AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A randomized, Phase 3, open label study evaluating subcutaneous versus intravenous administration of isatuximab in combination with pomalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma (RRMM)**
Protocol number:	**EFC15951**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR650984 isatuximab/SARCLISA®**
Brief title:	**SC versus IV isatuximab in combination with pomalidomide and dexamethasone in RRMM**
Acronym:	**IRAKLIA**
Study phase:	**Phase 3**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**82 Avenue Raspail, 94250 Gentilly, FRANCE**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	143013
NCT:	NCT05405166
WHO:	U1111-1261-5846
EUDAMED:	CIV-22-06-039616
EU trial number	2023-508869-32
Other:	Not applicable

Pediatric investigation plan: Not applicable

Date: 10-Jul-2024 Total number of pages: 219

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	10-Jul-2024, Version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	03-Oct-2023, Version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	15-Mar-2023, Version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	11-Oct-2022, Version 1 (electronic 1.0)
Original Protocol		17-Feb-2022, Version 1 (electronic 3.0)

Amended protocol 04 (10 July 2024)

This amended protocol 04 (amendment 04) is considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union because it does not significantly impact the safety or rights of the participants, and/or the reliability and robustness of the data generated in the clinical trial.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to implement language related to new CTA European regulation, to correct typos and few inconsistencies, and to provide few clarifications.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	The Legal registered address has been added.	New address
Title page	EudraCT was replaced by EU trial number 2023-508869-32. "Pediatric investigational plan number: Not applicable" was added in the Regulatory agency identifier number(s) table.	To comply with EU CTR.
Section 1.1 Synopsis	The subsection "Regulatory agency identifier number(s)" was added. The heading "Overall design" was renamed to "Overall design synopsis". The heading "Intervention groups" was renamed to "Study arms and duration". The heading "Non-Investigational Medicinal Products (Premedication)" was renamed to "Auxilliary Medicinal Products (Premedication)".	To comply with recent update of Sanofi protocol template language.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA), Table 1, Footnote y and z	First and second sub-pointers in foontnote y and z updated replacing “or initiation of further anti-myeloma therapy” by “even if further anti-myeloma therapy is started before PD”.	To correct inconsistency between SoA table, footnotes y and z versus footnote d of the SoA and Section 4.5.
Section 6 Study intervention(s) and concomitant therapy	The text of this section was updated.	To comply with EU CTR.
Section 6.1.2 Auxillary medicinal products	The Section 6.1.2 “Non investigational medicinal products” was renamed to “Auxillary medicinal products”. The ATC codes for all standard premedication regimens were added.	To comply with EU CTR.
Section 6.2.1 Responsibilities	The sentence "study treatment" was updated by “IMP/AxMP/device” in this section.	To comply with EU CTR.
Section 6.5.5 Management of infusion reactions and injection site reactions	The text of Table 15 was updated as follows: ISRs: If during administration: Interrupt isatuximab administration and resume only with an administration with pauses after recovery to G1 or better. Report AE and AESI. In case the reaction occurs during the D-15 at-home administration, definitely stop the at-home injection and contact investigator site.	Applicable for manual push which is not method of administration in the study.
Section 6.5.6 Tumor lysis syndrome	The text of Table 17 was updated as follows: Laboratory TLS: ≥2 simultaneous abnormalities within 3 days prior to and up to 7 days after treatment start: • Uric acid >8 mg/dL (>475.8 µmol/L). • Potassium >6.0 mmol/L. • Phosphate >4.5 mg/dL (>1.5 mmol/L). • Corrected calcium <7.0 mg/dL (<1.75 mmol/L), ionized calcium <1.12 mg/dL (0.3 mmol/L).	To correct typo errors.
Section 6.7 Treatment of overdose	The text of this section was updated.	To comply with EU CTR.
Section 6.8 Prior and concomitant therapy	The Section “6.8 Prior and concomitant therapy” was added.	To comply with recent update of Sanofi protocol template language.
Section 7.2 Participant discontinuation/ Withdrawal from the Study	A few modifications were done in the Section 7.2 “Participant discontinuation/ Withdrawal from the Study” to clarify the procedures of participant discontinuation/withdrawal from the study.	To comply with recent update of Sanofi protocol template language.
Section 7.3 Lost to follow up	The phrase “he or she” was replaced by “the participant”.	To comply with EU CTR.

