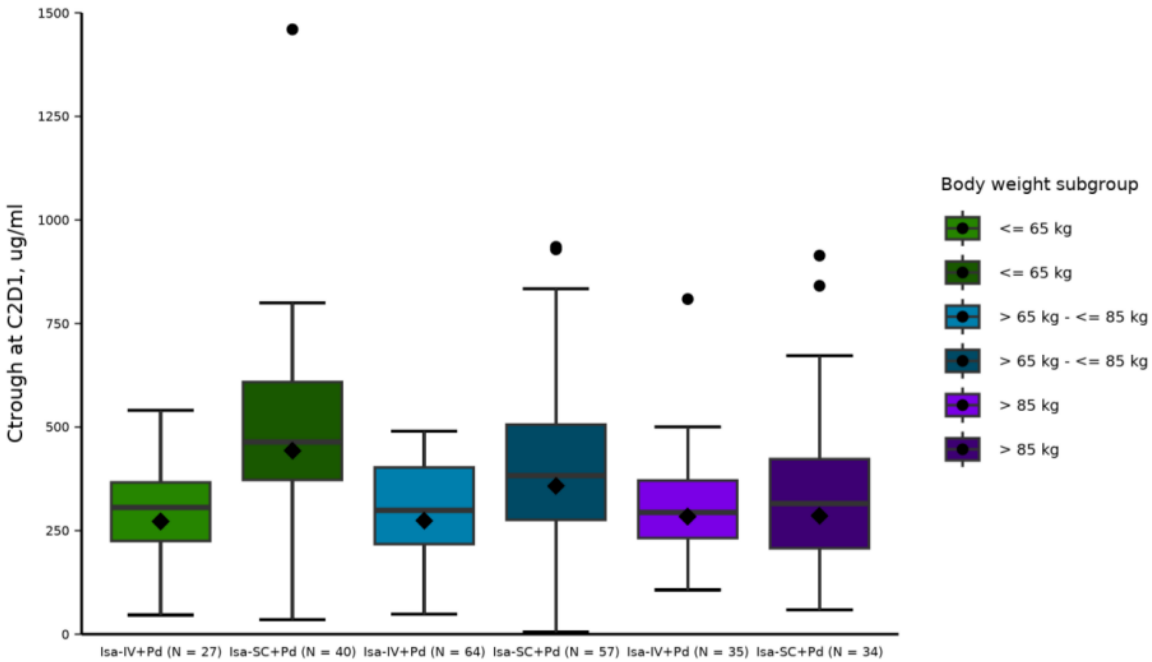
Key secondary endpoint VGPR+

Subgroup analyses for the majority of the prespecified subgroups were generally consistent with the primary analysis of VGPR or better in the overall ITT population. For the "75 years and older" subgroup, the analysis did not favour the Isa-IV arm (16/41 [39.0%] in Isa-SC vs. 19/54 [35.2%] in Isa-IV).

C_{trough} at 4 weeks

A subgroup analysis of C_{trough} at 4 weeks (corresponding to predose at Cycle 2 Day 1) by body weight was introduced post-hoc. Geometric mean ratios of Isa-SC versus Isa-IV were above 1 in all body weight categories: ≤65 kg subgroup (1.628 [90% CI: 1.294 to 2.048]), >65 to ≤85 kg subgroup (1.303 [90% CI: 1.089 to 1.560]), and >85 kg subgroup (1.006 [90%CI: 0.817 to 1.239]). Graphical representation of C_{trough} by body weight at Cycle 2 Day 1 is provided in Figure 19.

Figure 19: Boxplot of C_{trough} at 4 weeks by body weight as per IRT - CT4W-PK population



The diamond symbol represents the geometric mean.

5.3.1.1.3.6. Pre-defined and post-hoc sensitivity analyses

Sensitivity analyses were conducted to evaluate ORR per Investigator assessment based on the ITT population, ORR per IRC assessment based on the PP population, and ORR per Investigator assessment based on the PP population (Table 21).

Table 21: Summary of overall response rate per Investigator - ITT population in study EFC15951

	Isa-IV + Pd (N=268)	Isa-SC + Pd (N=263)
Best overall response [n(%)]		
Stringent complete response (sCR)	14 (5.2)	13 (4.9)
Complete response (CR)	47 (17.5)	34 (12.9)
Very good partial response (VGPR)	67 (25.0)	75 (28.5)
Partial response (PR)	67 (25.0)	67 (25.5)
Minimal response (MR)	10 (3.7)	16 (6.1)
Stable disease (SD)	40 (14.9)	45 (17.1)
Progressive disease (PD)	7 (2.6)	2 (0.8)
Non progressive disease (NON-PD)	0	0
Unconfirmed progressive disease (uPD)	1 (0.4)	0
Not evaluable/Not assessed (NE)	15 (5.6)	11 (4.2)
Overall response rate (sCR, CR, VGPR or PR) [n(%)]	195 (72.8)	189 (71.9)
95% CI[a]	0.6701 to 0.7800	0.6601 to 0.7721
Relative risk (95% CI)[b]		
vs Isa-IV+Pd		0.988 (0.888 to 1.098)
P-value using Farrington-Manning method[c]		
vs Isa-IV+Pd		0.0015
Odds ratio (95% CI)[d]		
vs Isa-IV+Pd		0.956 (0.654 to 1.398)

CI: confidence interval, sCR: stringent complete response, CR: complete response, VGPR: very good partial response, PR: partial response.

a Two-sided 95% CI estimated using the Clopper-Pearson method.

b Two-sided 95% CI estimated using Farrington-Manning method. Statistically significance will be met if lower limit of 95% CI is greater or equal to 0.839

c One-sided significance level is 0.025

d Two-sided 95% CI estimated using Miettinen-Nurminen Score method.

e

5.3.2. Clinical studies in special populations

Table 22: Clinical studies in special populations

	Non-controlled trials: IZALCO IsaSoCut TCD15484	Controlled trials: IRAKLIA GMMG-HD8
Renal impairment* patients (Subjects number /total number)	8/222	5/330
Hepatic impairment** patients (Subjects number /total number)	2/222	1/330
Paediatric patients <18 years (Subjects number /total number)	N/A	N/A
Age 65-74 (Subjects number /total number)	97/222	103/332
Age 75-84 (Subjects number /total number)	43/222	54/332***
Age 85+ (Subjects number /total number)	0/222	Unknown***
Other (Subjects number /total number)	N/A	N/A

* Renal impairment is defined as severe renal disease (≥15 - < 30 mL/min/1.73m^2
** Hepatic impairment is defined as having Grade 3 or 4 liver failure
*** 54 participants that were treated with Isa-SC in study IRAKLIA were 75 years or older. The oldest participant was 86, Q1 = 59 years, median = 66 years, Q3 = 74 years.

5.3.3. In vitro biomarker test for patient selection for efficacy

Not applicable

5.3.4. Supportive studies

A total of four supportive clinical trials were submitted.

Study TCD15484 was a Phase Ib dose-finding study and is described in the clinical pharmacology section.

Phase III study IIT17041 (GMMG-HD8) included an Isa-SC and an Isa-IV arm and the secondary objective of the study was to assess non-inferiority of both methods of administration in terms of ORR at the end of induction. An efficacy and safety interim analysis was performed on the first 142 randomized participants. Due to the immaturity of the data, this study is considered supportive, and not pivotal.

Studies ACT17453 and IIT17756 did not have an internal Isa-IV control arm and cross-study comparisons were made to equivalent Isa-IV studies. Results on efficacy both studies are considered to be of limited value due to the lack of comparator; the safety results are assessed as part of the All Isa-SC pool.

Study IIT17041 (GMMG-HD8)

Study IIT17041 (GMMG-HD8) is an Investigator-sponsored prospective, multicentre, randomized, open-label, Phase III study to evaluate the efficacy and safety of Isa-SC+VRd versus Isa-IV+VRd as induction therapy in Te NDMM patients. Participants were randomized in a 1:1 ratio to isatuximab IV or isatuximab

SC (administered by OBDS) stratified by R-ISS stages I/II versus III versus not classified, and body weight (<66 kg, 66-85 kg, >85 kg).

As this study included an internal comparator, efficacy of Isa-SC and Isa-IV could be compared, even though the data is quite preliminary (142 out of 514 patients).

The primary endpoint VGPR or better rate, as assessed by the Investigator based on IMWG criteria were similar between both groups, 73.9% (95% CI: 61.9%, 83.8%) in the Isa-SC+VRd and 78.1% (95% CI: 66.9%, 86.9%) in the Isa-IV+VRd group. At the end of the induction phase, 62 (89.9%, 95% CI: 80.2% to 95.8%) participants in the Isa SC+VRd group and 64 (87.7%, 95% CI: 77.9% to 94.2%) in the Isa-IV+VRd group reached at least a partial response as assessed by the Investigator. There were 57 (82.6%, 95% CI: 71.6% to 90.7%) responders (CR, VGPR or PR) in the Isa-SC+VRd group and 63 (86.3%, 95% CI: 76.2% to 93.2%) responders in the Isa-IV+VRd group for ORR based on the IRC assessment.

A complete response at the end of the induction, as per Investigator, was reached in 17 (24.6%; 95% CI: 15.0% to 36.5%) participants in the Isa-SC+VRd group and 25 (34.2%; 95% CI: 23.5% to 46.3%) in the Isa-IV+VRd, respectively. The CR rate in the Isa-SC+VRd group was similar to the one of the Isa-IV+VRd group of registrational Study IIT15403 (GMMG-HD7) (24.8%).

Study ACT17453 (IZALCO)

Study ACT17453 (IZALCO) is a randomized sequential, Phase II, open-label, multi-cohorts study evaluating Isa-SC in combination with Kd in RRMM patients having received 1 to 3 prior lines of therapy. It is the only study in which SC delivery of isatuximab with the OBDS was compared to manual SC administration of isatuximab. In the first part of the study, accelerated injection duration of Isa-SC administered manually (manual administration using a commercially available syringe set) was assessed in two sentinel cohorts. In the second part of the study, 74 participants were randomized in a 3:1 ratio to isatuximab SC manually from Cycle 1/Day 1 and isatuximab SC via OBDS. After the first 3 cycles, the delivery method was switched for each participant (from OBDS to manual, and vice versa) for 3 additional cycles. At Cycle 7, each participant chose their preferred method of administration for the rest of the study. Participants from the first part with isatuximab SC manually administered were also offered to switch to OBDS at Cycle 7.

The study met its primary endpoint of ORR. The ORR by IRC was 79.7% with a 95% CI of 68.8% to 88.2% and corresponding 1-sided p-value of 0.0043, which met statistical significance (<0.025) to reject a null hypothesis of ORR ≤65%. VGPR or better rate as assessed per IRC was achieved in 62.2% participants and was consistent with the VGPR or better rate by Investigator of 60.8%. The CR or better rate by IRC was 21.6%. The key secondary endpoint was proportion of participants preferring OBDS over manual administration. Among the 47 participants in Cohort 3 who were evaluable for participant preference, 35 participants (74.5% with a 95% CI from 59.6% to 86.0%) preferred OBDS administration (1 sided p-value of 0.0004, which was statistically significant to reject a null hypothesis of rate of 50%), while 8 participants (17.0%) preferred manual administration, and 4 participants (8.5%) had no preference. The ORR and VGPR or better rates evaluated by IRC were similar between Cohort 3 starting with manual administration and Cohort 3 starting with OBDS administration (81.0% versus 79.2% ORR and 66.7% versus 62.5 % VGPR or better rate, respectively).

ORR per IRC during the first 6 months of treatment was similar between Isa-SC+Kd and Isa-IV+Kd (Study EFC15246, IKEMA), with 79.7% (95% CI: 68.8% to 88.2%) and 86.0% (95% CI: 80.0% to 90.8%), respectively. VGPR or better rate per IRC was also similar between Isa-SC+Kd and Isa-IV+Kd, with 54.1% (95% CI: 42.1% to 65.7%) and 58.7% (95% CI: 51.1% to 66.0%), respectively. While these results shed some light on the efficacy of Isa-SC+Kd in RRMM patients, the comparison between studies

IZALCO and IKEMA is not sufficient to conclude or support non-inferiority of Isa-SC+Kd to Isa-IV+Kd in RRMM patients.

Study IIT17756 (IsaSoCut)

IIT17756 (IsaSoCut) is a Phase II, open-label, single-arm, multicentre study evaluating the efficacy, safety, and PK of Isa-SC administered via an OBDS in combination with VRd in patients with Ti NDMM. The historical comparator for this study is Study EFC12522 (IMROZ).

The median duration of exposure was 11.99 months (range 1.8 to 15.0). The primary endpoint was VGPR+ rate. The VGPR or better rate per Investigator assessment was 87.8% (95% CI: 78.2% to 94.3%). The ORR per Investigator assessment was 97.3% (95% CI: 90.6% to 99.7%). The rate of CR or better per Investigator assessment was 24.3% (95% CI: 15.1% to 35.7%).

A cross-study comparison to Study EFC12522 (IMROZ) was made for the first 8 months. ORR per IRC during the first 8 months of treatment was similar in Isa-SC+VRd and Isa IV+VRd participants, with ORRs of 97.3% (95% CI: 90.6% to 99.7%) and 89.1% (95% CI: 84.7% to 92.6%). VGPR or better rate per IRC was also similar between Isa-SC+VRd and Isa-IV+VRd participants, with VGPR+ rates of 85.1% (95% CI: 75.0% to 92.3%) and 83.0% (95% CI: 78.0% to 87.3%), respectively. It was not possible to compare CR rates during the first 8 months between both studies, as BMA for CR was only taken after 8 months in Study IIT17756.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.6. Overall discussion and conclusions on clinical efficacy

5.3.6.1. Discussion

This line extension concerns the registration of a new pharmaceutical form of isatuximab, namely a solution for SC administration applicable to all currently approved indications.

In addition to the pivotal study, supportive studies were submitted, in order to cover all populations and combinations for which isatuximab is currently approved. However, it is not necessary to demonstrate non-inferiority for every single drug combination and in every single patient population. Solid PK data from a controlled study can be extrapolated to other treatment combinations. Therefore, discussion of the data of the supportive studies in this document will be brief.

5.3.6.1.1. Pivotal study EFC15951 (IRAKLIA)

Study design

Study population

Participants of 18 years or older were eligible for inclusion in study EFC15951 if they had RRMM and had received at least 1 prior line of anti-myeloma therapy, including lenalidomide and a PI (bortezomib, carfilzomib or ixazomib), given alone or in combination. Participants who received only one prior line of therapy had to be lenalidomide refractory. Patients with primary refractory multiple myeloma, an ECOG status > 2, and patients who were previously treated with an anti-CD38 antibody (< 9 months prior to randomisation) or pomalidomide were excluded.

Isatuximab is approved with the pom/dex combination after at least two prior lines of therapy, based on registrational Isa-IV study EFC14335 (ICARIA). The in- and exclusion criteria of study EFC15951 appropriately reflect the RRMM patient population for which the combination of isatuximab, pomalidomide and dexamethasone is approved, except that patients could also be included after first relapse. Therefore, the study population is broader than the approved indication. 30.1% of participants had received only one prior line of therapy, so the majority of participants is in line with the approved indication.

Study EFC15951 has an internal comparator (i.e. the Isa-IV arm), and therefore, comparison to the registrational study is not essential for interpreting the results regarding non-inferiority to Isa-IV. Furthermore, patients in both studies had to have been previously treated with lenalidomide *and* a PI, which is more important than the actual number of prior lines.

The study population of study EFC15951 is, therefore, considered appropriate.

Randomisation and blinding

All eligible participants were randomly assigned to a treatment group (SC or IV arm) in a 1:1 ratio using an interactive response technology (IRT). Participant were stratified according to MM isotype (IgG versus non-IgG), body weight (≤65 kg, >65 - ≤85 kg, and >85 kg) and number of prior lines (1-2 versus ≥3). The randomisation strategy is agreed; stratification factors are considered clinically relevant.

Administration of isatuximab SC or IV was open-label, which is acceptable, since the routes of administration (SC vs. IV) are very different. The IRC was blinded for study treatment group, which considered appropriate.

Study assessments

. Response criteria for each category are in agreement with the IMWG criteria, and measurements were performed at a sufficiently frequent rate to appropriately assess response to treatment.

Objectives, endpoints and estimands

Primary Objective and its estimands

There were two co-primary objectives:

1) To demonstrate non-inferiority of efficacy between isatuximab SC and isatuximab IV in combination with Pd based on ORR according to the 2016 IMWG criteria (sCR+CR+VGPR+PR) assessed by an IRC.

2) To demonstrate non-inferiority of PK between isatuximab SC and isatuximab IV in combination with Pd through comparing C_{trough} at steady state (corresponding to pre-dose at C6D1).

The non-inferiority of ISA- SC relative to Isa- IV was to be concluded if both endpoints were shown to be non-inferior.

The co-primary endpoint ORR is acceptable in a setting where different methods of administration of the same drug are compared. The efficacy of the IPd triplet in RRMM has already been demonstrated in registrational study EFC14335 (ICARIA). The other co-primary endpoint of C_{trough} at steady state is also acceptable, as it is a good indication of exposure and stability of drug levels in the blood at steady state.

The estimand for the non-inferiority efficacy objective is agreed. As part of the evalaluation of non-inferiority it is also relevant to evaluate whether the intercurrent events are balanced between the Isa-SC and Isa-IV arms. The non-inferiority margin for the efficacy objective was considered to be sufficiently justified.

The estimand to establish PK non-inferiority has been described in terms of a principal stratum estimand, formally this is not correct as it is not possible to identify patients that would meet the defined criteria

regardless of the treatment allocation. The selection of patients based on the specified criteria does not readily translate to a population of interest. It is, however, acknowledged that this approach is standard in PK and the full translation to an estimand is challenging.

Secondary Objectives and estimands

Both co-primary endpoints are supported by secondary endpoints within the same category (i.e. response assessment through VGPR+ rate and PK assessment through CT4W). VGPR+ rate and ORR are very similar endpoints that only differ in the in- or exclusion of patients with a PR. Nonetheless, VGPR+ rate can be considered supportive for efficacy, as it zooms in on patients with a very good response to IPd. Previous studies have shown that CT4W was a good predictor for efficacy. Therefore, this endpoint can also be considered supportive of efficacy. Incidence of IRs is considered a clinically relevant endpoint, as the goal of the SC formation is to reduce IRs. Interpretation of the results of the PESQ, while relevant, are complicated by the fact that the study is open label.

Regarding the definition of the estimands, as noted for the primary PK endpoint, the secondary PK estimand and the safety estimand are defining analysis samples rather than patient populations which makes a full definition of the estimand difficult.

Statistical methods

The planned analyses based on the ITT population and the sample size and planned subgroup analyses were considered acceptable to address the question of interest.

Results

Conduct of the study

Protocol amendments had minor impact, no changes were made to the definition of the co-primary endpoints or secondary endpoints, and therefore, the amendments are not considered to have affected interpretation of the results of the study.

Major protocol deviations were mostly related to inclusion and exclusion criteria, randomization and assessment/procedure and were balanced between treatment groups, with no apparent distribution pattern, and, therefore, were unlikely to have had an impact on the overall outcome of the study.

Participant flow and numbers analysed

The study was ongoing at data cut-off. In both the Isa-SC and the Isa-IV arm, more than 75% of the patients were still in the study, with death being the most important reason for study discontinuation in both arms (19.0% and 18.3% in Isa-SC and Isa-IV, respectively). Full treatment discontinuation rate was approximately 43% for both Isa-IV and Isa-SC. The main reason for discontinuation was PD, which was 30.8% in the Isa-SC and 24.3% in the Isa-IV arm. A high discontinuation rate due to PD is expected in a study with relapsed/refractory MM. Treatment discontinuation due to adverse events was equal in both groups, namely 8.4% for Isa-SC and 9.0% for Isa-IV. There is an apparent imbalance in treatment discontinuation for "PD" (n=81 for Isa-SC and n = 65 for Isa-IV) and "Other" reasons (n = 8 for Isa-SC and n = 18 for Isa-IV). The category of patients having discontinued treatment due to "Other" reasons also mainly consists of patients discontinuing due to expected PD, which did not fully meet the IMWG criteria, and was therefore listed as "Other". Overall, there are 87 cases of progressions according to the investigator in the SC arm (n=81 cases of PD meeting IMWG criteria and n=6 not meeting IMWG criteria, listed as "Other"), and 77 in the IV arm (n=65 cases of PD meeting IMWG criteria and n=12 not meeting IMWG criteria, listed as "Other"). Thus, the imbalance in treatment discontinuation for "PD" relies mainly on the imbalance of reporting progressive disease according to IMWG criteria. Discontinuation of treatment due to PD, without taking IMWG criteria into account, is balanced between the arms.

Baseline data

The baseline demographic and disease characteristics are comparable across the two study arms (≤10% difference) and are representative of the target population.

The baseline characteristics for the PP-PK analysis set were also sufficiently balanced between the study arms. The slight disbalance in ECOG performance status is not expected to affect the PK.

Outcomes and estimations

Co-primary endpoints

The study met its co-primary endpoints, showing that Isatuximab SC is non-inferior to Isatuximab IV in terms of ORR as assessed IRC according to IMWG criteria, and in terms of C_{trough} at steady state.

ORR was 71.1% (95% CI: 0.6522 to 0.7651) in the Isa-SC arm and 70.5% (95% CI: 0.6467 to 0.7591) in the Isa-IV arm; relative risk = 1.008 (95% CI: 0.903 to 1.126). The lower limit of the 95% CI is higher than the pre-defined non-inferiority margin of 0.6312, thereby demonstrating non-inferiority. The number of participants with a best overall response of sCR or CR was similar between treatment arms (47 [17.9%] participants in the Isa-SC arm and 55 [20.5%] participants in the Isa-IV arm). Sensitivity analyses for ORR consisted of ORR by investigator in the ITT, and ORR by IRC/investigator in the per protocol population. Results of the ORR sensitivity analyses were consistent with the co-primary ORR analysis results.

The mean±SD $C_{trough,SS}$ (Cycle 6 Day 1 pre-dose) was higher for Isa-SC (499±259 µg/mL, N=121) than for Isa-IV (340±169 µg/mL, N=121), and the corresponding geometric mean ratio for C_{trough} was 1.532 (90% CI: 1.316-1.784). Non-inferiority of Isa-SC over Isa-IV was confirmed, as the lower limit of the 90% CI was greater than the non-inferiority margin of 0.80.

Key secondary endpoints

Isa-SC is non-inferior to Isa-IV in terms of VGPR+ rate, with a VGPR+ rate of 46.4% in the Isa-SC arm and of 45.9% in the Isa-IV arm (relative risk = 1.011 [95% CI; 0.841 to 1.215]). The lower limit of the 95% CI is higher than the pre-defined non-inferiority margin of 0.6312.

The mean±SD of the C_{trough} of isatuximab at 4 weeks was 421±215 µg/mL in the Isa-SC arm compared to 302±117 µg/mL in the Isa-IV arm. The ratio of geometric means (90% CI) of Isa-SC/Isa-IV was 1.302 (1.158 to 1.465). Non-inferiority of Isa-SC over Isa-IV was confirmed, as the lower limit of the 90% CI was greater than the non-inferiority margin of 0.80.

As expected, a statistically significantly lower incidence of systemic IRs induced by isatuximab were observed in the Isa-SC arm (4 [1.5%]) compared to the Isa-IV arm (66 [25.0%]), with a relative risk (95% CI) of Isa-SC versus Isa-IV of 0.061 (0.022 to 0.164), p<0.0001. 99.9% of the administrations with OBDS were completed without injection interruption, compared to 98.6% with IV administration. The median duration of first infusion/injection in the Isa-SC arm was 13 minutes (range 5 to 37) compared to 208.5 minutes (range 30 to 1112) in the Isa-IV arm. These data clearly demonstrate the lower patient and HCP burden associated with SC administration (also refer to safety discussion).

Due to the open-label nature of the study and patient awareness of the 'old' and the 'new' method of administration, the results on patient satisfaction with the injection method are difficult to interpret. However, the differences between the groups are large, especially for the "very satisfied" category, and it is plausible that SC administration is less burdensome to patients than IV administration.

From a statistical perspective, the method of considering those who did not respond to the questionnaire at a specific timepoint and those who discontinued treatment as "not satisfied" makes strong assumptions

and may have resulted in a different treatment effect being estimated than was initially intended. Given the consistent response over time, and particularly toward the start of the study when most participants responded to the questionnaire, this concern is alleviated.

Other secondary endpoints

The median duration of response was not reached in either treatment arm. The time to first response based on disease assessment by the IRC was similar in the Isa-SC arm (2.04 months) compared with the Isa-IV arm (1.91 months). The time to best response based on disease assessment by the IRC was similar in the Isa-SC arm (4.60 months) compared to the Isa-IV arm (3.94 months). Based on updated interim data, 122 (46.4%) and 115 (42.9%) participants had PFS events in the Isa-SC+Pd and Isa-IV+Pd arms, respectively. The estimated median (95% CI) PFS time was 20.34 months (16.986 to 25.561) and 26.91 months (15.934 to NC), respectively. The stratified HR was 1.108 (95% CI: 0.856 to 1.434). At the time of the cut-off date, a total of 153 (57.1%) and 141 (53.6%) participants in the Isa-IV + Pd and Isa-SC+Pd groups, respectively, did not have a PFS event and were censored. The main reason for censoring was administrative censoring. The rates of censoring in other censoring categories were balanced between the arms, which provides further reassurance of the similarity between the two modes of administration.

Based on updated OS data, the incidence of participants who had a death event was 77 (29.3%) participants in the Isa-SC+Pd arm and 73 (27.2%) participants in the Isa-IV+Pd arm, with a stratified HR of 1.029 (95% CI: 0.746 to 1.420). At the time of the cut-off date, a total of 195 (72.8%) and 186 (70.7%) participants in the Isa-IV+Pd and Isa-SC+Pd groups, respectively, were alive and censored for the OS analysis. The main reason for censoring was administrative censoring (78.5% and 74.2% in the Isa-IV+Pd and Isa-SC+Pd groups, respectively). There were 13 (6.7%) participants in the Isa-IV+Pd group and 4 (2.2%) participants in the Isa-SC+Pd group classified as lost to follow-up. While the percentage of patients lost to follow up in the Isa-IV+Pd group is slightly higher, this is not considered to be a concern regarding the overall conclusions.

Based on the data provided, including the maturity of the data, the reasons for censoring, and the repeated crossing the Kaplan-Meier curves, it is reasonable to conclude that the estimated HRs for PFS and OS are above 1 due to randomness rather than any true differences between the methods of administration.

Patient satisfaction was assessed using the Patient Experience and Satisfaction Questionnaire (PESQ). In the ITT population, the incidence of patients who responded as satisfied or as very satisfied with the injection method used to administer isatuximab (item-8 of the PESQ), was 70 % in the Isa-SC + Pd arm and 53.4% in the Isa-IV + Pd arm with an adjusted relative risk of 1.304 (95% CI: 1.136 to 1.496). Due to the open-label design of the study, a bias cannot be ruled out.

Subgroup analyses

Subgroup analyses for the majority of the prespecified subgroups showed consistent results with the primary ORR analysis in the overall ITT population, with the exception of age ≥75 years old and extreme body weight (>100 kg).

In participants of 75 years of age and older, the ORR was substantially lower in the Isa-SC arm compared to the Isa-IV arm (ORR [95% CI]: 57.4% [0.4321 to 0.7077] vs 80.5% [0.6513 to 0.9118]; relative risk [95% CI] 0.713 [0.532 to 0.941]). VGPR+ was also analysed in the 75 years of age and older subgroup. VGPR+ was more or less the same in Isa-IV (16/41 [39.0%] as in Isa-IV 19/54 [35.2%]). This would indicate that the observed ORR difference within this subgroup is largely explained by a higher PR rate in the Isa-IV arm (which, by deduction, is 41% in Isa-IV and 22.2% in Isa-SC). Patients in the Isa-SC arm were predisposed to a worse response. More participants (+ 10 percentage points) had plasmacytomas at

study entry compared to the Isa-IV arm (17/54 [31.5%] versus 9/41 [22.0%]), and more participants (+ 17 percentage points) in the Isa-SC arm had disease that was refractory to lenalidomide at last regimen compared with the Isa-IV arm (37/54 [68.5%] versus 21/41 [51.2%]). Given the observed imbalance in these factors, an adjusted risk ratio was requested for which the factors 'plasmacytoma at study entry' and 'refractory to lenalidomide at last regime' were adjustment factors in the analysis. This adjusted RR was 0.789 (95% CI: 0.616 to 1.013). As the 95% CI of the adjusted analysis covers 1, this provides sufficient reassurance that the imbalance in disease characteristics was the driving factor behind the lower ORR in the Isa-SC arm. In combination with the fact that age had no effect on the exposure of Isa-SC in the PopPK analysis, it is expected that Isa-SC is equally effective in this subgroup of patients.

Weight was also an important factor for subgroup analysis, as Isa-SC is given in a flat dose, whereas Isa-IV was calculated as a weight-based dose. The ORR by body weight category (≤50 kg, >50 to ≤100 kg, and >100 kg) showed comparable ORR in the ≤50 kg subgroup (9/16 [56.3%] in the Isa-SC arm versus 9/15 [60.0%] in the Isa-IV arm) and in the >50 to ≤100 kg subgroup (163/225 [72.4%] in the Isa-SC arm versus 161/231 [69.7%] in the Isa-IV arm). However, in the heaviest body weight subgroup of >100 kg, ORR was substantially lower in the Isa-SC arm compared with the Isa-IV arm (68.2% versus 86.4%). However, it should be noted that the ORR seems exceptionally high for the Isa-IV arm in the >100 kg group, rather than being too low for the isa-SC arm. There were also clear differences in baseline and disease characteristics between the Isa-SC and the Isa-IV arm in this weight category, possibly pointing to a worse baseline prognosis in the isa-SC arm. It is thus not possible to reliably compare clinical efficacy between Isa-SC and Isa-IV in this subgroup.

A post-hoc subgroup analysis of C_{trough} at 4 weeks (corresponding to pre-dose at Cycle 2 Day 1) by body weight (≤65 kg, >65 to ≤85 kg and >85 kg) showed that exposure was higher with Isa-SC than with Isa-IV in these subgroups, although the difference became smaller as body weight increased. Furthermore, bodyweight is a significant covariate influencing Isa-SC PK in the popPK model. However, the predicted exposure in the highest body weight group is in line with the exposure of Isa-IV. The current dataset does not indicate that heavier individuals are underdosed. Nonetheless, the number of patients with a high weight is limited, as can be expected in a population of older RRMM patients. Therefore, a warning in the SmPC is , to state that data in the highest weight category are limited, and thereby it cannot be unequivocally concluded that efficacy is the same in these individuals when a flat dose is administered.

5.3.6.1.2. Supportive studies

One controlled and two uncontrolled supportive studies were submitted, in addition to the dose-finding study and the pivotal trial, with the aim of covering all populations for which isatuximab is currently approved (RRMM, NDMM Ti, NDMM Te) and covering each combination of drugs (IPd, IKd and IVRd).

Study IIT17041 (GMMG-HD8) included an internal comparator, efficacy of Isa-SC and Isa-IV could be compared, even though the data is quite preliminary. The primary endpoint VGPR or better rate was similar between both groups (73.9% in Isa-SC+VRd and 78.1% in Isa-IV+VRd), supporting that efficacy of isatuximab is not affected by the method of administration. As the pivotal study has sufficiently demonstrated non-inferiority of Isa-SC and Isa-IV, a data update for study GMMG-HD8 is not considered necessary to assess the B/R balance.

Study ACT17453 (IZALCO) was the only study that compared manual injection with injection through the OBDS. The cross-over design of the study complicated interpretability of the results on the efficacy of manual injection versus administration via the OBDS. PK results comparing both methods were part of the other secondary endpoints. Based on these data, the difference between manual and OBDS administration is limited. There is no indication of a PK effect when comparing both methods of administration, although the test group was limited in size).

5.3.6.2. Conclusions on the clinical efficacy

In the pivotal trial EFC15951 (IRAKLIA), non-inferiority of the SC formulation to the IV formulation has been demonstrated as the lower point of the confidence intervals of the co-primary efficacy (ORR) and PK ($C_{trough, SS}$) endpoints were larger than the pre-defined non-inferiority margins.

One pivotal study is deemed sufficient to assess the non-inferiority of Isa-SC over Isa-IV and is thereby sufficient to bridge the SC formulation to all indications of the IV formulation

Based on the demonstrated non-inferiority of Isa-SC+Pd in the pivotal trial, supported by data from controlled study GMMG-HD8, it can be agreed that the SC formulation should be granted the same indications as authorised for the IV formulation. An uncertainty remains regarding the exposure in patient with a high body weight. To this end, a warning in the SmPC is warranted to inform prescribers that data in the highest weight category are limited, and thereby it cannot be unequivocally concluded that efficacy is the same in these individuals when a flat dose is administered.

The MAH aims to register the SC formulation with the option of administering the drug through the OBDS or via manual injection. The clinical data provided for the manual injection method are scarce, not many patients were dosed manually. Nonetheless, since there is no indication of a PK effect when comparing both methods of administration, and since it is not likely that efficacy will differ between manual injection and OBDS administration, this uncertainty can be accepted.

5.4. Clinical safety

5.4.1. Safety data collection

A pooled safety analysis is provided including the 5 studies as discussed in the efficacy section of this report: Phase 3 studies (EFC15951 and IIT17041), Phase 2 studies (ACT17453 and IIT17756), and Phase 1 study (TCD15484).

A pooled analysis was conducted and describes the safety profile of SC isatuximab by each combination regimen and the overall safety profile of all SC isatuximab treated relapsed and/or refractory multiple myeloma (RRMM) or NDMM participants from five studies.

5.4.2. Pooling strategy

Data are presented within the same table by each combination regimen, and for the all Isa-SC treated patients as described below:

- Isa-SC+Pd: Study EFC15951 (N: 263) and Study TCD15484 (N:44) pooled
- Isa-SC+Kd: Study ACT17453 (N:74)
- Isa-SC+VRd: Study IIT17756 (N:74) and study IIT17041 (N:67) pooled
- All Isa-SC: pooled from all five studies

In addition, for the Phase 2 clinical studies without an IV control arm (i.e., ACT17453 and IIT17756), the cross-study comparison with the corresponding Isa-IV studies were performed for the analysis of the selected adverse events (AEs) between Isa-SC and the Isa-IV combination regimen. To account for differences in duration of follow-up between Isa-IV and Isa-SC studies, only safety data collected from first dose of study treatment up to a fixed time window for each patient were summarized and compared. The comparison is as follows.

- Isatuximab+Kd in RRMM: Isa-SC+Kd of Study ACT17453 (IZALCO) versus Isa-IV+Kd of Study EFC15246 (IKEMA) study during the first 6 months of treatment.
- Isatuximab+VRd in patients with transplant ineligible NDMM: Isa-SC+VRd of Study IIT17756 (IsaSoCut) versus Isa-IV+VRd of Study EFC12522 (IMROZ) during the first 8 months of treatment.

5.4.3. Patient exposure

5.4.3.1. Disposition

Table 23: Disposition of participants - All Isa-SC - Safety population - SCS

n (%)	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Enrolled/Randomized and treated Participants	307 (100)	74 (100)	141 (100)	522 (100)
Still on treatment	149 (48.5)	53 (71.6)	130 (92.2)	332 (63.6)
Participants with permanent full study intervention discontinuation	158 (51.5)	21 (28.4)	11 (7.8)	190 (36.4)
Main reasons for full study intervention discontinuation				
Adverse event	24 (7.8)	7 (9.5)	7 (5.0)	38 (7.3)
Progressive disease	105 (34.2)	11 (14.9)	2 (1.4)	118 (22.6)
Poor compliance to protocol	0	0	0	0
Withdrawal by subject	6 (2.0)	2 (2.7)	0	8 (1.5)
Other reason	23 (7.5)	1 (1.4)	2 (1.4)	26 (5.0)
Premature treatment discontinuation of any (at least 1) study treatment	33 (10.7)	6 (8.1)	21 (14.9)	60 (11.5)
Main reasons for premature treatment discontinuation of any (at least 1) study treatment				
Adverse event	32 (10.4)	6 (8.1)	16 (11.3)	54 (10.3)
Other reason	1 (0.3)	0	5 (3.5)	6 (1.1)
Premature treatment discontinuation of isatuximab	0	0	0	0
Main reasons for premature treatment discontinuation of isatuximab				
Adverse event	0	0	0	0
Other reason	0	0	0	0
Premature treatment discontinuation of at least one other study treatment(excluding Isatuximab)	33 (10.7)	6 (8.1)	21 (14.9)	60 (11.5)
Main reasons for premature treatment discontinuation of at least one other study treatment (excluding isatuximab)				
Adverse event	32 (10.4)	6 (8.1)	16 (11.3)	54 (10.3)
Other reason	1 (0.3)	0	5 (3.5)	6 (1.1)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

n (%)	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)

Premature treatment discontinuation is not collected for study IIT17041.

5.4.3.2. Exposure

Table 24: Extent of overall exposure - All Isa-SC - Safety population - SCS

	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Total number of cycles started	3262	642	1122	5026
Total Number of cycles started by participant				
Number	307	74	141	522
Mean (SD)	10.6 (7.2)	8.7 (3.5)	8.0 (5.1)	9.6 (6.4)
Median	9.0	9.0	9.0	9.0
Q1 ; Q3	6.0 ; 14.0	7.0 ; 11.0	3.0 ; 13.0	5.0 ; 13.0
Min ; Max	1 ; 48	1 ; 16	1 ; 16	1 ; 48
Total Number of cycles started by participant [n(%)]				
At least 1 cycle	307 (100)	74 (100)	141 (100)	522 (100)
At least 2 cycles	294 (95.8)	70 (94.6)	139 (98.6)	503 (96.4)
At least 3 cycles	286 (93.2)	68 (91.9)	135 (95.7)	489 (93.7)
At least 4 cycles	278 (90.6)	67 (90.5)	72 (51.1)	417 (79.9)
At least 5 cycles	264 (86.0)	65 (87.8)	72 (51.1)	401 (76.8)
At least 6 cycles	244 (79.5)	63 (85.1)	72 (51.1)	379 (72.6)
At least 7 cycles	211 (68.7)	59 (79.7)	72 (51.1)	342 (65.5)
At least 8 cycles	179 (58.3)	48 (64.9)	72 (51.1)	299 (57.3)
At least 9 cycles	154 (50.2)	38 (51.4)	71 (50.4)	263 (50.4)
At least 10 cycles	136 (44.3)	32 (43.2)	70 (49.6)	238 (45.6)
At least 11 cycles	118 (38.4)	23 (31.1)	64 (45.4)	205 (39.3)
At least 12 cycles	103 (33.6)	16 (21.6)	56 (39.7)	175 (33.5)
At least 13 cycles	94 (30.6)	6 (8.1)	42 (29.8)	142 (27.2)
At least 14 cycles	81 (26.4)	5 (6.8)	30 (21.3)	116 (22.2)
At least 15 cycles	74 (24.1)	5 (6.8)	12 (8.5)	91 (17.4)
At least 16 cycles	60 (19.5)	3 (4.1)	2 (1.4)	65 (12.5)
At least 17 cycles	52 (16.9)	0	0	52 (10.0)
At least 18 cycles	45 (14.7)	0	0	45 (8.6)
At least 19 cycles	42 (13.7)	0	0	42 (8.0)
At least 20 cycles	39 (12.7)	0	0	39 (7.5)
At least 21 cycles	28 (9.1)	0	0	28 (5.4)
At least 22 cycles	25 (8.1)	0	0	25 (4.8)
At least 23 cycles	24 (7.8)	0	0	24 (4.6)
At least 24 cycles	15 (4.9)	0	0	15 (2.9)
At least 25 cycles	15 (4.9)	0	0	15 (2.9)
Duration of exposure (months)				
Number	307	74	141	522
Mean (SD)	10.26 (6.99)	7.93 (3.35)	8.20 (4.14)	9.37 (6.00)
Median	8.28	7.85	9.20	8.28
Q1 ; Q3	5.75 ; 13.60	6.11 ; 10.61	4.17 ; 12.06	5.03 ; 12.16
Min ; Max	0.3 ; 45.8	0.2 ; 15.1	0.7 ; 15.0	0.2 ; 45.8
Duration of exposure (weeks)				
Number	307	74	141	522

	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Mean (SD)	44.62 (30.40)	34.49 (14.56)	35.65 (18.01)	40.76 (26.10)
Median	36.00	34.14	40.00	36.00
Q1 ; Q3	25.00 ; 59.14	26.57 ; 46.14	18.14 ; 52.43	21.86 ; 52.86
Min ; Max	1.1 ; 199.1	1.0 ; 65.6	3.0 ; 65.3	1.0 ; 199.1
Duration of treatment exposure (months)				
Number	307	74	141	522
At least 3 months	280 (91.2)	67 (90.5)	135 (95.7)	482 (92.3)
At least 6 months	219 (71.3)	57 (77.0)	75 (53.2)	351 (67.2)
At least 12 months	92 (30.0)	5 (6.8)	37 (26.2)	134 (25.7)
At least 18 months	42 (13.7)	0	0	42 (8.0)
More than 24 months	13 (4.2)	0	0	13 (2.5)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

Duration was calculated at the study lever per individual study definitions.