Section # and Name	Description of Change	Brief Rationale
Section 8 Study assessmets and procedures	The following bullet was added: "In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements [see Appendix 9 (Section 10.9)]."	To comply with EU CTR.
Section 8.1 Administrative [and general/baseline] procedures	The Section 8.1 "Administrative [and general/baseline] procedures was added".	To comply with EU CTR.
Section 8.2 Efficacy assessments	Section 8.2 updated replacing "or initiation of further anti-myeloma therapy" by "even if further anti-myeloma therapy is started before PD".	To correct inconsistency between Section 8.2 versus footnote d of the SoA and Section 4.5.
Section 8.4.4 Clinical safety laboratory tests	The text of this section was updated.	To comply with EU CTR.
Section 8.6 Adverse events (AEs), serious adverse events (SAEs) and other safety reporting	The text of this section was updated.	To comply with EU CTR.
Section 8.6.1 Time period and frequency for collecting AE and SAE information	The sentence "he or she" was replaced by "Investigator".	To comply with EU CTR.
Section 8.6.6 Adverse event of special interest	The overdose definition was moved from "Section 8.6.6 Adverse event of special interest" to "Section 6.7 Treatment of overdose".	To comply with EU CTR.
Section 8.6.7 Medication errors or misuses of medicinal product	The Section "8.6.7 Medication errors or misuses of medicinal product" was added.	To comply with EU CTR.
Section 8.6.8 Guidelines for reporting product complaints	The abbreviation "NIMP" was replaced by "AxMP".	To comply with EU CTR.
Section 8.9 Immunogenicity assessments	The text of this section was updated.	To comply with recent update of Sanofi protocol template language.
Section 8.12 Use of biological samples and data for future research	Major updates were done in this section for the collection, storage and future use of biological samples from clinical trial subjects. Additional details were included.	To comply with EU CTR Additional details were included for better clarification.

Section # and Name	Description of Change	Brief Rationale
Section 10.1.1 Regulatory and ethical considerations	Language from the previous EU directive was replaced with new language from the new EU regulation.	To comply with EU CTR.
Section 10.1.3 Informed consent process	The text of this section was updated.	To comply with EU CTR.
Section 10.1.4 Data Protection	The subsection “Protection of participant data” was renamed to “Protection of participant personal data”. Two bullet points were added in the “Protection of participant personal data” subsection. Small modifications were done (eg “participants” instead of “the participant”, addition of “when applicable” etc). The subsection “Protection of data related to professionals involved in the study” was renamed to “Protection of personal data related to professionals involved in the study”. The link of the TransCelerate Investigator Registry (IR) project was added. The address was changed from “54 rue La Boétie 75008” to “46 avenue de la Grande Armée – 75017”.	To comply with EU CTR.
Section 10.1.6 Dissemination of clinical study data and results	The Section 10.1.6 “Dissemination of clinical study data” was renamed to “Dissemination of clinical study data and results”. The following 2 sentences were added to this section: “At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use “coded” data of all the study participants to independently verify the study’s results.” “For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).” In the subsection “Professionals involved in the study or in the drug development program” the guidance “Implementation of Drug Clinical Trial Information Registration and Disclosure (‘Notification No. 28’)” was renamed to “Drug Clinical Trial Registration and Information Disclosure ‘Management Practice (Trial Implementation)’”.	To comply with EU CTR.
Section 10.1.8 Source documents	The text of this section was updated.	To comply with EU CTR.
Section 10.1.9 Study and site start and closure	The text of the subsection “First act of recruitment” was updated.	To comply with EU CTR.
Section 10.3.1 Definition of AE	The phrase: “or more severe than expected for the participant’s condition” was added at the first bullet point. The bullet point: “Signs, symptoms, or the clinical sequelae of any medication errors and misuse with the IMP” was added.	To comply with EU CTR.
Section 10.3.2 Definition of SAE	A few modifications were done in the “f) Other situations subsection”.	To comply with EU CTR.