5.4.3.3. Cycle delays

Table 25: Cycle delays - All Isa-SC - Safety population - SCS

	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Number of treated participants	307	74	141	522
Participants with at least 1 cycle delayed [n (%)]	195 (63.5)	46 (62.2)	59 (41.8)	300 (57.5)
Between 4 and 7 days	62 (20.2)	20 (27.0)	25 (17.7)	107 (20.5)
More than 7 days	133 (43.3)	26 (35.1)	34 (24.1)	193 (37.0)
More than 14 days	61 (19.9)	9 (12.2)	16 (11.3)	86 (16.5)
Number of cycles started	3262	642	1122	5026
Cycles delayed [n (%)]	429 (13.2)	83 (12.9)	87 (7.8)	599 (11.9)
Between 4 and 7 days	220 (6.7)	50 (7.8)	47 (4.2)	317 (6.3)
More than 7 days	209 (6.4)	33 (5.1)	40 (3.6)	282 (5.6)
More than 14 days	70 (2.1)	9 (1.4)	18 (1.6)	97 (1.9)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

5.4.3.4. Isatuximab exposure by administration method

There were 522 patients receiving Isa-SC patients, among them 490 patients received Isa-SC with OBDS and 32 patients with infusion pump and manual administration.

The isatuximab exposure at 1 400 mg summary by administration method was provided in Table 26.

Table 26 Extent of isatuximab exposure at 1 400mg dose by study and administration method - Safety population.

	TCD15484		EFC15951	ACT17453		IIT17041	IIT17756	All Isa-SC
	Infusion pump (N=10)	OBDS (N=22)	OBDS (N=263)	Manual (N=74)	OBDS (N=64)	OBDS (N=67)	OBDS (N=74)	OBDS (N=490)
Total number of doses	418	697	5145	597	700	679	1853	9074
Total number of cycles started	209	356	2536	272	370	195	927	4384
Total number of cycles started by participant								
Number	10	22	263	73	64	67	74	490
Mean (SD)	20.9 (14.4)	16.2 (11.6)	9.6 (5.7)	3.7 (2.8)	5.8 (2.4)	2.9 (0.4)	12.5 (2.5)	8.9 (6.0)
Median	18.0	10.5	8.0	3.0	6.0	3.0	13.0	8.0
Q1 ; Q3	12.0 ; 32.0	7.0 ; 29.0	6.0 ; 13.0	3.0 ; 3.0	4.0 ; 8.0	3.0 ; 3.0	12.0 ; 14.0	4.0 ; 13.0
Min ; Max	1 ; 48	2 ; 34	1 ; 29	1 ; 16	1 ; 10	1 ; 3	2 ; 16	1 ; 34
Duration of isatuximab exposure (weeks)								
Number	10	22	263	74	64	67	74	490
Mean (SD)	86.99 (61.40)	68.38 (49.64)	39.24 (23.64)	14.93 (11.27)	22.62 (9.93)	18.06 (3.35)	50.94 (9.96)	37.25 (24.23)
Median	74.79	45.07	34.00	12.29	22.00	18.00	52.14	32.00
Q1 ; Q3	46.29 ; 136.29	32.00 ; 130.00	23.43 ; 53.00	12.00 ; 13.86	14.00 ; 32.50	18.00 ; 19.00	46.29 ; 56.43	18.86 ; 51.14
Min ; Max	3.0 ; 198.9	6.0 ; 138.3	1.0 ; 118.9	1.0 ; 65.6	2.0 ; 39.0	3.0 ; 27.7	6.0 ; 65.3	1.0 ; 138.3
Duration of isatuximab exposure (months)								
Number	10	22	263	74	64	67	74	490
Mean (SD)	20.00 (14.12)	15.73 (11.42)	9.03 (5.44)	3.43 (2.59)	5.20 (2.28)	4.15 (0.77)	11.71 (2.29)	8.57 (5.57)
Median	17.20	10.37	7.82	2.83	5.06	4.14	11.99	7.36
Q1 ; Q3	10.64 ; 31.34	7.36 ; 29.90	5.39 ; 12.19	2.76 ; 3.19	3.22 ; 7.47	4.14 ; 4.37	10.64 ; 12.98	4.34 ; 11.76
Min ; Max	0.7 ; 45.7	1.4 ; 31.8	0.2 ; 27.3	0.2 ; 15.1	0.5 ; 9.0	0.7 ; 6.4	1.4 ; 15.0	0.2 ; 31.8

Note: Duration was calculated at the study level by the actual administration method.
The number of cycles by each administration method will be counted based on the actual administration method. There was a special case in ACT17453 study, in which participants used 1 dose with wrong administration method in the middle of a cycle and switched back in the next dose. For these participants, the planned administration method was considered for that cycle.
The percentage is calculated among participants who were exposed to 1400mg isatuximab and had at least one dose using the corresponding administration method.

5.4.4. Adverse events

Study EFC15951

An overview of the treatment emergent adverse events (TEAEs) in study EFC15951 is presented in Table 27.

Table 27: Overview of treatment-emergent adverse events (TEAEs) in Study EFC15951 - Safety population

n (%)	Isa-IV + Pd (N=264)	Isa-SC + Pd (N=263)
Participants with any TEAE	255 (96.6)	255 (97.0)
Participants with any grade ≥3 TEAE	201 (76.1)	215 (81.7)
Participants with any grade 3 or 4 TEAE	198 (75.0)	213 (81.0)
Participants with any grade 5 TEAE [a]	19 (7.2)	18 (6.8)
Participants with any treatment emergent SAE	127 (48.1)	139 (52.9)
Participants with any TEAE leading to permanent full discontinuation	23 (8.7)	22 (8.4)
Participants with any TEAE leading to permanent partial discontinuation of isatuximab	0	0
Participants with any TEAE leading to permanent partial discontinuation of pomalidomide	14 (5.3)	9 (3.4)
Participants with any TEAE leading to permanent partial discontinuation of dexamethasone	7 (2.7)	13 (4.9)
Participants with any treatment emergent AESI	7 (2.7)	13 (4.9)
Participants with any grade ≥3 treatment emergent AESI	5 (1.9)	4 (1.5)
Participants with any treatment-related TEAE	226 (85.6)	228 (86.7)
Participants with any grade ≥3 treatment-related TEAE	170 (64.4)	173 (65.8)
Participants with any treatment-related SAE	78 (29.5)	71 (27.0)
Participants with any NIMP related TEAE (any grade)	12 (4.5)	2 (0.8)
Participants with any injector device related TEAE (any grade)	NA	9 (3.4)
Participants with any grade ≥3 injector device related TEAE	NA	1 (0.4)

TEAE: treatment-emergent adverse events, SAE: serious adverse events, AESI: adverse event of special interest, NIMP: non investigational medicinal product, NA: not applicable

[a] TEAE with fatal outcome during the treatment period

n (%) = number and percentage of participants with at least one TEAE

Note: Permanent full discontinuation is the discontinuation of all study drugs. When all study drugs are not discontinued at the same time, the reason for permanent full discontinuation is the reason for discontinuation of the last study drug stopped.

Permanent partial discontinuation of isatuximab (respectively pomalidomide, dexamethasone) is the discontinuation of isatuximab (respectively pomalidomide, dexamethasone) and at least one other study drug is continued.

Adverse events were coded using NCI CTCAE version 5.0 for toxicity grades.

Pregnancy and overdose, if any, for which toxicity is not collected in CRF, are not taken into account in the Grade ≥3 TEAE

Study IIT17041

An overview of TEAEs in IIT17041 is provided in **Table 28**.

Table 28: Overview of treatment-emergent adverse events in Study IIT17041 - Safety population

	Isa-IV+VRd (N=71)	Isa-SC+VRd (N=67)
Participants with any TEAE	71 (100)	66 (98.5)
Participants with any grade ≥ 3 TEAE	61 (85.9)	53 (79.1)
Participants with any grade 5 TEAE[a]	1 (1.4)	2 (3.0)
Participants with any treatment-emergent SAE	23 (32.4)	26 (38.8)
Participants with any TEAE leading to permanent discontinuation of isatuximab	4 (5.6)	2 (3.0)
Participants with any TEAE related to investigational device (OBDS)	NA	8 (11.9)
Participants with any TEAE related to medical procedure	47 (66.2)	26 (38.8)
Participants with any TEAE related to isatuximab	54 (76.1)	49 (73.1)
Participants with any treatment-emergent AESI[b]	3 (4.2)	5 (7.5)
Participants with any grade ≥3 treatment-emergent AESI[b]	2 (2.8)	0

SC: Subcutaneous, IV: Intravenous, TEAE: Treatment-emergent adverse event, AESI: Adverse event of special interest, SAE: Serious adverse event, OBDS: On-Body Delivery System

n (%) = number and percentage of participants with at least one TEAE.

[a] TEAE with fatal outcome during the treatment-emergent period

	Isa-IV+VRd (N=71)	Isa-SC+VRd (N=67)

[b] AESIs include IR of grade >=3, injection site reaction: Grade 1 lasting >24 hours or grade >=2, pregnancy, overdose and second primary malignancy

Note: If the assessment of the relationship to Isatuximab/OBDS/Medical procedure is missing for an AE, this AE will be assumed as related to IMP.

All Isa-Sc pool

The data for the All Isa-SC (N=522) are presented in Table 29.

Table 29: Overview of Treatment-Emergent Adverse Events - All Isa-SC - Safety population – SCS

N(%)	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Participants with any TEAE (any grade)	299 (97.4)	69 (93.2)	140 (99.3)	508 (97.3)
Participants with any treatment-related TEAE (any grade)	269 (87.6)	57 (77.0)	123 (87.2)	449 (86.0)
Participants with any TEAE of grade ≥ 3	257 (83.7)	40 (54.1)	119 (84.4)	416 (79.7)
Participants with any treatment-related TEAE of grade ≥ 3	210 (68.4)	26 (35.1)	99 (70.2)	335 (64.2)
Participants with any TEAE of grade 3-4	255 (83.1)	39 (52.7)	119 (84.4)	413 (79.1)
Participants with any grade 5 TEAE with fatal outcome during the treatment period	20 (6.5)	4 (5.4)	4 (2.8)	28 (5.4)
Participants with any AESI	23 (7.5)	2 (2.7)	20 (14.2)	45 (8.6)
Participants with any AESI of grade ≥ 3	7 (2.3)	1 (1.4)	2 (1.4)	10 (1.9)
Participants with any IR (excluding symptoms)	6 (2.0)	2 (2.7)	8 (5.7)	16 (3.1)
Participants with any IR of grade ≥ 3 (excluding symptoms)	1 (0.3)	0	0	1 (0.2)
Participants with any ISR	30 (9.8)	6 (8.1)	26 (18.4)	62 (11.9)
Participants with any ISR of grade ≥ 3	0	0	0	0
Participants with any injector device related TEAE (any grade)	11 (3.6)	1 (1.4)	19 (13.5)	31 (5.9)
Participants with any grade ≥ 3 injector device related TEAE	2 (0.7)	0	5 (3.5)	7 (1.3)
Participants with any serious TEAE	169 (55.0)	30 (40.5)	59 (41.8)	258 (49.4)
Participants with any serious treatment-related TEAE	82 (26.7)	16 (21.6)	26 (18.4)	124 (23.8)
Participants with any TEAE leading to permanent full discontinuation	24 (7.8)	6 (8.1)	3 (2.1)	33 (6.3)
Participants with any TEAE leading to premature discontinuation of isatuximab	0	0	2 (1.4)	2 (0.4)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

Study IIT17041 didn't report the discontinuation of IMPs other than Isatuximab.

Percentages are calculated using the number of participants treated as denominator.

5.4.5. Most frequent TEAE

Study EFC15951

The number TEAEs with an incidence >=5% in any treatment group by PT are presented in Table 30.

Table 30: Number (%) of participants with TEAEs with an incidence >=5% in any treatment group by PT (worst grade by participant) in Study EFC15951- Safety population

	Isa-IV + Pd (N=264)		Isa-SC + Pd (N=263)	
Preferred Term [n(%)]	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Any event	255 (96.6)	201 (76.1)	255 (97.0)	215 (81.7)
Neutropenia	82 (31.1)	82 (31.1)	84 (31.9)	83 (31.6)
Upper respiratory tract infection	63 (23.9)	4 (1.5)	60 (22.8)	4 (1.5)
Diarrhoea	53 (20.1)	2 (0.8)	52 (19.8)	4 (1.5)
Fatigue	37 (14.0)	3 (1.1)	51 (19.4)	10 (3.8)
Pneumonia	53 (20.1)	41 (15.5)	51 (19.4)	39 (14.8)
Neutrophil count decreased	41 (15.5)	41 (15.5)	48 (18.3)	48 (18.3)
Insomnia	39 (14.8)	12 (4.5)	39 (14.8)	7 (2.7)
Constipation	34 (12.9)	0	38 (14.4)	0
Covid-19	40 (15.2)	5 (1.9)	33 (12.5)	7 (2.7)
Back pain	22 (8.3)	2 (0.8)	25 (9.5)	3 (1.1)
Oedema peripheral	31 (11.7)	3 (1.1)	22 (8.4)	0
Asthenia	21 (8.0)	1 (0.4)	20 (7.6)	2 (0.8)
Cough	22 (8.3)	0	20 (7.6)	0
Bronchitis	17 (6.4)	2 (0.8)	19 (7.2)	2 (0.8)
Dizziness	14 (5.3)	0	19 (7.2)	0
Nausea	21 (8.0)	1 (0.4)	19 (7.2)	2 (0.8)
Peripheral sensory neuropathy	18 (6.8)	0	19 (7.2)	0
Pyrexia	18 (6.8)	1 (0.4)	19 (7.2)	3 (1.1)
Thrombocytopenia	16 (6.1)	14 (5.3)	17 (6.5)	16 (6.1)
Anaemia	11 (4.2)	10 (3.8)	16 (6.1)	15 (5.7)
Influenza	9 (3.4)	3 (1.1)	16 (6.1)	1 (0.4)
Muscle spasms	25 (9.5)	0	16 (6.1)	0
Nasopharyngitis	17 (6.4)	0	16 (6.1)	0
Abdominal pain	6 (2.3)	0	15 (5.7)	1 (0.4)
Dyspnoea	16 (6.1)	2 (0.8)	15 (5.7)	2 (0.8)
Platelet count decreased	15 (5.7)	15 (5.7)	15 (5.7)	14 (5.3)
Urinary tract infection	18 (6.8)	4 (1.5)	15 (5.7)	5 (1.9)
Arthralgia	17 (6.4)	3 (1.1)	12 (4.6)	0
Headache	15 (5.7)	0	12 (4.6)	0
Influenza like illness	14 (5.3)	0	12 (4.6)	0
Tremor	17 (6.4)	3 (1.1)	9 (3.4)	0
Pain in extremity	14 (5.3)	0	7 (2.7)	1 (0.4)
Infusion related reaction	66 (25.0)	3 (1.1)	5 (1.9)	1 (0.4)

TEAE: treatment-emergent adverse events, PT: preferred term

MEDDRA 27.0, NCI CTCAE version 5.0

n (%) = number and percentage of participants with at least one TEAE

Note: Table sorted by decreasing frequency of PT for all grades in Isa-SC + Pd arm

Only PT with an incidence ≥5% in at least one treatment group are presented.

Pregnancy and overdose, if any, for which toxicity is not collected in CRF, are not taken into account in the Grade ≥3 TEAE

Study IIT17041

The number (%) of participants with TEAEs with an incidence ≥5% in any treatment group by SOC and PT is presented in Table 31.

Table 31: Number (%) of participants with TEAEs with an incidence ≥5% in any treatment group by Primary SOC and PT (worst grade by participant) in Study IIT17041 - Safety population

	Isa-IV+VRd (N=71)		Isa-SC+VRd (N=67)	
Primary System Organ Class Preferred Term n(%)	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Any event	71 (100)	61 (85.9)	66 (98.5)	53 (79.1)
Infections and infestations	35 (49.3)	13 (18.3)	28 (41.8)	13 (19.4)
Infection	6 (8.5)	0	6 (9.0)	2 (3.0)
Pneumonia	6 (8.5)	5 (7.0)	5 (7.5)	4 (6.0)
Covid-19	3 (4.2)	2 (2.8)	4 (6.0)	2 (3.0)
Upper respiratory tract infection	4 (5.6)	0	3 (4.5)	0
Urinary tract infection	4 (5.6)	1 (1.4)	1 (1.5)	0
Blood and lymphatic system disorders	46 (64.8)	36 (50.7)	45 (67.2)	38 (56.7)
Lymphopenia	25 (35.2)	18 (25.4)	31 (46.3)	23 (34.3)
Neutropenia	30 (42.3)	14 (19.7)	23 (34.3)	20 (29.9)
Thrombocytopenia	15 (21.1)	8 (11.3)	17 (25.4)	13 (19.4)
Anaemia	13 (18.3)	6 (8.5)	15 (22.4)	5 (7.5)
Leukopenia	15 (21.1)	4 (5.6)	13 (19.4)	7 (10.4)
Metabolism and nutrition disorders	8 (11.3)	3 (4.2)	15 (22.4)	6 (9.0)
Hypocalcaemia	2 (2.8)	1 (1.4)	6 (9.0)	3 (4.5)
Hypokalaemia	3 (4.2)	2 (2.8)	5 (7.5)	1 (1.5)
Nervous system disorders	29 (40.8)	7 (9.9)	28 (41.8)	6 (9.0)
Polyneuropathy	11 (15.5)	1 (1.4)	14 (20.9)	2 (3.0)
Peripheral sensory neuropathy	8 (11.3)	3 (4.2)	2 (3.0)	0
Gastrointestinal disorders	21 (29.6)	5 (7.0)	17 (25.4)	3 (4.5)
Diarrhoea	9 (12.7)	3 (4.2)	9 (13.4)	2 (3.0)
Constipation	6 (8.5)	0	7 (10.4)	0
Skin and subcutaneous tissue disorders	6 (8.5)	1 (1.4)	9 (13.4)	1 (1.5)
Rash	6 (8.5)	1 (1.4)	7 (10.4)	0
General disorders and administration site conditions	28 (39.4)	6 (8.5)	24 (35.8)	6 (9.0)
Oedema peripheral	3 (4.2)	0	8 (11.9)	0
Fatigue	5 (7.0)	1 (1.4)	7 (10.4)	2 (3.0)
Pyrexia	7 (9.9)	1 (1.4)	3 (4.5)	1 (1.5)
Pain	5 (7.0)	2 (2.8)	0	0
Investigations	33 (46.5)	28 (39.4)	27 (40.3)	17 (25.4)
Lymphocyte count decreased	18 (25.4)	18 (25.4)	10 (14.9)	9 (13.4)
Neutrophil count decreased	12 (16.9)	8 (11.3)	6 (9.0)	4 (6.0)
White blood cell count decreased	10 (14.1)	5 (7.0)	6 (9.0)	0
C-reactive protein increased	6 (8.5)	1 (1.4)	3 (4.5)	0
Gamma-glutamyltransferase increased	5 (7.0)	1 (1.4)	3 (4.5)	0
Platelet count decreased	10 (14.1)	6 (8.5)	2 (3.0)	2 (3.0)
Weight decreased	6 (8.5)	0	2 (3.0)	0

SC: Subcutaneous, IV: Intravenous, TEAE: Treatment-emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 27.0, NCI-CTCAE version 5.0
n (%) = number and percentage of participants with at least one TEAE.

Primary System Organ Class Preferred Term n(%)	Isa-IV+VRd (N=71)		Isa-SC+VRd (N=67)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3

Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in 'All grades' of the Isa-SC+VRd treatment group.

Pregnancy and overdose, if any, for which toxicity is not collected in eCRF, are only counted in the All grades events

Only SOC with at least one PT >= 5% in at least one treatment group are presented.