Section # and Name	Description of Change	Brief Rationale
Section 10.3.3 Recording and follow-up of AE and/or SAE	In the subsection "Assessment of intensity" the definitions of mild, moderate and severe AEs and SAEs were updated. In the subsection "Assessment of causality" the following bullet points were updated: • For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products. • The Investigator must review and provide an assessment of causality for each AE/SAE, and document this in the medical notes. • There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.**	To comply with EU CTR.
Section 10.7 Appendix 7: Medical devices AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies	The Section 10.7 Appendix 7: "AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies" was renamed to "Medical devices, AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies".	To comply with EU CTR.
Section 10.7.4 Recording and follow-up of medical device, AE and/or SAE and device deficiencies	The Section 10.7.4 "Recording and follow-up of AE and/or SAE and device deficiencies" was renamed to Section 10.7.4 "Recording and follow-up of medical device AE and/or SAE and device deficiencies". In the subsection "Assessment of intensity" the definitions of mild, moderate and severe AEs and SAEs were updated. In the subsection "Assessment of causality" the following bullet points were updated: • The Investigator will also consult the Investigator's Brochure (IB) and Product Information, for marketed products, as part of the assessment. • The Investigator must review and provide an assessment of causality for each AE/SAE/device deficiency, and document this in the medical notes. The subsection "Follow-up of AE/SAE/device deficiency" was renamed to "Follow-up of medical device AE/SAE/device deficiency".	To comply with EU CTR.

Section # and Name	Description of Change	Brief Rationale
Section 10.7.5 Reporting of medical device SAEs	The Section 10.7.5 “Reporting of SAEs” was renamed to Section 10.7.5 “Reporting of medical device SAEs”. The subsection “SAE reporting to the Sponsor via an electronic data collection tool” was renamed to “Medical device SAE reporting to the Sponsor via an electronic data collection tool”.	To comply with EU CTR.
Section 10.8 Appendix 8: Country-specific/region requirements	The Section 10.8 Appendix 8 “Country-specific requirements” was renamed to Section 10.8 Appendix 8 “Country-specific/region requirements”.	To comply with EU CTR.
Section 10.10 Appendix 10: Collection, storage and future use of data and human biological samples	The Appendix “Collection, storage and future use of data and human biological samples” was added.	To comply with EU CTR.
Section 10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)	The Section 10.10.1 “Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)” was added.	To comply with EU CTR.
Section 10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014)	The Section 10.10.2 “Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014)” was added.	To comply with EU CTR.
Throughout	Minor editorial, typographical error corrections and document formatting revisions	Minor, therefore, have not been summarized.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A randomized, Phase 3, open label study evaluating subcutaneous versus intravenous administration of isatuximab in combination with pomalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma (RRMM)

Brief title:

SC versus IV isatuximab in combination with pomalidomide and dexamethasone in RRMM

Regulatory agency identifier number(s):

IND:	143013
NCT:	NCT05405166
WHO:	U1111-1261-5846
EUDAMED:	CIV-22-06-039616
EU trial number	2023-508869-32
Other:	Not applicable

Pediatric investigation plan: Not applicable.

Rationale:

The combination of intravenous (IV) isatuximab with pomalidomide and dexamethasone has demonstrated clinical efficacy with an acceptable and manageable safety profile in the ICARIA-MM (NCT02990338) Phase 3 trial. In 2020, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) granted approval to this combination for the treatment of adults with RRMM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI).

Isatuximab IV administration is approved with the fixed-volume infusion method allowing the IV infusion to be given during 75 minutes from the 3rd infusion onwards. A subcutaneous (SC) administration within several minutes allows for a shorter duration of administration compared to the currently approved IV route with the intent to optimize the convenience of administration, enhance comfort and quality of life of the patients, and reduce health care resources. Therefore, SC administration of isatuximab is considered as a desirable alternative to the current approved IV administration, in particular for the long duration of treatment required in multiple myeloma (MM).

Device-mediated SC administration can offer a number of benefits to both health care professionals (HCPs) and patients, including controlled delivery and simplified user interface, and could ultimately be used by a qualified HCP in the outpatient setting or at patient's home.