All Isa-SC pool

The results per SOC and PT for the All Isa-SC pool are presented in Table 32.

Table 32: Number (%) of participants with TEAEs with an incidence >= 10% (all grades) or >= 5% (grade >= 3) by SOC and PT - All Isa-SC - Safety population - SCS

Primary System Organ Class Preferred Term [n(%)]	Isa-SC+Pd (N=307)		Isa-SC+Kd (N=74)		Isa-SC+VRd (N=141)		All Isa-SC (N=522)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any event	299 (97.4)	257 (83.7)	69 (93.2)	40 (54.1)	140 (99.3)	119 (84.4)	508 (97.3)	416 (79.7)
Infections and infestations	227 (73.9)	108 (35.2)	58 (78.4)	14 (18.9)	76 (53.9)	24 (17.0)	361 (69.2)	146 (28.0)
Upper respiratory tract infection	67 (21.8)	4 (1.3)	28 (37.8)	1 (1.4)	4 (2.8)	0	99 (19.0)	5 (1.0)
Pneumonia	52 (16.9)	40 (13.0)	12 (16.2)	7 (9.5)	9 (6.4)	5 (3.5)	73 (14.0)	52 (10.0)
Covid-19	42 (13.7)	9 (2.9)	9 (12.2)	0	11 (7.8)	3 (2.1)	62 (11.9)	12 (2.3)
Blood and lymphatic system disorders	145 (47.2)	138 (45.0)	15 (20.3)	12 (16.2)	113 (80.1)	97 (68.8)	273 (52.3)	247 (47.3)
Neutropenia	117 (38.1)	116 (37.8)	7 (9.5)	6 (8.1)	80 (56.7)	57 (40.4)	204 (39.1)	179 (34.3)
Lymphopenia	0	0	0	0	80 (56.7)	72 (51.1)	80 (15.3)	72 (13.8)
Thrombocytopenia	21 (6.8)	20 (6.5)	7 (9.5)	5 (6.8)	39 (27.7)	32 (22.7)	67 (12.8)	57 (10.9)
Anaemia	28 (9.1)	21 (6.8)	5 (6.8)	3 (4.1)	29 (20.6)	12 (8.5)	62 (11.9)	36 (6.9)
Leukopenia	5 (1.6)	5 (1.6)	0	0	15 (10.6)	9 (6.4)	20 (3.8)	14 (2.7)
Febrile neutropenia	17 (5.5)	17 (5.5)	1 (1.4)	1 (1.4)	0	0	18 (3.4)	18 (3.4)
Psychiatric disorders	87 (28.3)	18 (5.9)	12 (16.2)	3 (4.1)	33 (23.4)	1 (0.7)	132 (25.3)	22 (4.2)
Insomnia	51 (16.6)	13 (4.2)	9 (12.2)	2 (2.7)	22 (15.6)	0	82 (15.7)	15 (2.9)
Nervous system disorders	100 (32.6)	14 (4.6)	15 (20.3)	1 (1.4)	75 (53.2)	13 (9.2)	190 (36.4)	28 (5.4)
Peripheral sensory neuropathy	27 (8.8)	0	3 (4.1)	0	37 (26.2)	2 (1.4)	67 (12.8)	2 (0.4)
Vascular disorders	47 (15.3)	7 (2.3)	19 (25.7)	6 (8.1)	26 (18.4)	9 (6.4)	92 (17.6)	22 (4.2)
Hypertension	13 (4.2)	5 (1.6)	10 (13.5)	3 (4.1)	6 (4.3)	5 (3.5)	29 (5.6)	13 (2.5)
Gastrointestinal disorders	153 (49.8)	12 (3.9)	22 (29.7)	2 (2.7)	74 (52.5)	9 (6.4)	249 (47.7)	23 (4.4)
Diarrhoea	70 (22.8)	4 (1.3)	8 (10.8)	0	39 (27.7)	2 (1.4)	117 (22.4)	6 (1.1)
Constipation	52 (16.9)	0	2 (2.7)	0	39 (27.7)	2 (1.4)	93 (17.8)	2 (0.4)

Primary System Organ Class Preferred Term [n(%)]	Isa-SC+Pd (N=307)		Isa-SC+Kd (N=74)		Isa-SC+VRd (N=141)		All Isa-SC (N=522)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Skin and subcutaneous tissue disorders	60 (19.5)	3 (1.0)	5 (6.8)	1 (1.4)	44 (31.2)	4 (2.8)	109 (20.9)	8 (1.5)
Erythema	2 (0.7)	0	0	0	16 (11.3)	0	18 (3.4)	0
Musculoskeletal and connective tissue disorders	121 (39.4)	15 (4.9)	19 (25.7)	3 (4.1)	46 (32.6)	8 (5.7)	186 (35.6)	26 (5.0)
Back pain	39 (12.7)	4 (1.3)	4 (5.4)	0	15 (10.6)	1 (0.7)	58 (11.1)	5 (1.0)
General disorders and administration site conditions	160 (52.1)	30 (9.8)	27 (36.5)	4 (5.4)	72 (51.1)	12 (8.5)	259 (49.6)	46 (8.8)
Fatigue	65 (21.2)	13 (4.2)	7 (9.5)	0	11 (7.8)	2 (1.4)	83 (15.9)	15 (2.9)
Oedema peripheral	31 (10.1)	0	5 (6.8)	0	22 (15.6)	1 (0.7)	58 (11.1)	1 (0.2)
Asthenia	29 (9.4)	5 (1.6)	0	0	24 (17.0)	2 (1.4)	53 (10.2)	7 (1.3)
Pyrexia	23 (7.5)	3 (1.0)	8 (10.8)	1 (1.4)	11 (7.8)	1 (0.7)	42 (8.0)	5 (1.0)
Injection site reaction	9 (2.9)	0	1 (1.4)	0	23 (16.3)	0	33 (6.3)	0
Investigations	77 (25.1)	57 (18.6)	4 (5.4)	1 (1.4)	42 (29.8)	17 (12.1)	123 (23.6)	75 (14.4)
Neutrophil count decreased	48 (15.6)	48 (15.6)	0	0	6 (4.3)	4 (2.8)	54 (10.3)	52 (10.0)
Lymphocyte count decreased	0	0	0	0	10 (7.1)	9 (6.4)	10 (1.9)	9 (1.7)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

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

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5.4.6. Adverse drug reactions

Since this concerns a line extension for isatuximab, the ADR profile has been described for the already authorised indications for the IV formulation. The MAH provided a pooled analysis of IV and SC study results which showed that isatuximab 1400 mg subcutaneous (N=522) in combination therapies was overall consistent with the known safety profile of isatuximab 10 mg/kg intravenous (N=2 134) in monotherapy or in combination therapies. Differences were observed in systemic administration reactions with a lower incidence reported with isatuximab subcutaneous (3.1%) versus isatuximab intravenous (33.5%). Injection site reactions associated with isatuximab subcutaneous administration were reported in 1.48% of injections (11.9% of patients), all Grade ≤2.

5.4.7. AEs of special interest, serious adverse events and deaths, other significant events

5.4.7.1. Serious ADRs

Study EFC15951

Treatment-emergent SAEs were reported at a similar incidence in the Isa-SC+Pd arm and in the Isa-IV+Pd arm (difference of less than 5%) (139 [52.9%] and 127 [48.1%], respectively).

The most frequently reported treatment-emergent SAEs (≥2% of participants) (all grades, regardless of causal relationship) by primary PT were: pneumonia (38 [14.4%] in the Isa-SC+Pd arm and 36 [13.6%] in the Isa-IV+Pd arm), febrile neutropenia (9 [3.4%] and 5 [1.9%]), COVID-19 (6 [2.3%] and 7 [2.7%]), COVID-19 pneumonia (6 [2.3%] and 6 [2.3%]), acute kidney injury (6 [2.3%] and 2 [0.8%]), platelet count decreased (4 [1.5%] and 9 [3.4%]), and disease progression (4 [1.5%] and 6 [2.3%]).

The most frequently reported treatment-emergent SAEs (≥2% of participants) assessed as related to IMP were: pneumonia (22 [8.4%] and 24 [9.1%] in the Isa-SC+Pd and Isa-IV+Pd arms, respectively), febrile neutropenia (7 [2.7%] and 5 [1.9%]), and platelet count decreased (3 [1.1%] and 9 [3.4%]).

Study IIT17041

Incidence of all grade treatment-emergent SAEs was slightly higher for the Isa-SC+VRd arm (26 [38.8%] participants than for the Isa-IV+VRd arm (23 [32.4%] participants). This difference may be due to the small sample size.

Pneumonia was the most frequently reported PT (≥5%) for all grades: 4 (6.0%) participants in the Isa-SC+VRd arm and 5 (7.0%) participants in the Isa-IV+VRd arm. Pneumonia was also the most frequently reported treatment-emergent SAE (all grades) related to isatuximab (2 [3.0%] participants and 4 [5.6%] participants, respectively).

All Isa-SC pool

The number (%) of participants who experienced serious TEAEs in the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups is presented in Table 33.

Table 33: Number (%) of participants with serious TEAEs with an incidence >= 2% (all grades) by SOC and PT - All Isa-SC - Safety population - SCS

	Isa-SC+Pd (N=307)		Isa-SC+Kd (N=74)		Isa-SC+VRd (N=141)		All Isa-SC (N=522)	
Primary System Organ Class Preferred Term [n(%)]	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any event	169 (55.0)	154 (50.2)	30 (40.5)	26 (35.1)	59 (41.8)	50 (35.5)	258 (49.4)	230 (44.1)
Infections and infestations	109 (35.5)	101 (32.9)	16 (21.6)	14 (18.9)	24 (17.0)	22 (15.6)	149 (28.5)	137 (26.2)
Pneumonia	39 (12.7)	36 (11.7)	7 (9.5)	7 (9.5)	5 (3.5)	4 (2.8)	51 (9.8)	47 (9.0)
Covid-19 pneumonia	9 (2.9)	8 (2.6)	0	0	4 (2.8)	4 (2.8)	13 (2.5)	12 (2.3)
Covid-19	8 (2.6)	8 (2.6)	0	0	3 (2.1)	3 (2.1)	11 (2.1)	11 (2.1)
Septic shock	2 (0.7)	2 (0.7)	2 (2.7)	2 (2.7)	1 (0.7)	1 (0.7)	5 (1.0)	5 (1.0)
Dengue fever	1 (0.3)	0	2 (2.7)	1 (1.4)	0	0	3 (0.6)	1 (0.2)
Blood and lymphatic system disorders	26 (8.5)	26 (8.5)	2 (2.7)	2 (2.7)	1 (0.7)	1 (0.7)	29 (5.6)	29 (5.6)
Febrile neutropenia	13 (4.2)	13 (4.2)	1 (1.4)	1 (1.4)	0	0	14 (2.7)	14 (2.7)
Nervous system disorders	9 (2.9)	6 (2.0)	0	0	8 (5.7)	8 (5.7)	17 (3.3)	14 (2.7)
Syncope	0	0	0	0	3 (2.1)	3 (2.1)	3 (0.6)	3 (0.6)
Respiratory, thoracic and mediastinal disorders	12 (3.9)	9 (2.9)	4 (5.4)	3 (4.1)	1 (0.7)	0	17 (3.3)	12 (2.3)
Pulmonary oedema	0	0	2 (2.7)	1 (1.4)	0	0	2 (0.4)	1 (0.2)

Primary System Organ Class Preferred Term [n(%)]	Isa-SC+Pd (N=307)		Isa-SC+Kd (N=74)		Isa-SC+VRd (N=141)		All Isa-SC (N=522)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Renal and urinary disorders	10 (3.3)	9 (2.9)	3 (4.1)	2 (2.7)	1 (0.7)	1 (0.7)	14 (2.7)	12 (2.3)
Acute kidney injury	8 (2.6)	8 (2.6)	2 (2.7)	2 (2.7)	1 (0.7)	1 (0.7)	11 (2.1)	11 (2.1)
General disorders and administration site conditions	13 (4.2)	11 (3.6)	4 (5.4)	3 (4.1)	6 (4.3)	4 (2.8)	23 (4.4)	18 (3.4)
Pyrexia	5 (1.6)	3 (1.0)	2 (2.7)	1 (1.4)	2 (1.4)	1 (0.7)	9 (1.7)	5 (1.0)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

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

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5.4.7.2. Deaths

In study EFC15951, the incidence of deaths was similar for SC and IV. During the treatment-emergent period (also called study treatment period) and post treatment period, 50 (19.0%) participants died in the Isa-SC+Pd arm, and 46 (17.4%) participants died in the Isa-IV+Pd arm, most frequently due to disease progression in Isa-SC+Pd arm (30 [11.4%] participants) and Isa-IV+Pd (23 [8.7%] participants).

In study IIT17041, there were 2 (3.0%) deaths during the entire study in the Isa-SC+VRd arm and 2 (2.8%) in the Isa-IV+VRd arm. The TEAEs leading to death in the Isa-SC+VRd arm included post-procedural pulmonary embolism and septic shock. The TEAE leading to death in the Isa-IV+VRd arm was pulmonary embolism. One participant (1.4%) in the Isa-IV+VRd arm died in the follow-up period (174 days after study start and 119 days after last IMP). None of these deaths were considered related to isatuximab.

In the All Isa-SC group, deaths that occurred during the treatment period were reported for 29 (5.6%) participants; 17 of the 29 deaths were due to AEs (Table 34).

Table 34: Number (%) of deaths by study period and cause of death - All Isa-SC - Safety population - SCS

n(%)	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Death during the treatment period or post-treatment period[b]	68 (22.1)	10 (13.5)	4 (2.8)	82 (15.7)
Disease progression	42 (13.7)	3 (4.1)	0	45 (8.6)
Adverse Event	12 (3.9)	4 (5.4)	2 (1.4)	18 (3.4)
Other	14 (4.6)	3 (4.1)	2 (1.4)	19 (3.6)
Death during the treatment period[a]	21 (6.8)	4 (5.4)	4 (2.8)	29 (5.6)
Disease progression	6 (2.0)	0	0	6 (1.1)
Adverse Event	12 (3.9)	3 (4.1)	2 (1.4)	17 (3.3)
Other	3 (1.0)	1 (1.4)	2 (1.4)	6 (1.1)
Death during post-treatment period[b]	47 (15.3)	6 (8.1)	0	53 (10.2)
Disease progression	36 (11.7)	3 (4.1)	0	39 (7.5)
Adverse Event	0	1 (1.4)	0	1 (0.2)
Other	11 (3.6)	2 (2.7)	0	13 (2.5)

n(%)	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Death within 60 days from first dose	9 (2.9)	0	2 (1.4)	11 (2.1)
Disease progression	3 (1.0)	0	0	3 (0.6)
Adverse Event	5 (1.6)	0	1 (0.7)	6 (1.1)
Other	1 (0.3)	0	1 (0.7)	2 (0.4)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

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

[a] Includes all deaths occurring from the first dose of study drugs up to the last dose of study treatment + 30 days.

[b] Includes all deaths occurring >30 days after the last dose of study treatment.

In the All Isa-SC group, 27 (5.2%) participants had fatal TEAEs or Grade 5 post-treatment AEs not in the context of disease progression. The most frequently reported fatal TEAEs were pneumonia (6 [1.1%] participants) and death (3 [0.6%] participants) (Table 35).

Table 35: Number (%) of participants with fatal TEAEs or Grade 5 post-treatment AEs not in the context of disease progression by SOC and PT - All Isa-SC - Safety population - SCS

Primary System Organ Class Preferred Term [n(%)]	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Any event	17 (5.5)	6 (8.1)	4 (2.8)	27 (5.2)
Infections and infestations	12 (3.9)	3 (4.1)	1 (0.7)	16 (3.1)
Pneumonia	5 (1.6)	1 (1.4)	0	6 (1.1)
COVID-19	2 (0.7)	0	0	2 (0.4)
Lower respiratory tract infection	1 (0.3)	1 (1.4)	0	2 (0.4)
Sepsis	2 (0.7)	0	0	2 (0.4)
Septic shock	1 (0.3)	0	1 (0.7)	2 (0.4)
Meningitis	0	1 (1.4)	0	1 (0.2)
Meningitis listeria	1 (0.3)	0	0	1 (0.2)
Staphylococcal sepsis	1 (0.3)	0	0	1 (0.2)
Nervous system disorders	1 (0.3)	0	0	1 (0.2)
Haemorrhagic stroke	1 (0.3)	0	0	1 (0.2)
Cardiac disorders	1 (0.3)	0	2 (1.4)	3 (0.6)
Cardio-respiratory arrest	1 (0.3)	0	1 (0.7)	2 (0.4)
Myocardial infarction	0	0	1 (0.7)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	2 (2.7)	0	2 (0.4)
Acute pulmonary oedema	0	1 (1.4)	0	1 (0.2)
Acute respiratory distress syndrome	0	1 (1.4)	0	1 (0.2)
General disorders and administration site conditions	3 (1.0)	1 (1.4)	0	4 (0.8)
Death	2 (0.7)	1 (1.4)	0	3 (0.6)
Sudden death	1 (0.3)	0	0	1 (0.2)
Injury, poisoning and procedural complications	0	0	1 (0.7)	1 (0.2)
Post procedural pulmonary embolism	0	0	1 (0.7)	1 (0.2)

Primary System Organ Class Preferred Term [n(%)]	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

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

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5.4.7.3. TEAEs related to the on-body delivery system

In the All Isa-SC group 30 (6.1%) participants experienced a TEAE related to the OBDS (all grades) of which 7 (1.4%) were Grade ≥3 events. The most frequently reported TEAE was injection site reaction (ISR) (17 [3.5%]) participants; none of the ISRs were Grade ≥3 events (Table 36).

Table 36: Number (%) of participants with TEAEs related to the wearable injector device by primary SOC and PT among participants who ever used the OBDS device - SCS

	Isa-SC+Pd (N=285)		Isa-SC+Kd (N=64)		Isa-SC+VRd (N=141)		All Isa-SC (N=490)	
Primary System Organ Class Preferred Term [n(%)]	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3
Any event	10 (3.5)	2 (0.7)	1 (1.6)	0	19 (13.5)	5 (3.5)	30 (6.1)	7 (1.4)
Blood and lymphatic system disorders	1 (0.4)	1 (0.4)	0	0	4 (2.8)	3 (2.1)	5 (1.0)	4 (0.8)
Neutropenia	1 (0.4)	1 (0.4)	0	0	2 (1.4)	1 (0.7)	3 (0.6)	2 (0.4)
Lymphopenia	0	0	0	0	2 (1.4)	2 (1.4)	2 (0.4)	2 (0.4)
Skin and subcutaneous tissue disorders	2 (0.7)	0	0	0	0	0	2 (0.4)	0
Erythema	1 (0.4)	0	0	0	0	0	1 (0.2)	0
Rash	1 (0.4)	0	0	0	0	0	1 (0.2)	0
General disorders and administration site conditions	6 (2.1)	0	1 (1.6)	0	12 (8.5)	0	19 (3.9)	0
Injection site reaction	5 (1.8)	0	0	0	12 (8.5)	0	17 (3.5)	0
Injection site erythema	0	0	1 (1.6)	0	0	0	1 (0.2)	0
Injection site induration	0	0	1 (1.6)	0	0	0	1 (0.2)	0
Injection site pain	1 (0.4)	0	0	0	0	0	1 (0.2)	0
Injection site pruritus	0	0	1 (1.6)	0	0	0	1 (0.2)	0
Investigations	1 (0.4)	1 (0.4)	0	0	4 (2.8)	2 (1.4)	5 (1.0)	3 (0.6)
Lymphocyte count decreased	0	0	0	0	3 (2.1)	2 (1.4)	3 (0.6)	2 (0.4)
White blood cell count decreased	0	0	0	0	2 (1.4)	0	2 (0.4)	0
Gamma-glutamyltransferase increased	0	0	0	0	1 (0.7)	0	1 (0.2)	0
Platelet count decreased	1 (0.4)	1 (0.4)	0	0	0	0	1 (0.2)	1 (0.2)
Injury, poisoning and procedural complications	0	0	0	0	1 (0.7)	0	1 (0.2)	0

Primary System Organ Class Preferred Term [n(%)]	Isa-SC+Pd (N=285)		Isa-SC+Kd (N=64)		Isa-SC+VRd (N=141)		All Isa-SC (N=490)	
	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3	All grades	Grade ⩾3
Infusion related reaction	0	0	0	0	1 (0.7)	0	1 (0.2)	0

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

The TEAEs of neutropenia, lymphopenia, lymphocyte count decreased, white blood cell count decreased, gamma-glutamyltransferase increased, and platelet count decreased listed in Table 36 were not related to the OBDS and were considered to be reporting errors mainly in Study IIT17041. Systemic events in Study IIT17041 were recorded as related to OBDS in error.

5.4.7.4. At-home administration

In study EFC15951, 6 out of 21 countries participated in home administration where regulations allowed and it was logistically implementable. At the DCO 06 November 2024 (primary analysis of the IRAKLIA study), 12 patients received at home administration corresponding to a number of at home visits of 55. No injection interrupted and no device related-event were reported, except for one episode of grade 1 ISR. No safety event, including no systemic IR, was linked to at home visits. The median (range) duration of at-home Isa-SC injections (13.5 minutes) was similar to the duration in participants who received all Isa-SC injections at the site.

5.4.8. Other significant adverse events

5.4.8.1. Injection site reaction

Study EFC15951

Overall, ISRs of any grade occurred in 11 (4.2%) participants in the Isa-SC+Pd arm (N=263). ISRs in the Isa-IV+Pd arm were not applicable. Most participants with an ISR, had a single episode (8 of 11). For 4 participants, the first ISR was at the first injection, and for 7 participants, the first occurrence was at a subsequent injection. Of 5145 isatuximab injections given, 19 (0.37%) injections resulted in an ISR, of which 18 were Grade 1 and 1 was Grade 2 and most injections (17 [89.5%]), the ISR resolved within the same day, with only 2 (10.5%) lasting until the next day or beyond.

Of 12 participants with at least one isatuximab injection performed at home, only 1 (0.4%) had at an ISR. The ISR occurred at Cycle 6 Day 15 and was a single Grade 1 episode; no other AE was linked to at home visits.

Most ISR symptoms were in the SOC of General disorders and administration site conditions in 11 (4.2%) participants, most frequently injection site erythema (7 [2.7%] participants), injection site pain and injection site swelling (4 [1.5%] participants each).

Study IIT17041

Overall, 6 (9.0%) participants in the Isa-SC+VRd arm experienced ISRs (4 Grade 1 and 2 Grade 2), and 3 (4.2%) participants in the Isa-IV+VRd arm (2 Grade 1 and 1 Grade 3), representing 0.9% (6/679) of

SC injections associated with an ISR and 0.4% (3/725) of IV infusions. The participants experienced each a single episode of ISR that occurred in the majority of the SC participants (83.3%) following the day of injection. One of the ISR in the Isa-IV+VRd arm was registered as ISR by mistake. Actually, this was an IR. The ISR duration was >2 days for 5 (83.3%) participants in the Isa-SC+VRd arm and 2 (66.7%) participants in the Isa-IV+VRd arm. All participants recovered from the ISR.

All Isa-SC pool

The pooled data analysis of ISRs was performed according to the Investigator's reporting of ISRs in eCRFs. (Table 37).

Table 37: Injection site reactions - Number (%) of participants experiencing injection site reactions based on Investigator assessment by SOC and PT - All Isa-SC - Safety population – SCS

	Isa-SC+Pd (N=307)		Isa-SC+Kd (N=74)		Isa-SC+VRd (N=141)		All Isa-SC (N=522)	
Primary System Organ Class Preferred Term [n(%)]	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any event	30 (9.8)	0	6 (8.1)	0	26 (18.4)	0	62 (11.9)	0
Gastrointestinal disorders	0	0	1 (1.4)	0	0	0	1 (0.2)	0
Abdominal distension	0	0	1 (1.4)	0	0	0	1 (0.2)	0
General disorders and administration site conditions	30 (9.8)	0	5 (6.8)	0	25 (17.7)	0	60 (11.5)	0
Injection site reaction	9 (2.9)	0	1 (1.4)	0	22 (15.6)	0	32 (6.1)	0
Injection site erythema	12 (3.9)	0	2 (2.7)	0	2 (1.4)	0	16 (3.1)	0
Injection site bruising	5 (1.6)	0	1 (1.4)	0	0	0	6 (1.1)	0
Injection site induration	2 (0.7)	0	2 (2.7)	0	0	0	4 (0.8)	0
Injection site pain	3 (1.0)	0	0	0	0	0	3 (0.6)	0
Injection site haematoma	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Injection site haemorrhage	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Injection site inflammation	0	0	0	0	1 (0.7)	0	1 (0.2)	0
Injection site plaque	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Injection site pruritus	0	0	1 (1.4)	0	0	0	1 (0.2)	0
Puncture site bruise	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Puncture site reaction	0	0	0	0	1 (0.7)	0	1 (0.2)	0
Injury, poisoning and procedural complications	0	0	1 (1.4)	0	1 (0.7)	0	2 (0.4)	0
Chemical phlebitis	0	0	1 (1.4)	0	0	0	1 (0.2)	0
Infusion related reaction	0	0	0	0	1 (0.7)	0	1 (0.2)	0

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

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

MedDRA 27.0

5.4.8.2. Systemic infusion reactions

Study EFC15951

Overall, systemic IRs of any grade occurred in 4 (1.5%) participants (0.12%) injections in the Isa-SC+Pd arm and 66 (25.0%) participants (1.33%) injections in the Isa-IV+Pd arm. In the Isa-IV+Pd arm, most of the participants had systemic IRs that were Grade 2 (57 of 66 participants with a systemic IR), while in

the Isa-SC+Pd arm, the majority were Grade 1 (3 of 4 participants with an IR). One (0.4%) participant in the Isa-SC+Pd arm had Grade 3 systemic IRs, and 3 (1.1%) participants in the Isa-IV+Pd arm had Grade 3 systemic IRs. There were no Grade 4 or Grade 5 (fatal) systemic IRs. There were no participants in the Isa-SC+Pd arm and 2 (0.8%) participants in the Isa-IV+Pd arm with at least 2 episodes of systemic IRs at the same infusion.

No participants experienced a systemic IR when isatuximab was administered at home (note: Fifty-five injections in 12 patients were performed at home).

Study IIT17041

Overall, 1 (1.5%) participant in the Isa-SC+VRd arm and 5 (7.0%) participants in the Isa-IV+VRd arm experienced systemic IRs with 1 (1.4%) participant in the Isa-IV+VRd arm experiencing a Grade 4 event. The participant in the Isa-SC+VRd arm experienced a Grade 1 IR event. IRs occurred on the same day of isatuximab infusion for the IV participants, but 3 days after isatuximab injection for the SC participant.

All Isa-SC pool

In the All Isa-SC group, systemic IR were reported in 16 (3.1%) participants. The most frequently reported PT was infusion related reaction (14 [2.7%] participants). In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, systemic IR (all grades) occurred in 6 (2.0%) participants, 2 (2.7%) participants, and 8 (5.7%) participants, respectively. There is 1 (0.3%) participant who experienced 1 episode of Grade 3 systemic IR in the Isa-SC+Pd group. Two (0.7%) participants in the Isa-SC+Pd group experienced systemic IR that were severe. For the few participants who experienced IRs in the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups most were rated Grade 1 or Grade 2. Most of the participants had 1 episode.

Symptoms of IR were not collected using a specified CRF for IIT17041 and IIT17756. These studies are excluded from this analysis. In the All Isa-SC group, 8 (2.1%) participants had symptoms of IRs. The most frequently reported symptoms of IRs were pyrexia (3 [0.8%] participants), and dyspnoea and sinus tachycardia (2 [0.5%] participants for each). Symptoms of infusion reactions (all grades) occurred in 6 (2.0%) participants in the Isa-SC+Pd group and 2 (2.7%) participants in the Isa-SC+Kd group.

5.4.8.3. Second primary malignancies

In study EFC15951, second primary malignancies were reported with a similar incidence in the Isa SC+Pd arm (12 [4.6%] participants) and the Isa-IV+Pd arm (7 [2.7%] participants).

In study IIT17041, there were no participants with reported second primary malignancies.

In the All Isa-SC group, SPMs (all grades) that occurred during the treatment and post treatment periods were reported in 23 (4.4%) participants.

In pooled data from the clinical trials of isatuximab intravenous and subcutaneous formulations (N=2656), SPMs were reported in 144 patients (5.4%), with a rate of 3.0 per 100 person-years. SPM were skin cancer in 89 patients (3.4%), solid tumours other than skin cancer in 52 patients (2.0%), and haematological malignancy in 8 patients (0.3%). In studies that collected this information (N=2518), permanent full treatment discontinuation due to SPM occurred in 26 patients (1.0%).

5.4.8.4. Respiratory events

Study EFC15951

In EFC15951, the incidence of TEAEs in the SOC Respiratory, thoracic and mediastinal disorders was very similar in the Isa-SC+Pd and Isa-IV+Pd groups (64 [24.3%] and 65 [24.6%], respectively)

Study IIT17041

In IIT17041, a similar percentage of participants in the Isa-SC+VRd arm (19 [28.4%]) and in the Isa-IV+VRd arm (19 [26.8%]) experienced respiratory infections. Pneumonia and COVID-19 were the most frequently reported respiratory infections. Five (7.5%) participants in the Isa-SC+VRd arm and 6 (8.5%) participants in the Isa-IV+VRd arm reported events of pneumonia. Four (6.0%) participants in the Isa-SC+VRd arm and 3 (4.2%) participants in the Isa-IV+VRd arm reported events of COVID-19.

All Isa-SC pool

Lower respiratory infection TEAEs

In the All Isa-SC group, lower respiratory infection TEAEs (all grades) occurred in 104 (19.9%) participants of which 18 (3.4%) were Grade ≥3 events. The most frequently reported lower respiratory infection TEAEs (≥5% of participants) by PT were cough 39 (7.5%) participants and dyspnoea 33 (6.3%) participants.

In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, lower respiratory TEAEs (all grades) occurred in 71 (23.1%) participants, 15 (20.3%) participants, and 18 (12.8%) participants, respectively. Grade ≥3 events occurred in 12 (3.9%) participants, 4 (5.4%) participants, and 2 (1.4%) participants, respectively.

In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, the most frequently reported lower respiratory infection TEAEs (≥5% of participants in any group) by PT were: cough (24 [7.8%] participants, 5 [6.8%] participants, and 10 [7.1%] participants, respectively) and dyspnoea (20 [6.5%] participants, 6 [8.1%] participants, and 7 [5.0%] participants, respectively).

No participants in any of the treatment groups had lower respiratory infection AEs that occurred in the post-treatment period.

Respiratory infection TEAEs

In the All Isa-SC group, respiratory infection TEAEs (all grades) occurred in 315 (60.3%) participants of which 109 (20.9%) were Grade ≥3 events. The most frequently reported respiratory infection TEAEs (≥10% of participants) were upper respiratory tract infection (99 [19.0%] participants), pneumonia (73 [14.0%] participants), and COVID-19 (62 [11.9%] participants). The highest incidence for Grade ≥3 events was for pneumonia 52 (10.0%) participants.

In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, respiratory infection TEAEs (all grades) occurred in 202 (65.8%) participants, 55 (74.3%) participants, and 58 (41.1%) participants, respectively.

The most frequently reported respiratory infection TEAEs (≥10% of participants in any group) by PT were in the Isa-SC+Pd and Isa-SC+Kd groups: upper respiratory tract infection (67 [21.8%] and 28 [37.8%] participants, respectively); pneumonia (52 [16.9%] and 12 [16.2%] participants, respectively); and COVID-19 (42 [13.7%] and 9 [12.2%] participants, respectively). No TEAEs met the ≥10% threshold in the Isa-SC+VRd group.

The highest incidence for Grade ≥3 events was for pneumonia (40 [13.0%] participants) in the Isa-SC+Pd group.

5.4.8.5. Laboratory neutropenia and neutropenic complications

In study EFC15951, the proportion of participants with a Grade 3 neutropenia was similar between treatment arms (33.5% and 30.3% in the Isa-SC+Pd arm and Isa-IV+Pd arm, respectively). There was a trend for a lower proportion of participants with Grade 4 neutropenia in the Isa-IV+Pd arm compared with the Isa-SC+Pd arm (50.6% in Isa-SC+Pd and 43.2% in Isa IV+Pd).

An analysis of Grade ≥3 laboratory neutropenia by body weight was performed. Overall, the incidence of Grade ≥3 laboratory neutropenia was similar across all body weight subgroups and was similar between both arms for the lowest body weight subgroup of ≤65 kg.

In study IIT17041, the frequency of all-grade neutropenia based on laboratory assessments is similar between both arms, with 43.9% of participants in the Isa-SC+VRd arm and 42.3% of the participants in the Isa-IV+VRd arm, as well as for Grade ≥3 laboratory neutropenia, 10.6% versus 14.1%, respectively.

The frequency of all grade neutropenia reported as an AE is lower in the SC arm (34.3%) than in the IV arm (42.3%), but higher for Grade ≥3 neutropenia in SC (29.9% versus 19.7%, respectively). However, this did not translate into higher incidence of neutropenic complication in the SC arm: there were no neutropenic complications in Isa-SC+VRd arm, while a total of 4 (5.6%) participants in the Isa-IV+VRd arm had neutropenic complications.

In the All Isa-SC group, the number (%) of participants with neutropenia (based on laboratory abnormalities) of Grade 3 and Grade 4 was 145 (28.0%) participants and 170 (32.8%) participants, respectively.

In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, the number (%) of participants with Grade 3 neutropenia (based on laboratory abnormalities) was 104 (34.1%) participants, 10 (13.7%) participants, and 31 (22.1%) participants, respectively. The percentage of participants with Grade 4 neutropenia was 157 (51.5%) participants, 1 (1.4%) participant, and 12 (8.6%) participants, respectively. The high incidence of neutropenia in the Isa-SC+Pd group was most likely due to the combination with pomalidomide, as neutropenia is also a known side effect of pomalidomide. The incidence of laboratory neutropenia in the Isa-SC+VRd studies may be underestimated since neutropenia was first to be reported as an AE.

In the All Isa-SC group, the number (%) of participants with neutropenic complications of Grade 3, Grade 4, and Grade 5 was 27 (5.2%) participants, 13 (2.5%) participants, and 3 (0.6%) participants respectively.

In the Isa-SC+Pd group, Grade 3 neutropenic complications occurred in 25 (8.1%) participants, Grade 4 in 12 (3.9%) participants, and Grade 5 in 3 (1.0%) participants. Three (1.0%) participants had neutropenic complications with fatal outcomes during the treatment period.

In the Isa-SC+Kd and Isa-SC+VRd groups, Grade 3 neutropenic complications occurred in (1 [1.4%] and 1 [0.7%] participants, respectively). No participant in the Isa-SC+Kd and Isa-SC+VRd groups had neutropenic complication with fatal outcome.

5.4.8.6. Infections and severe infections

Study EFC15951

In EFC15951, the incidence of participants with TEAE all grades and Grade ≥3 from the SOC Infections and infestations was similar between the treatment arms. All grades were reported in 197 (74.9%) participants and 192 (72.7%) participants, and Grade ≥3 was reported in 94 (35.7%) participants and 87 (33.0%) participants in Isa-SC+Pd arm and Isa-IV+Pd arm, respectively.

Study IIT17041

In IIT17041, the number (%) of participants with TEAEs in the SOC of Infections and infestations was 28 (41.8%) participants in the Isa-SC+VRd arm and 35 (49.3%) participants in the Isa-IV+VRd arm) with similar incidence of Grade ≥3 AE (19.4% in Isa-SC+VRd arm versus 18.3% in Isa-IV+VRd arm).

All Isa-SC pool

Severe infections

In the pooled analysis, severe infections were defined as any Grade ≥3 event or Grade ≥2 event if involving the lung/lower respiratory tract (pneumonia, upper respiratory tract infection, bronchitis).

In the All Isa-SC group, severe infections (all grades) were reported in 149 (28.5%) participants and Grade ≥3 in 137 (26.2%) participants. The most frequently reported PT (all grades) was pneumonia (51 [9.8%] participants). For Grade ≥3 events, the most frequently reported PT was also pneumonia (47 [9.0%] participants).

The number (%) of participants who experienced severe infections was highest in the Isa-SC+Pd group (109 [35.5%] participants). Pneumonia (all grades) was reported in 39 (12.7%) participants. For Grade ≥3 events, the most frequently reported PT was pneumonia: 36 (11.7%) participants.

Infections

In the All Isa-SC group, 361 (69.2%) participants experienced any infection of which 146 (28.0%) were Grade ≥3 events. The most frequently reported PTs (incidence ≥ 10%) were upper respiratory tract infection (99 [19.0%] participants, pneumonia (73 [14.0%] participants, and COVID-19 (62 [11.9%] participants). In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, the number of participants who experienced any infection was 227 (73.9%) participants, 58 (78.4%) participants, and 76 (53.9%) participants, respectively

5.4.8.7. Tumour lysis syndrome

No events of tumour lysis syndrome were reported in any of the 5 studies (EFC15951, ACT17453, IIT17756, IIT17041, and TCD15484) or in the All Isa-SC pool.

5.4.8.8. Peripheral neuropathy

In studies EFC15951and IIT17041, the incidence of peripheral neuropathies (HLGT) was similar between arms and most events were low grade.

In EFC15951; the Isa-SC+Pd and Isa-IV+Pd arms, peripheral neuropathies were reported in 27 (10.3%) participants and 21 (8.0%) participants, respectively. The most frequently reported PT was peripheral sensory neuropathy (19 [7.2%] participants and 18 [6.8%] participants, respectively).

In Study IIT17041, the incidence of peripheral neuropathies (HLGT) was similar in the two arms and most events were low grade. In the Isa-SC+VRd and Isa-IV+VRd arms, peripheral neuropathies were reported in 17 (25.4%) participants and 21 (29.6%) participants, respectively. The most frequently reported PT was polyneuropathy (14 [20.9%] participants and 11 [15.5%] participants, respectively)

In the All Isa-SC group, peripheral neuropathy events were experienced by 96 (18.4%) participants with 5 (1.0%) participants having Grade ≥3 events. The number (%) of participants with peripheral neuropathy events was highest in the Isa-SC+VRd group (54 [38.3%] participants). The most frequently reported TEAE in this group was peripheral sensory neuropathy (37 [26.2%] participants). The higher

incidence in the Isa-SC+VRd group was most likely attributed to bortezomib which has a known side effect of peripheral neuropathy.

The schedule of administration differs between study IIT17756 and the Isa-IV study EFC12522, with lower dose of bortezomib and dexamethasone. In cross-study comparison, the incidence of peripheral neuropathy was notably lower in study IIT17756 (33 [44.6%] participants) than in EFC12522 (150 [57.0%] participants); the severity was also overall lower in study IIT17756, with 20.3% versus 30.4% for Grade 2 peripheral neuropathy, 1.4% versus 8.0% for Grade 3 peripheral neuropathy, and 0% versus 0.8% for Grade 4 peripheral neuropathy. A lower incidence of TEAE leading to bortezomib reduction due to SOC Nervous system disorders was also observed in IIT17756 compared with EFC12522, 18.9% versus 36.9%, with no Grade ≥3 TEAES versus 6.5%, respectively.

5.4.8.9. Discontinuation due to adverse events

Definitive treatment discontinuation was defined as discontinuation of all study intervention or the last ongoing study drug. Of note, study IIT17041 was excluded from this analysis because the data were collected differently than in the other studies, as definitive treatment discontinuation was not defined.

Study EFC15951: In study EFC15951, 22 (8.4%) and 23 (8.7%) participants in the Isa-SC+Pd and Isa-IV+Pd arms, respectively, had TEAEs leading to permanent full discontinuation.

Study IIT17041: In study IIT17041, TEAEs leading to permanent discontinuation of isatuximab (regardless of relationship with study treatment) occurred infrequently and at a similar rate in both treatment arms (2 [3.0%] participants in the Isa-SC+VRd arm and 4 [5.6%] participants in the Isa-IV+VRd arm).

All Isa-SC pool: In the All Isa-SC group, TEAEs (all grades) leading to permanent full treatment discontinuation were reported in 33 (7.3%) participants of which 31 (6.8%) were Grade ≥3 events. The most frequently reported TEAEs (all grades) in 3 or more participants that led to definitive treatment discontinuation were pneumonia (4 [0.9%] participants) and death (3 [0.7%] participants) (Table 38).

Table 38: TEAEs leading to definitive discontinuation - Number (%) of participants with TEAEs leading to permanent full discontinuation by SOC and PT (excluding IIT17041) - All Isa-SC - Safety population - SCS

	Isa-SC+Pd (N=307)		Isa-SC+Kd (N=74)		Isa-SC+VRd (N=74)		All Isa-SC (N=455)	
Primary System Organ Class Preferred Term [n(%)]	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any event	24 (7.8)	22 (7.2)	6 (8.1)	6 (8.1)	3 (4.1)	3 (4.1)	33 (7.3)	31 (6.8)
Infections and infestations	11 (3.6)	11 (3.6)	2 (2.7)	2 (2.7)	1 (1.4)	1 (1.4)	14 (3.1)	14 (3.1)
Pneumonia	4 (1.3)	4 (1.3)	0	0	0	0	4 (0.9)	4 (0.9)
Covid-19	2 (0.7)	2 (0.7)	0	0	0	0	2 (0.4)	2 (0.4)
Lower respiratory tract infection	1 (0.3)	1 (0.3)	1 (1.4)	1 (1.4)	0	0	2 (0.4)	2 (0.4)
Sepsis	2 (0.7)	2 (0.7)	0	0	0	0	2 (0.4)	2 (0.4)
Meningitis	0	0	1 (1.4)	1 (1.4)	0	0	1 (0.2)	1 (0.2)
Meningitis listeria	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Pneumocystis jirovecii infection	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Pyelonephritis	0	0	0	0	1 (1.4)	1 (1.4)	1 (0.2)	1 (0.2)
Septic shock	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Staphylococcal sepsis	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7)	2 (0.7)	0	0	0	0	2 (0.4)	2 (0.4)

Primary System Organ Class Preferred Term [n(%)]	Isa-SC+Pd (N=307)		Isa-SC+Kd (N=74)		Isa-SC+VRd (N=74)		All Isa-SC (N=455)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Invasive breast carcinoma	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Myelodysplastic syndrome	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Blood and lymphatic system disorders	2 (0.7)	2 (0.7)	0	0	0	0	2 (0.4)	2 (0.4)
Anaemia	2 (0.7)	2 (0.7)	0	0	0	0	2 (0.4)	2 (0.4)
Nervous system disorders	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Haemorrhagic stroke	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Cardiac disorders	1 (0.3)	1 (0.3)	0	0	2 (2.7)	2 (2.7)	3 (0.7)	3 (0.7)
Cardio-respiratory arrest	1 (0.3)	1 (0.3)	0	0	1 (1.4)	1 (1.4)	2 (0.4)	2 (0.4)
Myocardial infarction	0	0	0	0	1 (1.4)	1 (1.4)	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	2 (0.7)	0	2 (2.7)	2 (2.7)	0	0	4 (0.9)	2 (0.4)
Acute pulmonary oedema	0	0	1 (1.4)	1 (1.4)	0	0	1 (0.2)	1 (0.2)
Acute respiratory distress syndrome	0	0	1 (1.4)	1 (1.4)	0	0	1 (0.2)	1 (0.2)
Interstitial lung disease	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Pneumonitis	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Skin and subcutaneous tissue disorders	0	0	1 (1.4)	1 (1.4)	0	0	1 (0.2)	1 (0.2)
Erythema multiforme	0	0	1 (1.4)	1 (1.4)	0	0	1 (0.2)	1 (0.2)
Renal and urinary disorders	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Acute kidney injury	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
General disorders and administration site conditions	3 (1.0)	3 (1.0)	1 (1.4)	1 (1.4)	0	0	4 (0.9)	4 (0.9)
Death	2 (0.7)	2 (0.7)	1 (1.4)	1 (1.4)	0	0	3 (0.7)	3 (0.7)
Sudden death	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Investigations	2 (0.7)	2 (0.7)	0	0	0	0	2 (0.4)	2 (0.4)
Neutrophil count decreased	2 (0.7)	2 (0.7)	0	0	0	0	2 (0.4)	2 (0.4)
Platelet count decreased	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: IIT17756 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study and IIT17756 study.

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

MedDRA 27.0

Adverse events leading to premature treatment discontinuation

Premature treatment discontinuation was defined as the discontinuation of at least one of the study treatments and continuation of at least one study treatment. No participants had premature discontinuation of isatuximab.

5.4.9. Any dose modification

In the All Isa-SC group, TEAEs (all grades) leading to any dose modification were reported in 407 (78.0%) participants of which 294 (56.3%) were Grade ≥3 events. The most frequently reported

TEAE (all grades with incidence ≥10%) that led to any dose modification was neutropenia (120 [23.0%] participants of which 117 [22.4%] participants had Grade ≥3 events).

In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, TEAEs (all grades) leading to any dose modification were reported 272 (88.6%) participants, 60 (81.1%) participants, and 75 (53.2%) participants, respectively. The most frequently reported TEAEs that led to any dose modification in the Isa-SC+Pd group, were neutropenia (98 [31.9%] participants) and neutrophil count decreased (45 [14.7%] participants), in the Isa-SC+Kd group the TEAE was upper respiratory tract infection (19 [25.7%] participants), and in the Isa-SC+VRd group the TEAEs were neutropenia and peripheral sensory neuropathy (15 [10.6%] participants for each).

Isatuximab dose modification

In the All Isa-SC group, TEAEs (all grades) leading to isatuximab dose modification were reported in 303 (58.0%) participants of which 229 (43.9%) were Grade ≥3 events. The most frequently reported TEAEs (all grades) that led to isatuximab dose modification were neutropenia (87 [16.7%] participants of which 86 [16.5%] were Grade ≥3 events), upper respiratory tract infection (47 [9.0%] participants of which 3 [0.6%] were Grade ≥3 events), and pneumonia (44 [8.4%] participants of which 34 [6.5%] were Grade ≥3 event.

In the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups, TEAEs (all grades) leading to isatuximab dose modification were reported 219 (71.3%) participants, 50 (67.6%) participants, and 34 (24.1%) participants, respectively. The most frequently reported TEAEs (all grades) that led to isatuximab dose modification was neutropenia (69 [22.5%] participants) and pneumonia 35 [11.4%] participants) in the Isa-SC+Pd group, upper respiratory tract infection (16 [21.6%] participants) in the Isa-SC+Kd group, and neutropenia (11 [7.8%] participants) in the Isa-SC+VRd group.

Drug interruption

In the All Isa-SC group, TEAEs (all grades) leading to any drug interruption were reported in 3 (0.6%) participants. TEAEs (all grades) that led drug interruption were COVID-19, COVID-19 pneumonia, and septic shock. These events were all in the Isa-SC-Pd group.

Isatuximab drug interruption corresponds to an interruption of isatuximab *during the injection.* In the All Isa-SC group, TEAEs (all grades) leading to isatuximab drug interruption were reported in 3 (0.6%) participants. TEAEs (all grades) that led isatuximab drug interruption were COVID-19, COVID-19 pneumonia, and septic shock. These events were all in the Isa-SC-Pd group.

5.4.10. Safety in special populations

Table 39: AEs by age range

	Isa-SC				Isa-IV			
MedDRA Terms	<65 (N=226)	65-74 (N=199)	75-84 (N=92)	>=85 (N=5)	<65 (N=939)	65-74 (N=900)	75-84 (N=284)	>=85 (N=11)
Total AEs	220 (97.3)	194 (97.5)	89 (96.7)	5 (100)	877 (93.4)	877 (97.4)	271 (95.4)	11 (100)
Serious AEs[a] - Total	99 (43.8)	103 (51.8)	53 (57.6)	3 (60.0)	431 (45.9)	519 (57.7)	171 (60.2)	8 (72.7)
- Fatal	7 (3.1)	12 (6.0)	9 (9.8)	1 (20.0)	60 (6.4)	84 (9.3)	37 (13.0)	4 (36.4)

- Hospitalization/prolong existing hospitalization	77 (34.1)	89 (44.7)	51 (55.4)	2 (40.0)	308 (32.8)	452 (50.2)	156 (54.9)	8 (72.7)
- Life-threatening	8 (3.5)	8 (4.0)	6 (6.5)	0	54 (5.8)	74 (8.2)	29 (10.2)	1 (9.1)
- Disability/incapacity	0	0	0	0	4 (0.4)	6 (0.7)	3 (1.1)	0
- Other (medically significant)	4 (1.8)	7 (3.5)	6 (6.5)	0	38 (4.0)	70 (7.8)	22 (7.7)	2 (18.2)
AE leading to drop-out[b]	11 (4.9)	14 (7.0)	7 (7.6)	1 (20.0)	59 (6.3)	121 (13.4)	40 (14.1)	3 (27.3)
Psychiatric disorders	51 (22.6)	59 (29.6)	20 (21.7)	2 (40.0)	242 (25.8)	330 (36.7)	104 (36.6)	5 (45.5)
Nervous system disorders	67 (29.6)	81 (40.7)	39 (42.4)	3 (60.0)	404 (43.0)	539 (59.9)	164 (57.7)	7 (63.6)
Cardiac disorders	13 (5.8)	23 (11.6)	13 (14.1)	1 (20.0)	230 (24.5)	385 (42.8)	144 (50.7)	9 (81.8)
Vascular disorders	33 (14.6)	35 (17.6)	23 (25.0)	1 (20.0)	261 (27.8)	397 (44.1)	127 (44.7)	6 (54.5)
Cerebrovascular disorders	0	0	0	0	0	3 (0.3)	0	0
Infections and infestations	153 (67.7)	140 (70.4)	63 (68.5)	5 (100)	531 (56.5)	668 (74.2)	199 (70.1)	7 (63.6)
Sum of postural hypotension (LLT), falls, black outs, syncope, dizziness, ataxia, fractures	34 (15.0)	43 (21.6)	29 (31.5)	3 (60.0)	156 (16.6)	248 (27.6)	107 (37.7)	5 (45.5)

The Isa-IV pool includes EFC12522, EFC14335, EFC15246, IIT15403, TCD11863, TCD13983, TCD14079, TCD14906, TED10893, TED14095, TED14154, TED15085 as well as the Isa-IV arm in EFC15951 and IIT17041 study. The Isa-SC pool includes ACT17453, EFC15951, IIT17041, IIT17756, TCD15484 study.

[a] The serious criteria were not collected in IIT17041 study. Thus, the IIT17041 study was excluded from "Fatal", "Hospitalization/prolong existing hospitalization", "Life-threatening", "Disability/incapacity", "Other (medically significant)" summary.

[b] AE leading to full permanent treatment discontinuation was not collected in IIT17041 study. Thus, the IIT17041 study was excluded.

Table 40: AE by special population

	Isa-SC			Isa-IV		
MedDRA Terms	Hepatically impaired* n (%) (N=75)	Renally impaired** n (%) (N=380)	Pregnant n (%) (N=0)	Hepatically impaired* n (%) (N=250)	Renally impaired** n (%) (N=1512)	Pregnant n (%) (N=0)
Total AEs	73 (97.3)	370 (97.4)	0	237 (94.8)	1445 (95.6)	0
Serious AEs[a] - Total	35 (46.7)	197 (51.8)	0	126 (50.4)	826 (54.6)	0
- Fatal	5 (6.7)	25 (6.6)	0	30 (12.0)	144 (9.5)	0
- Hospitalization/ prolong existing hospitalization	29 (38.7)	173 (45.5)	0	105 (42.0)	676 (44.7)	0
- Life-threatening	5 (6.7)	18 (4.7)	0	20 (8.0)	123 (8.1)	0
- Disability/incapacity	0	0	0	0	9 (0.6)	0
- Other (medically significant)	2 (2.7)	15 (3.9)	0	13 (5.2)	95 (6.3)	0
AE leading to drop-out[b]	4 (5.3)	29 (7.6)	0	23 (9.2)	168 (11.1)	0

The Isa-IV pool includes EFC12522, EFC14335, EFC15246, IIT15403, TCD11863, TCD13983, TCD14079, TCD14906, TED10893, TED14095, TED14154, TED15085 as well as the Isa-IV arm in EFC15951 and IIT17041 study. The Isa-SC pool includes ACT17453, EFC15951, IIT17041, IIT17756, TCD15484 study.

[a] The serious criteria were not collected in IIT17041 study. Thus, the IIT17041 study was excluded from "Fatal", "Hospitalization/prolong existing hospitalization", "Life-threatening", "Disability/incapacity", "Other (medically significant)" summary.

[b] AE leading to full permanent treatment discontinuation was not collected in IIT17041 study. Thus, the IIT17041 study was excluded.

* Hepatic impairment is defined as all the following impairment regardless of severity: 1) Mild: ULN < Total Bilirubin ⩽ 1.5*ULN and AST = Any or Total Bilirubin ⩽ ULN and AST > ULN, 2) Moderate: 1.5*ULN < Total Bilirubin ⩽ 3*ULN and AST = Any, 3) Severe: Total Bilirubin > 3*ULN and AST = Any.

** Renal impairment is defined as CrCL <90 and ⩾15 mL/min/1.73m2.

The following intrinsic categories were reported: age group 1 (<65, 65-74, ≥75 years), age group 2 (<65, 65-74, 75-84, ≥85 years, gender, race, body weight group 1(≤65 kg, >65 to ≤85 kg, >85 kg), body weight group 2 (≤50 kg, >50 to ≤100 kg, >100 kg), hepatic status, and renal status.

Due to the imbalance in the number of participants in the Isa-SC+Pd, Isa-SC+Kd, and Isa-SC+VRd groups (N=307, N=74, and N=141, respectively) and especially when the number of participants are further subdivided in the various categories, it becomes difficult to interpret the subgroup results across

the 3 groups. As such, the findings for intrinsic factors are focused on the All Isa-SC group as the sample size is greater (N=522). Overall, for all intrinsic categories a high percentage of participants experienced 1 or more TEAEs. In the All Isa-SC group for all intrinsic categories, the percentage of participants experiencing any TEAE ranged from 92.9% to 100% and for Grade ≥3 TEAEs the percentage ranged from 70.0% to 89.3%.

Besides body weight no other clinically relevant trends were noted.

For subgroup analysis of body weight it was concluded that there was no notable impact from SC flat 1400 mg isatuximab dosing across Weight Group 1 (≤65 kg, >65 to ≤85 kg, >85 kg), except:

- Incidence for any TEAE with a fatal outcome during the treatment period was lower in the >85 kg group (2.8%) compared with the ≤65 kg and >65 to ≥85 weight groups (7.5% and 5.5%, respectively). This was not reflected in the extreme body weight ≤50 kg subgroup where the incidence of fatal TEAE during the treatment period was similar between the different extreme body weight categories (3.6% in ≤50 kg, 5.8% in the >50 to ≤100 kg subgroup, and 2.3% in the > 100 kg subgroup).
- The incidence of laboratory neutropenia (Grade ≥3) was higher in the ≤50 kg weight group (17/18; 94.4%) compared with the >100 kg weight group (18/2378.4%The incidence of neutropenic complications (including neutropenic infection and febrile neutropenia) across the three body weight groups was: 16.7%, 20.7%, and 26.1% among patients ≤50 kg, >50 to ≤100 kg, and >100 kg, respectively..

In analysis by Weight Group 2:

- Incidence of Grade ≥3 TEAEs was higher in the <50 kg weight group (89.3%) compared with the >50 to <100 kg and >100 kg weight groups (79.2% and 79.1%, respectively). However, no higher incidence of serious TEAEs, fatal TEAEs and TEAEs leading to definitive treatment discontinuation was observed in this extreme low bodyweight subgroup.

5.4.11. Immunological events

Study EFC15951

In EFC15951, the number of ADA positive participants was low, and no apparent effect of positive ADA was observed on safety. However, a higher incidence of thrombocytopenia (Grade 3 and above) was observed in ADA-positive participants compared with ADA-negative participants in both treatment arms (4 [36.4%] of 11 ADA positive participants compared with 59 [24.2%] of 244 ADA negative participants in Isa-SC+Pd arm and 10 [43.5%] of 23 ADA positive participants compared with 46 [19.9%] of 231 ADA negative participants in Isa-IV+Pd arm).

Study IIT17041

All 51 participants with either ADA positive or negative status experienced TEAEs. In the Isa-IV+VRd arm, 1 (25.0%) participant in the ADA positive group, and 5 (20.8%) in the ADA negative group experienced treatment-emergent SAEs. In the Isa-SC+VRd arm, 2 (50.0%) in the ADA positive group and 6 (31.6%) in the ADA negative group experienced treatment-emergent SAEs. One (4.2%) participant in the ADA negative group from the IV arm had an TEAE leading to permanent discontinuation of isatuximab, while there were none in the ADA positive group, nor in the SC arm.

All Isa-SC pool

The potential impact of treatment-induced ADAs on several safety parameters was assessed including IRs, TEAEs, SAEs, TEAEs leading to permanent discontinuation of study treatment, neutropenia, neutropenic complications, thrombocytopenia, and haemorrhagic complications. No apparent effect of positive ADA was observed on safety.

With respect to the incidence of thrombocytopenia (Grade 3 and above) Table 41 shows the incidences observed in the All-Isa SA pool.

Table 41: Summary of impact of ADA to isatuximab on clinical safety - All-Isa-SC - ADA population - SCS

	RRMM										NDMM					
	EFC15951		TCD15484		ACT17453		Isa-SC+Pd		Isa-SC		IIT17041		IIT17756		Isa-SC	
	Isa-SC+Pd (N=255)		Isa-SC+Pd (N=44)		Isa-SC+Kd (N=72)		Pool (N=299)		RRMM Pool (N=371)		Isa-SC+VRd (N=23)		Isa-SC+VRd (N=65)		NDMM Pool (N=88)	
Clinical safety (AE)	ADA Positive (N=11)	ADA Negative (N=244)	ADA Positive (N=4)	ADA Negative (N=40)	ADA Positive (N=3)	ADA Negative (N=69)	ADA Positive (N=15)	ADA Negative (N=284)	ADA Positive (N=18)	ADA Negative (N=353)	ADA Positive (N=4)	ADA Negative (N=19)	ADA Positive (N=10)	ADA Negative (N=55)	ADA Positive (N=14)	ADA Negative (N=74)
Grade ≥3 Thrombocytopenia	4 (36.4)	59 (24.2)	1 (25.0)	11 (27.5)	1 (33.3)	13 (19.1)	5 (33.3)	70 (24.6)	6 (33.3)	83 (23.6)	0	0	3 (30.0)	14 (25.5)	3 (21.4)	14 (18.9)

5.4.12. Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction studies were conducted with isatuximab following SC administration. The effects of pomalidomide, carfilzomib, bortezomib, lenalidomide, and dexamethasone on isatuximab PK, and the effects of isatuximab on the PK of those drugs, has been described in the prior isatuximab IV submissions. Concomitant administration of isatuximab with these drugs did not alter isatuximab exposure, or vice versa.

5.4.13. Vital signs and laboratory findings

In studies EFC15951 and IIT17041, the frequency of hematology abnormalities was similar between Isa-SC and Isa-IV.

In the All Isa-SC group, the hematology parameters that had the highest incidence of Grade 3 and Grade 4 abnormalities (Table 42) were the following:

Neutrophil count decreased

In the All Isa-SC group, Grade 3 and Grade 4 neutrophil count decreased during the treatment period was reported in 145 (28.0%) participants and 170 (32.8%) participants, respectively.

Grade 3 and Grade 4 neutrophil count decreased during the treatment period was reported in 104 (34.1%) and 157 (51.5%) participants, respectively, in the Isa-SC+Pd group, 10 (13.7%) and 1 (1.4%) participant, respectively, in the Isa-SC+Kd group, and 31 (22.1%) and 12 (8.6%) participants, respectively, in the Isa-SC+VRd group. The higher incidences of neutrophil count decreased in the Isa-SC+Pd group were most likely attributed to the combination with pomalidomide which has also a known side effect of neutropenia.

White blood cell decreased

In the All Isa-SC group, Grade 3 and Grade 4 white blood cell decreased during the treatment period was reported in 180 (34.7%) participants and 44 (8.5%) participants, respectively.

Lymphocytes decreased

In the All Isa-SC group, Grade 3 and Grade 4 lymphocytes decreased during the treatment period was reported in 212 (40.9%) participants and 59 (11.4%) participants, respectively.

Table 42: Summary of laboratory results (hematology) during the treatment period (worst grade per participant) - All Isa-SC - Safety population -SCS

n/N(%)	Isa-SC+Pd (N=307)	Isa-SC+Kd (N=74)	Isa-SC+VRd (N=141)	All Isa-SC (N=522)
Anemia				
All grades	294/305 (96.4)	73/73 (100)	127/140 (90.7)	494/518 (95.4)
Grade 1	133/305 (43.6)	34/73 (46.6)	63/140 (45.0)	230/518 (44.4)
Grade 2	109/305 (35.7)	24/73 (32.9)	54/140 (38.6)	187/518 (36.1)
Grade 3	52/305 (17.0)	15/73 (20.5)	10/140 (7.1)	77/518 (14.9)
Grade 4	0/305	0/73	0/140	0/518
Platelet count decreased				
All grades	263/305 (86.2)	65/73 (89.0)	80/140 (57.1)	408/518 (78.8)
Grade 1	141/305 (46.2)	35/73 (47.9)	45/140 (32.1)	221/518 (42.7)
Grade 2	42/305 (13.8)	16/73 (21.9)	15/140 (10.7)	73/518 (14.1)
Grade 3	38/305 (12.5)	8/73 (11.0)	12/140 (8.6)	58/518 (11.2)
Grade 4	42/305 (13.8)	6/73 (8.2)	8/140 (5.7)	56/518 (10.8)
White blood cell decreased				
All grades	300/305 (98.4)	54/73 (74.0)	118/140 (84.3)	472/518 (91.1)
Grade 1	31/305 (10.2)	21/73 (28.8)	53/140 (37.9)	105/518 (20.3)
Grade 2	80/305 (26.2)	22/73 (30.1)	41/140 (29.3)	143/518 (27.6)
Grade 3	148/305 (48.5)	11/73 (15.1)	21/140 (15.0)	180/518 (34.7)
Grade 4	41/305 (13.4)	0/73	3/140 (2.1)	44/518 (8.5)
Neutrophil count decreased				
All grades	298/305 (97.7)	38/73 (52.1)	85/140 (60.7)	421/518 (81.3)
Grade 1	9/305 (3.0)	12/73 (16.4)	16/140 (11.4)	37/518 (7.1)
Grade 2	28/305 (9.2)	15/73 (20.5)	26/140 (18.6)	69/518 (13.3)
Grade 3	104/305 (34.1)	10/73 (13.7)	31/140 (22.1)	145/518 (28.0)
Grade 4	157/305 (51.5)	1/73 (1.4)	12/140 (8.6)	170/518 (32.8)
Lymphocytes decreased				
All grades	287/305 (94.1)	66/73 (90.4)	122/140 (87.1)	475/518 (91.7)
Grade 1	27/305 (8.9)	9/73 (12.3)	10/140 (7.1)	46/518 (8.9)
Grade 2	104/305 (34.1)	14/73 (19.2)	40/140 (28.6)	158/518 (30.5)
Grade 3	126/305 (41.3)	38/73 (52.1)	48/140 (34.3)	212/518 (40.9)
Grade 4	30/305 (9.8)	5/73 (6.8)	24/140 (17.1)	59/518 (11.4)

Note: Isa-SC+Pd: Pooled from EFC15951 study and TCD15484 study in RRMM participants; Isa-SC+Kd: Study ACT17453 in RRMM participants; Isa-SC+VRd: Pooled from IIT17756 study and IIT17041 study in NDMM participants; All Isa-SC: Pooled isatuximab SC treatment in combination of background regimens combining EFC15951 study, TCD15484 study, ACT17453 study, IIT17041 study and IIT17756 study.

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

5.4.14. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.15. Cross study comparison

For the key clinical studies without a control arm (ie, ACT17453 and IIT17756), a cross-study comparison with the corresponding Isa-IV studies was performed for the analysis of the selected adverse events (AEs) between Isa-SC and the Isa-IV combination regimen. To account for differences in duration of follow-up between Isa-IV and Isa-SC studies, only safety data collected from first dose of study treatment up to a fixed time window for each patient was summarized and compared.

- Comparison of Isa-SC+Kd (Study ACT17453 [IZALCO]) versus Isa-IV+Kd (Study EFC15246 [IKEMA]) during the first 6 months of treatment in RRMM participants. In general, the overall safety profile of Isa-SC+Kd was similar to Isa-IV+Kd, except the notable lower rate of IRs with Isa-SC+Kd.
- Comparison of Isa-SC+VRd (Study IIT17756 [IsaSoCut]) versus Isa-IV+VRd (Study EFC12522 [IMROZ]) during the first 8 months of treatment in NDMM-TI participants. In general, taking into consideration the differences in hematologic adverse event reporting and the bortezomib dosing administration schedule, the overall safety profile of Isa-SC+VRd is similar to Isa-IV+VRd, except a lower rate of systemic IRs.

5.4.16. Overall discussion and conclusions on clinical safety

5.4.16.1.1. Overall assessment of available safety data

The safety data from the comparative (SC vs IV) studies EFC15951 (IRAKLIA, Isa+Pd) and IIT17041 (GMMG-DH8, Isa+VRd) are presented together with a pooled analysis (n=522) describing the safety profile of SC isatuximab by each combination regimen from five studies (Isa-SC+Pd: EFC15951 and TCD15484; Isa-SC+Kd: ACT17453; Isa-SC+VRd: IIT17756 and IIT1704).

In the All Isa-SC group the median duration of overall exposure was 8.28 months (range: 0.2 to 45.8) with 67.2% with at least 6 months of exposure and 25.7% at least 12 months exposure. Thus, the safety database and exposure are considered sufficient for safety evaluation of Isa-SC.

In the All Isa-SC group, 97.3% participants had TEAEs (any grade), 79.7% had TEAEs of Grade ≥3, 49.4% participants had serious TEAEs, and 6.3% participants had TEAE leading to permanent full discontinuation. Interpretation of the results of this pooled analysis is challenging due to different combination treatments in different populations (RRMM and NDMM), and imbalances in the number of participants in the groups (307, 74, and 141, respectively). The randomised study EFC15951 (IRAKLIA) showed a consistent safety profile between IV and SC administration, with the exception of any injector device related TEAE (any grade; 3.4% (9 participants). For study IIT17041 (GMMG-DH8) more variation between SC and IV is observed, this is likely due to the smaller amount of study participants (n=74) leading to les precision. Although there is a difference between Isa-IV+VRd and Isa-SC+VRd regarding the TEAE related to the medical procedure (66.2% vs 38.8%), the data is considered unreliable due to differences in interpretation of causality to Isa at the study sites or this IIT study (IIT17041). In general, the absolute difference in TEAEs between SC and IV is small.

In the All Isa-SC group, the most frequently reported TEAEs (≥15% for all grades) were neutropenia (39.1%), diarrheoa (22.4%), upper respiratory tract infection (19.0%), constipation (17.8%), fatigue (15.9%), insomnia (15.7%), and lymphopenia (15.3%). As expected, the incidence of the most frequent TEAE differed per backbone regimen with neutropenia most frequently observed with the Isa-SC+Pd, upper respiratory tract infection with Isa-SC+Kd, and cytopenia (neutropenia, lymphopenia) for the Isa-SC+VRd combination. In study EFC15951 and IIT17041, the incidence of the most frequently reported

TEAEs for Isa-SC, at the PT level, was generally similar between SC and IV. With the exception of fatigue (19.4% versus 14.0%) and infusion reactions (1.9% versus 25.0%) SC vs IV in study EFC15951, both mainly grade 1-2. For study IIT17041 lymphopenia was reported more in the SC arm (46.3% versus 35.2%) and neutropenia was reported less in the SC arm compared to the IV arm (34.3% versus 42.3%), as were infusion reactions (1.5% versus 7.0%). The AE incidence among studies cannot be readily compared as there was a difference in data collection methods between Sanofi sponsored studied (EFC15951 [IRAKLIA] and TCD15484, the Isa-SC+Pd pool and ACT17453 [IZALCO], the Isa-SC+Kd pool) and investigator initiated studies (IIT17041 and IIT17756). In the IIT studies the investigator first reported a cytopenia lab abnormality as a TEAE (e.g. optional), whereas in Sanofi sponsored studies cytopenia was systematically reported a lab abnormality. This has led to a higher incidence of cytopenic TEAEs in the Isa SC+VRd pool (ie, studies IIT17041 and IIT17756) compared to the Sanofi Sponsored studies (ie, Isa-SC+Pd pool and Isa-SC+Kd pool).

Treatment-related TEAEs were in general as expected for Isa treatment with the respective backbones.

Overall treatment-emergent SAEs were reported at a similar incidence between the SC and IV administration in study EFC15951, whereas in study IIT17041 the incidence was slightly higher in the SC arm (38.8%) vs IV arm (32.4%), although this difference is likely enlarged due to the small sample size. In the All Isa-SC pool 49.4% of patients had a serious TEAE (all grades) of 44.1% had a grade ≥3 event, the most frequently reported (>5%) grade ≥3 serious TEAEs was pneumonia (9%).

In study EFC15951 there were 6 deaths in the IV arm reported as related to the study treatment (during study period due to pneumonia (2), fulminant hepatitis (1), erysipelas (1); post treatment period due to pneumonia (1) and myocardial infarction and bacterial pneumonia (1). In study IIT17041 there were no deaths considered related to isatuximab. There were 27 fatal TEAEs or grade 5 post-treatment AEs (mainly in Isa-SC+Pd, n=17) due to pneumonia (n=5). Pneumonia is a known ADR also observed within Isa-IV.

There were 522 patients receiving Isa-SC, among them 490 patients received Isa-SC with OBDS and 32 patients with infusion pump and manual administration. The majority of doses was administered via OBDS (9074) compared to manual (597) or infusion pump (418). In the All Isa-SC group, 30 (6.1%) participants experienced a TEAE related to the OBDS (all grades) of which 7 (1.4%) were Grade ≥3 events. The most frequently reported TEAE was injection site reaction (17 [3.5%]) participants; none of the ISRs were Grade ≥3 events.

Insufficient information has been presented to conclude how the safety (e.g. injection reactions) of the OBDS compares to manual injection.

At home administration was allowed after Cycle 6 Day 1, in EFC15951 only a limited number of injections (18 patients; DCO 29 Aug 2025) were performed at home by an HCP. Important for at-home administration are the precautions in case of a systemic reactions which are in the remit of the HCP. None of the at-home administrations led to a systemic IR.

Injection site reactions (ISR) with Isa-SC were reported in 11.9% (all Isa-SC pool) which represents app. 1.5% of the injections given, ISR were of low grade (no grade 3 events) and mostly resolved within one day. The incidence of ISR was significantly higher in the IVRd treated patients (15.6%) compared to the Isa-SC+Kd (1.4%) and Isa-SC+Pd (2.9%). The higher incidence of ISR (as PT) for Isa-SC+VRd is due to higher reporting in study IIT17756, whereas results from IIT17041 are in line with the reporting in the other backbone regimens (Pd and Kd). The higher incidence was not due to a longer exposure duration, likely this is due to the difference in reporting of this IIT study IIT17756. .

As expected, the incidence of systemic infusion reactions was lower in the SC arm than in the IV arm (study EFC15951 and IIT17041). Systemic IR were reported in 3.1% participants in the Isa-SC pool,

mainly related reaction of Grade 1 or Grade 2. The majority of patients in the all Isa-SC group had 1 event (14/16 cases) which occurred at the first injection (10/16 cases) and resolved within 3 days.

Second primary malignancy (SPM) has previously been described with Isa treatment and is described in the SmPC. In general the incidence of these events in SC studies was low and similar to the one in Isa-IV studies. In study IIT17041 there were no reports of SPM. The overall incidence of SPMs in Isa-SC exposed patients was 4.4%. In pooled analysis of Isa-SC and Isa-IV (N=2656), SPMs were reported in 144 patients (5.4%).

In the All Isa-SC group, the number (%) of participants with neutropenia (based on laboratory abnormalities) of Grade 3 and Grade 4 was 145 (28.0%) participants and 170 (32.8%) participants. A higher incidence was observed in the patients treated with pomalidomide, as expected. This resulted in neutropenic complications of Grade 3, Grade 4, and Grade 5 in 5.2%, 2.5%, and 0.6% participants respectively. Three (1.0%) participants in Isa-SC+Pd had neutropenic complications with fatal outcomes during the treatment period. Neutropenia is a well known ADR with Isa for which precautions and warnings have already been implemented in the SmPC of Isa-IV.

The incidence of laboratory neutropenia (Grade ≥3) was higher in the ≤50 kg weight group (17/18; 94.4%) compared with the >100 kg weight group (18/23; 78.4%). The incidence of neutropenic complications (including neutropenic infection and febrile neutropenia) across the three body weight groups was: 16.7%, 20.7%, and 26.1% among patients ≤50 kg, >50 to ≤100 kg, and >100 kg, respectively. The seemingly higher incidence of neutropenia complications in the higher body weight group is unreliable due to small patients numbers. A warning for a higher incidence of Grade 3-4 neutropenia for the extreme body weight groups (≤50 kg) has been included in SmPC section 4.4 to inform healthcare providers.

Grade ≥3 infections were observed in 26.2% participants in the all-IsaSC pool, with the highest incidence in the Isa-SC+Pd cohort pneumonia was most frequently reported (app. 12%). There was no difference between SC and IV formulation in study EFC15951 and IIT17041.

TEAEs leading to permanent full discontinuation occurred in similar percentage of participants between SC and IV arms. App. 7% of participants discontinued treatment mostly due to Grade ≥3 events in the SOC infections (mainly pneumonia [0.9%] participants) and death (3 [0.7%] participants). No participants had premature discontinuation of isatuximab. TEAEs (all grades) leading to isatuximab dose modification were frequent (58%) in the all-ISA-SC pool with as main TEAE neutropenia, pneumonia, upper respiratory tract infection which is as expected within this study population and backbone regimens. Drug interruption was rare within the All ISA-SC group (0.6%) as it was defined as interruption during the injection.

The incidence of treatment-induced ADAs was low, the potential impact on several safety parameters was assessed and no apparent effect was observed. Although limited patients were of ADA-positive, a higher incidence of thrombocytopenia (Grade 3 and above) was observed in ADA-positive patients compared with ADA-negative participants in SC treated patients in study EFC15951 and ACT17453. This was not observed in the pooled NDMM. Definitive conclusions are hampered by the small number of ADA positive patients and inconsistent findings across studies and treatment settings.

For the key clinical studies without a control arm (ie, ACT17453 and IIT17756), a cross-study comparison with the corresponding Isa-IV studies was performed for the analysis of the selected adverse events (AEs) between Isa-SC and the Isa-IV combination regimen. This demonstrated that Isatuximab SC demonstrated an overall safety profile similar to isatuximab IV in NDMM and RRMM participants with the exception of a lower rate of systemic infusion reaction associated with the SC route of administration.

5.4.16.1.2. Adverse drug reactions in the SmPC

The MAH has added per backbone regimen an ADR table in section 4.8 (SmPC) for the pooled dataset of IV and SC treated patients with isatuximab.

Table 43: Adverse reactions reported in patients with multiple myeloma treated with isatuximab subcutaneous or intravenous formulation in combination with pomalidomide and dexamethasone

System organ class Preferred term	Adverse reaction	Frequency	Incidence (N = 827)	
			Any Grade	Grade ≥3
Infections and infestations	Pneumonia [a]	Very common	28.4%	22.0%
	Upper respiratory tract infection	Very common	27.9%	2.1%
	Neutropenic infection	Very common	16.9%	8.3%
	Bronchitis	Very common	10.6%	1.6%
	Covid-19	Very common	10.2%	1.8%
	Herpes zoster	Common	1.2%	0.2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) [b]	Skin cancer	Common	4.2%	0.8%
	Solid tumour (non-skin cancer)	Common	1.7%	1.0%
	Haematology malignancy	Uncommon	0.5%	0.5%
Blood and lymphatic system disorders	Neutropenia [c]	Very common	51%	50.7%
	Thrombocytopenia	Common	8.5%	7.9%
	Anaemia	Common	6.9%	5.3%
	Febrile neutropenia	Common	5.3%	5.3%
	Lymphopenia	Not known	-	-
Immune system disorders	Anaphylactic reaction [d]	Uncommon	0.3%	0.3%
Metabolism and nutrition disorders	Decreased appetite	Common	5.3%	0.5%
Psychiatric disorders	Insomnia	Very common	16.7%	3.7%
Nervous system disorders	Peripheral sensory neuropathy	Very common	10.2%	0.5%
	Dizziness	Common	8.9%	0.2%
Cardiac disorders	Atrial fibrillation	Common	4.0%	1.9%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	12.3%	2.3%
	Cough	Very common	12.2%	0%

System organ class Preferred term	Adverse reaction	Frequency	Incidence (N = 827)	
			Any Grade	Grade ≥3
Gastrointestinal disorders	Diarrhoea	Very common	25.4%	1.5%
	Constipation	Very common	18.4%	0.1%
	Nausea	Very common	13.2%	0.5%
	Vomiting	Common	8.1%	0.5%
Musculoskeletal and connective tissue disorders	Back pain	Very common	14.5%	1.6%
	Arthralgia	Very common	10.8%	1.7%
	Muscle spasms	Very common	10.6%	0.2%
General disorders and administration site conditions	Fatigue	Very common	24.2%	3.6%
	Oedema peripheral	Very common	13.9%	0.7%
	Pyrexia	Very common	10.2%	1.2%
Investigations	Weight decreased	Common	2.9%	0.1%
Injury, poisoning and procedural complications	Systemic administration reaction[e] With isatuximab intravenous [f] With isatuximab subcutaneous [g] Injection site reactions [e g] With isatuximab subcutaneous	 Very common Common Common	 31.5% 2.0% 9.8%	 1.5% 0.3% 0%

[a] The term pneumonia is a grouping of terms.
[b] Based on second primary malignancies reported during study treatment period and during post-treatment period.
[c] Haematology laboratory values were recorded as TEAEs only if they led to treatment discontinuation and/or dose modification and/or fulfilled a serious criterion. The term neutropenia is a grouping of neutropenia and neutrophil count decrease.
[d] Based on post-marketing experience with intravenous isatuximab.
[e] See "Description of selected adverse reactions".
[f] Based on isatuximab intravenous arms of isatuximab SC and IV clinical studies (N=520).
[g] Based on isatuximab subcutaneous arms of isatuximab SC clinical studies (N=307).
MedDRA 27.00

Table 44: Adverse reactions reported in patients with multiple myeloma treated with isatuximab subcutaneous or intravenous formulation in combination with carfilzomib and dexamethasone

System organ class Preferred term	Adverse reaction	Frequency	Incidence (N = 251)	
			Any Grade	Grade ≥3
Infections and infestations	Upper respiratory tract infection	Very common	39.4%	2.8%
	Pneumonia [a]	Very common	30.3%	21.1%
	Bronchitis	Very common	18.7%	1.6%
	Nasopharyngitis	Very common	16.7%	0%
	Covid-19	Very common	15.1%	2.4%
	Respiratory tract infection	Very common	10.8%	1.2%
	Influenza	Very common	10.0%	1.2%
	Herpes zoster	Common	2.4%	0.4%
	Neutropenic infection	Common	2.0%	0.4%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) [b]	Skin cancer	Common	6.0%	1.6%
	Solid tumour (non-skin cancer)	Common	2.8%	2.4%
Blood and lymphatic system disorders	Neutropenia [c]	Common	8.0%	7.2%
	Anaemia	Common	6.0%	4.4%
	Thrombocytopenia	Common	4.8%	3.6%
	Febrile neutropenia	Common	1.2%	1.2%
	Lymphopenia	Not known	-	-
Immune system disorders	Anaphylactic reaction [d]	Uncommon	0.3%	0.3%
Psychiatric disorders	Insomnia	Very common	21.5%	5.2%
Nervous system disorders	Peripheral sensory neuropathy	Very common	12.7%	0%
	Dizziness	Common	4.4%	0%
Eye disorders	Cataract	Very common	13.1%	3.2%
Vascular disorders	Hypertension	Very common	31.5%	17.9%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	23.9%	4.4%
	Cough	Very common	17.9%	0%
Gastrointestinal	Diarrhoea	Very common	31.1%	2.0%

System organ class Preferred term disorders	Adverse reaction	Frequency	Incidence (N = 251)	
			Any Grade	Grade ≥3
	Nausea	Very common	16.7%	0%
	Vomiting	Very common	13.9%	0.8%
	Constipation	Very common	10.4%	0.4%
Musculoskeletal and connective tissue disorders	Back pain	Very common	19.9%	1.6%
	Arthralgia	Very common	17.1%	1.6%
	Muscle spasms	Very common	11.6%	0%
	Pain in extremity	Very common	11.6%	0%
General disorders and administration site conditions	Fatigue	Very common	25.1%	4.4%
	Asthenia	Very common	14.3%	1.6%
	Oedema peripheral	Very common	13.5%	0.4%
	Pyrexia	Very common	12.7%	1.6%
Injury, poisoning and procedural complications	Systemic administration reaction [e] With isatuximab intravenous [f] With isatuximab subcutaneous [g] Injection site reactions [e g] With isatuximab subcutaneous	 Very common Common Common	 47.5% 2.7% 8.1%	 0.6% 0% 0%

[a] The term pneumonia is a grouping of terms.
[b] Based on second primary malignancies reported during study treatment period and during post-treatment period.
[c] Haematology laboratory values were recorded as TEAEs only if they led to treatment discontinuation and/or dose modification and/or fulfilled a serious criterion. The term neutropenia is a grouping of neutropenia and neutrophil count decrease.
[d] Based on post-marketing experience with intravenous isatuximab.
[e] See "Description of selected adverse reactions".
[f] Based on isatuximab intravenous clinical study (N=177).
[g] Based on isatuximab subcutaneous clinical study (N=74).
MedDRA 27.0

Table 45: Adverse reactions reported in patients with multiple myeloma treated with isatuximab subcutaneous or intravenous formulation in combination with bortezomib, lenalidomide, and dexamethasone

System organ class Preferred term	Adverse reaction	Frequency	Incidence (N = 904)	
			Any Grade	Grade ≥3
Infections and infestations	Pneumonia [a]	Very common	19.9%	14.7%
	Upper respiratory tract infection	Very common	15.2%	0.7%

System organ class Preferred term	Adverse reaction	Frequency	Incidence (N = 904)	
			Any Grade	Grade ≥3
	Bronchitis	Very common	11.8%	1.7%
	Covid-19	Very common	11.3%	1.5%
	Neutropenic infection	Common	4.8%	1.8%
Neoplasms benign, malignant and unspecified (incl cysts and polyps) [b]	Skin cancer	Common	3.3%	1.0%
	Solid tumour (non-skin cancer)	Common	2.3%	1.5%
	Haematology malignancy	Uncommon	0.3%	0.1%
Blood and lymphatic system disorders	Neutropenia [c]	Very common	33.7%	28.8%
	Thrombocytopenia	Very common	13.2%	10.7%
	Lymphopenia	Very common	12.8%	11.2%
	Anaemia	Common	8.2%	4.3%
	Febrile neutropenia	Common	1.5%	1.4%
Immune system disorders	Anaphylactic reaction [d]	Uncommon	0.2%	0.2%
Psychiatric disorders	Insomnia	Very common	12.3%	1.9%
Nervous system disorders	Peripheral sensory neuropathy	Very common	29.2%	3.3%
	Polyneuropathy	Very common	10.0%	2.1%
	Dizziness	Common	7.0%	0.2%
Eye disorders	Cataract	Very common	15.8%	6.1%
Gastrointestinal disorders	Diarrhoea	Very common	29.9%	5.0%
	Constipation	Very common	22.9%	1.7%
	Vomiting	Common	5.4%	0.3%
Skin and subcutaneous tissue disorders	Rash	Very common	10.6%	2.0%
Musculoskeletal and connective tissue disorders	Back pain	Very common	11.9%	1.5%
General disorders and administration site conditions	Oedema peripheral	Very common	17.1%	0.3%
	Asthenia	Very common	14.8%	2.0%
	Fatigue	Very common	14.3%	3.0%
	Pyrexia	Very common	10.4%	1.0%

System organ class Preferred term	Adverse reaction	Frequency	Incidence (N = 904)	
			Any Grade	Grade ≥3
Investigations	Weight decreased	Common	6.1%	0.4%
Injury, poisoning and procedural complications	Systemic administration reaction [e] With isatuximab intravenous [f] With isatuximab subcutaneous [g] Injection site reactions [e g] With isatuximab subcutaneous	 Very common Common Very common	 19.9% 5.7% 18.4%	 1.2% 0% 0%

[a] The term pneumonia is a grouping of terms
[b] Based on second primary malignancies reported during study treatment period and during post-treatment period.
[c] The term neutropenia is a grouping of neutropenia and neutrophil count decrease.
[d] Based on post-marketing adverse reactions experience with intravenous isatuximab
[e] See "Description of selected adverse reactions".
[f] Based on isatuximab intravenous arms of isatuximab SC and IV clinical studies (N=763).
[g] Based on isatuximab subcutaneous arms of isatuximab SC clinical studies (N=141).
MedDRA 27.00

5.4.16.2. Conclusions on clinical safety

The overall safety profile of the Isa-SC administration is consistent with that of the IV formulation, except for a higher rate of low grade injection site reactions associated with the SC route of administration, and lower rate of infusion reactions. No new safety signals have been identified.

6. Risk management plan

The MAH has submitted a new version of RMP (version 3.2) with final sign of date 14/01/2026 to update the RMP in response to the Day 150 Committee for Medicinal Products for Human Use (CHMP) Assessment Report on the extension of the marketing authorization for Isatuximab (EMA/X/0000281242) dated 05-Jan-2026, to address the list of outstanding issues on European Union Risk Management Plan (EU-RMP).

7.1 Safety specification

6.1.1. Proposed safety specification

No changes of the safety specification were proposed.

Table 46: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs´test)
Important potential risks	Viral reactivation
Missing information	None

6.1.2. Discussion on proposed safety specification

PRAC Rapporteur's position:

The MAH is not proposing any changes to the list of safety concerns. This is endorsed.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

No changes of the routine pharmacovigilance activities were proposed.

The applicant did not propose any changes to the additional pharmacovigilance activities.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

No changes to the current routine pharmacovigilance activities are proposed. Routine pharmacovigilance activities are considered sufficient.

6.2.2.2. Additional pharmacovigilance activities

There are no additional pharmacovigilance activities ongoing or planned for this product.

6.3. Plans for post-authorisation efficacy studies

No imposed post-authorization efficacy studies are planned or ongoing for isatuximab.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 47. Planned routine risk minimisation measures

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

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

No changes of the routine risk minimisation activities were proposed.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

No changes in the routine risk minimisation measures are proposed by the MAH. The existing routine risk minimisation measures are sufficient to minimise the risks of the product in its SC form in the proposed indications.

6.4.2.2. Additional risk minimisation measures

No changes in the additional risk minimisation measures are proposed by the MAH. The current additional risk minimisation measures are sufficient to minimise the risks of the product in its SC form in the proposed indications.

6.4.2.3. Patients engagement on the risk minimisation activities

N/A

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The PRAC consider that the updated risk management plan version 3.2 is acceptable. The MAH is reminded that the RMP must be in line with the final clinical assessment report conclusions.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.1. Periodic Safety Update Reports submission requirements

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

8. Product information

8.1. Summary of Product Characteristics (SmPC)

See attached edited product information including Rapporteur assessment.

8.1.1. SmPC section 5.1 justification

The information in section 5.1 of the SmPC should be concise and limited to information that is relevant to the prescriber. Study EFC15951 (IRAKLIA) is considered pivotal to demonstrate that Isa-SC is non-inferior to Isa-IV. This study is therefore considered relevant. The Isa-IV studies that were used for registration of the approved isatuximab indications are pivotal, and are properly powered, for demonstrating the efficacy of isatuximab in the various combination regimens and patient populations. These data are relevant to the prescribers in terms of what to expect when giving isatuximab to their patients, and should therefore be described in full in the SmPC for isatuximab SC.

8.1.2. SmPC section 4.2 justification

The dosing schedules for the Isa-IV route of administration are considered to be the approved dosing schedules supporting the various indications of isatuximab. In the pivotal study (IRAKLIA), dosing of Isa-SC and Isa-IV was identical in frequency, meaning that it has been demonstrated that one SC dose of isatuximab is non-inferior to one dose of isatuximab IV in terms of PK. The dosing schedules as they were approved in the registrational Isa-IV studies, are reported in Section 4.2 of the SmPC, and not the schedules as they were used in the (mostly uncontrolled) Isa-SC trials.

8.2. Labelling

8.2.1. Package leaflet (PL)

See attached edited product information including Rapporteur assessment.

8.2.2. User consultation

8.2.2.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

MM is the second most-common adult blood cancer, with an estimated incidence in Europe of 4.5-6.0/100 000/year. MM is a cancer of the haemopoietic system that is characterized by uncontrolled clonal expansion of plasma cells in the bone marrow. These plasma cells produce an excess amount of abnormal antibodies (so called M protein) or fragments thereof that cause a range of health issues, including impairment of the immune system and increased blood viscosity. Patients often present with bone lesions, anaemia, hypercalcaemia and renal failure.

Isatuximab is currently administered using the IV formulation. In this procedure, the MAH is requesting authorisation for a newly developed SC formulation, which upon approval will be applicable to all current and future IV indications. The currently approved indications for isatuximab IV are:

- In combination with pomalidomide and dexamethasone for the treatment of adult patients with RRMM in the third line
- In combination with carfilzomib and dexamethasone for the treatment of adult patients with RRMM in the second line
- In combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with NDMM who are ineligible for autologous stem cell transplant
- in combination with bortezomib, lenalidomide, and dexamethasone, for the induction treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

9.1.2. Available therapies and unmet medical need

Throughout the treatment lines, fixed combinations of drugs are approved and the choice of therapy is mostly dependent on transplant eligibility at diagnosis (based mainly on age and performance status).

In transplant ineligible, older/frail patients, a typical first-line treatment strategy would consist of VRd combined with an anti-CD38 antibody (isatuximab/daratumumab ASCT-eligible patients with NDMM generally receive an induction therapy with the same quadruplet combination, followed by high-dose chemotherapy + ASCT, sometimes followed by consolidation treatment and commonly followed by lenalidomide maintenance therapy.

The choice of second- and third-line therapy in MM is based on several factors, including agents used in the first-line, response to prior treatment, the aggressiveness of the relapse, refractoriness to lenalidomide, and performance status. The use of consolidative ASCT in the second-line is 10–15%. Triplets are often used, consisting of combined PI + IMID-based therapies, along with the use of monoclonal antibodies.

Despite the significant progress that has been made in the management of multiple myeloma, the disease relapses and it remains an incurable malignancy, leaving room for improvement (e.g. prolonged disease control), particularly in the high risk patients.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.1. of this document.

The pivotal studyEFC15951 (IRAKLIA) is a randomised, open-label, controlled, phase III study in patients with relapsed and/or refractory multiple myeloma. Patients had received at least one prior therapy including lenalidomide and a proteasome inhibitor with disease progression on or within 60 days after the end of the lenalidomide therapy. Patients were treated with the IPd triplet, and isatuximab was either administered as 1400 mg subcutaneously (Isa-SC + PD arm) or 10 mg/kg intravenously (Isa-IV + PD arm). Treatment was administered in 28-day cycles until disease progression or unacceptable toxicity. Isatuximab was administered weekly in the first cycle and every two weeks thereafter.

A total of 531 patients were randomized in a 1:1 ratio to Isa-SC + PD (N=263) or Isa-IV + PD (N=268). Randomization was stratified by body weight (≤65 kg, >65-≤85 kg, >85 kg), myeloma isotype (IgG versus non-IgG), and the number of prior lines of therapy (1-2 versus ≥3).

Efficacy was analysed in the ITT population. IRAKLIA was designed to demonstrate non-inferiority of treatment with Isa-SC versus Isa-IV based on the co-primary efficacy endpoint ORR (NI margin 0.6312) and the PK endpoint of C_{trough} at steady state (corresponding to predose at Cycle 6 Day 1; NI margin 0.80). Safety data were derived from a pooled safety analysis including all five studies in which Isa-SC was tested: Phase 3 studies EFC15951 and IIT17041, Phase 2 studies ACT17453 and IIT17756, and Phase 1 study TCD15484, bringing the total safety population to 522 subjects.

9.3. Favourable effects

One pivotal study is deemed sufficient to assess the non-inferiority of Isa-SC over Isa-IV and is thereby sufficient to bridge the SC formulation to all indications of the IV formulation. The pivotal study (EFC15951; IRAKLIA) met its co-primary endpoints:

The ORR was 71.1% in the Isa-SC arm and 70.5% in the Isa-IV arm; relative risk = 1.008 (95% CI: 0.903 to 1.126). The lower limit of the 95% CI is higher than the pre-defined non-inferiority margin. Sensitivity analyses for ORR were consistent with the co-primary ORR analysis results. Subgroup analyses for the majority of the prespecified subgroups showed consistent results with the primary ORR analysis in the overall ITT population.

The mean±SD $C_{trough,SS}$ (Cycle 6 Day 1 pre-dose) was higher for Isa-SC (499±259 µg/mL, N=121) than for Isa-IV (340±169 µg/mL, N=121), and the corresponding geometric mean ratio for C_{trough} was 1.532 (90% CI: 1.316-1.784). Non-inferiority of the PK of Isa-SC over Isa-IV was confirmed.

Secondary endpoints of the IRAKLIA trial were supportive of the co-primary endpoints in terms of non-inferiority on VGPR+ rate (46.4% in the Isa-SC arm and of 45.9% in the Isa-IV arm) and mean±SD of the C_{trough} of isatuximab at 4 weeks (21±215 µg/mL in the Isa-SC arm compared to 302±117 µg/mL in the Isa-IV arm). Additionally, a significantly lower incidence of systemic IRs induced by isatuximab was observed in the Isa-SC arm (1.5% compared 25.0% for the Isa-IV arm with a relative risk (95% CI) of 0.061 (0.022 to 0.164), p<0.0001)

9.3.1. Uncertainties and limitations about favourable effects

While Isa-IV is dosed based on body weight, Isa-SC is administered as a flat dose, which may skew isatuximab PK in the extremes of the body weight categories. The popPK model revealed body weight as a significant covariate influencing Isa-SC PK. The ORR in this subgroup ("> 100 kg") was substantially

lower in the Isa-SC arm compared to the Isa-IV arm (68.2% versus 86.4%). However interpretation of efficacy data were impeded by the low number of patients and differences in baseline and disease characteristics. Therefore, a warning for a potential reduced efficacy in patients with bodyweight> 100 kg in the SmPC is warranted.

Study ACT17453 (IZALCO) was the only study in which SC delivery was compared between the OBDS and manual SC administration. The cross-over design and limited sample size of the study prevents interpretation of the efficacy of manual injection versus administration via the OBDS, but no indication of a PK effect between both administration methods was observed.

9.4. Unfavourable effects

The safety database and exposure is considered sufficient for safety evaluation of Isa-SC. Data from 2 controlled studies and a pooled dataset has been presented.

The randomised study EFC15951(IRAKLIA) showed a consistent safety profile between IV and SC administration, with the exception of any injector device related TEAE (any grade) in 3.4% for the SC administration (9 participants). For study IIT17041 (GMMG-DH8) more variation between SC and IV was observed, which is likely exacerbated by the smaller sample size. In general the absolute difference between SC and IV is small.

TEAEs leading to permanent full discontinuation occurred in similar proportion of patients between SC and IV arms (study EFC15951 and IIT17041). In the All Isa-SC pool, 6.3% participants had TEAE leading to permanent full discontinuation mostly due to Grade ≥3 events in the SOC infections.

In study EFC15951 and IIT17041, the incidence of the most frequently reported TEAEs for Isa-SC, at the PT level, was generally similar between SC and IV. A difference of >10% between SC and IV was only observed for infusion reactions (1.9% versus 25.0%; study EFC15951). The incidence of the most frequent TEAE differed per backbone regimen with neutropenia most frequently observed with the Isa-SC+Pd, upper respiratory tract infection with Isa-SC+Kd, and cytopenia (neutropenia, lymphopenia) for the VRd combination.

Overall treatment-emergent SAEs were reported at a similar incidence between the SC and IV administration in study EFC15951, whereas in study IIT17041 the incidence was slightly higher in the SC arm (38.8%) vs IV arm (32.4%), likely enlarged due to small sample size.

In study EFC15951 the proportion of patients with grade 3 neutropenia was similar between SC and IV, in study IIT17041 this was slightly higher in the SC arm (29.9 vs 19.7%) but did not results in a more neutropenic complications. In the All Isa-SC pool, a higher incidence was reported in the patients treated with pomalidomide. Three (1.0%) participants in Isa-SC+Pd had neutropenic complications with fatal outcomes during the treatment period.

Grade ≥3 infections were observed in 26.2% participants in the all-IsaSC pool, with the highest incidence in the Isa-SC+Pd cohort, pneumonia was most frequently reported (app. 12%). There was no difference between SC and IV formulation in study EFC15951 and IIT17041. In the All Isa-SC group 31 (6.1%) participants experienced a TEAE related to the OBDS (all grades). The most frequently reported TEAE was injection site reaction (17 [3.5%]) participants; none of the ISRs were Grade ⩾3 events.

As expected, the number of injection site reactions was higher in SC vs IV arm (study EFC15951 and IIT17041). Injection site reactions with Isa-SC were reported in 11.9% (all Isa-SC pool) which represents app. 1.5% of the injections given, the ISR were of low grade (no grade 3 events) and mostly resolved within one day.

The incidence of systemic infusion reactions was lower in the SC arm than in the IV arm (study EFC15951 and IIT17041). Systemic IR were reported in 3.1% participants in the Isa-SC pool, mainly related reaction of Grade 1 or Grade 2.

9.4.1. Uncertainties and limitations about unfavourable effects

The MAH aims to register the SC formulation with the option of administering the drug through the OBDS or via manual injection. Both administration methods are stated in SmPC section 4.2. Insufficient information has been presented to conclude how the safety (e.g. injection reactions) of the OBDS compares to manual injection. Based on PK, the difference between manual and OBDS administration is limited. Since there is no indication of a PK effect when comparing both methods of administration, and since it is not likely that efficacy and safety will differ substantially between manual injection and OBDS administration, this uncertainty can be accepted.

9.5. Effects Table

Table 48: Effects Table for Isatuximab 1400 mg for subcutaneous injection (data cut-off study EFC15951: 06 Nov 2024. Median follow-up time:12 months).

Effect (short description)	Isatuximab SC 1400 mg	Isatuximab IV 10 mg/kg	Uncertainties/ Strength of evidence	Ref
Favourable Effects				
Overall response rate (sCR, CR, VGPR or PR; evaluated by an IRC using the IMWG response criteria)	187/263 (71.1%)	189/268 (70.5%)	**SoE:** Relative risk [95% CI] vs Isa-IV = 1.008 [0.903 to 1.126]; Estimated using Farrington-Manning method. Non-inferiority was met, as the lower limit of the 95% CI is greater than 0.839. Supported by similar PK including co-primary endpoint of C_{trough} at steady state. **Unc:** subgroup analyses based on weight are not consistent with effect in full population.	Study EFC15951
Unfavourable Effects				
Effect (short description)	Isatuximab SC N=263	Isatuximab IV N=264	Uncertainties/ Strength of evidence	Ref
Injection site reactions	11 (4.2)%	0	Low grade, resolution within one day. TEAE related to the OBDS were injection related (erythema, rash, bruising, pain, etc)	Study EFC15951
Infusion related reactions	4 (1.5%)	66 (25%)	Low grade, resolved within 3 days. All Isa-SC pool: 3.1%	

Grade ≥3 infections	94 (35.7%)	87 (33.0%)	Pneumonia most reported. No difference between SC and IV in IIT17041. Grade ≥3 infections were observed in 26.2% participants in the all-IsaSC pool	Study EFC15951

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; PR: partial response; IRC: independent review committee; IMWG: international myeloma working group; CI: confidence interval; SC: subcutaneous; IV: intravenous; TEAE: treatment-emergent adverse event; PT: preferred term; Isa: isatuximab; Pd: pomalidomide + dexamethasone

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

In the present submission, non-inferiority of the isatuximab SC formulation compared to the IV formulation in terms of efficacy and PK has been demonstrated. The safety profile of both methods of administration was similar. The SC formulation differed from the IV formulation in terms of lower systemic infusion reactions, offset by more frequent low grade injection site reactions.

9.6.2. Balance of benefits and risks

Isatuximab, administered as an IV infusion, has a favourable balance of benefits and risks in RRMM, and NDMM. This can be extrapolated to the proposed new SC route of administration as there are no substantial differences in the PK, safety and efficacy between the IV and SC formulations.

9.7. Benefit-risk conclusions

9.7.1. At Day 210 –CHMP conclusions

The B/R for the SC formulation of isatuximab is positive.

Non-inferiority to the IV formulation has been adequately demonstrated. Thereby, it is justified that the same indications are granted to isatuximab SC as had already been granted to isatuximab IV.