The EFC15951 study is proposed to evaluate SC administration of isatuximab versus IV, in combination with pomalidomide and dexamethasone (Pd) using an Investigational injector device in participants with MM who have received at least one prior line of therapy including lenalidomide and a PI.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• Demonstrate the efficacy non-inferiority between isatuximab SC and isatuximab IV in combination with Pd.	• Overall response rate (ORR): defined as the proportion of participants with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) according to the 2016 International Myeloma Working Group (IMWG) criteria assessed by Independent Review Committee (IRC).
• Demonstrate the pharmacokinetic (PK) non-inferiority between isatuximab SC and isatuximab IV in combination with Pd.	• Observed concentration before dosing (C_{trough}) at steady state (corresponding to predose at C6D1).
Secondary	
Key Secondary	
• Demonstrate the efficacy non-inferiority between isatuximab SC and isatuximab IV in combination with Pd.	• Very Good Partial Response or better rate: defined as the proportion of participants with sCR, CR, and VGPR according to the 2016 International Myeloma Working Group (IMWG) criteria assessed by IRC.
• Demonstrate the PK non-inferiority between isatuximab SC and isatuximab IV in combination with Pd.	• Observed concentration before dosing (C_{trough}) at 4 weeks (ie, CT4W corresponding to predose at C2D1).
• Assess safety of isatuximab SC and IV in combination with Pd.	• Incidence rate of infusion-reactions (IRs).
• 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 patient experience and satisfaction questionnaire (PESQ).
Other Secondary	
• Assess efficacy of isatuximab SC compared to isatuximab IV in combination with Pd.	• Duration of response (DOR): defined as the time from the date of the first response to the date of first occurrence of progressive disease (PD) as determined by IRC or death from any cause, whichever happens first. DOR is determined only for participants who have achieved a response (PR or better). In the absence of PD or death before the analysis cut-off date, the DOR will be censored at the date of the last valid disease assessment performed prior to initiation of a further anti-myeloma treatment or the analysis cut-off date, whichever is earlier. Patients with two or more consecutive missed assessments prior to PD or death will be censored at the last valid disease assessment. Details about censoring rule will be provided in statistical analysis plan (SAP). • Time to first response (TT1R): defined as the time from randomization to the date of first IRC determined response (PR or better) that is subsequently confirmed. Details about censoring rule will be provided in SAP.

Objectives	Endpoints
	• Time to best response (TTBR): defined as the time from randomization to the date of first occurrence of IRC determined best overall response (PR or better) that is subsequently confirmed. Details about censoring rule will be provided in SAP. • Progression free survival (PFS): defined as the time from the date of randomization to the date of first documentation of PD as determined by IRC or the date of death from any cause, whichever comes first. Responses will be determined according to IMWG criteria. Progression based on paraprotein will be confirmed based on two consecutive assessments. PFS will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first. Patients with two or more consecutive missed assessments prior to PD or death will be censored at the last valid disease assessment. Details censoring rule will be provided in the SAP. • Overall survival (OS): defined as the time from the date of randomization to death from any cause. Participants without death prior to the analysis cut-off date will be censored at the last date the participant was known to be alive or the cut-off date, whichever is first. Details censoring rule will be provided in SAP. • PFS2: defined as time from the date of randomization to the date of first documentation of PD (as assessed by investigator) after initiation of further anti-myeloma treatment or death from any cause, whichever happens first. Same censoring rule applies as in the PFS endpoint.
• Assess safety of isatuximab SC and IV and local tolerability of isatuximab SC in combination with Pd.	• Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs). Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) that develop, worsen (according to the Investigator opinion), or become serious during the treatment period. The treatment period is defined as the time from first dose of study treatment up to 30 days after last dose of study treatment. • Laboratory parameters. • Injection site reactions (ISRs) – SC arm only. • Adverse events and laboratory parameters will be graded using NCI CTCAE v5.0.
• Characterize PK of isatuximab SC and IV in combination with Pd.	• PK concentrations.
• Assess the delivery performance of the (investigational) device injector.	• Number of successful injections with (investigational) isatuximab injector device defined as completion of administration per provided instructions for use with no use errors or technical issues, divided by the total number of injections.
• Assess the potential immunogenicity of isatuximab SC and IV in combination with Pd.	• Incidence of participants with anti-drug antibodies (ADA) against isatuximab

Objectives	Endpoints
• Assess the clinical outcome of isatuximab SC and IV in combination with Pd.	• Patient expectation at baseline and experience/satisfaction with Isatuximab will be assessed using the patient expectation questionnaire (PEQ), the patient experience and satisfaction PESQ, and the patient's assessment of treatment (PAT) questionnaires. • Health Resources Utilization will be assessed using the Health Resource Utilization and Productivity Questionnaire (HRUPQ). • Health-related quality of life will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) myeloma module with 20 items (QLQ-MY20) and EORTC quality of life questionnaire with 30 questions (QLQ-C30). • Health status will be assessed using the European Quality of Life Group questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L).
• Explore chromosomal abnormalities [mainly but not limited to t(4;14), t(14;16), del(17p) and gain(1q21+)], and potential association with clinical outcomes.	• Impact of abnormal cytogenetic subtypes on participant outcome.

For China, please see Section 10.8 details.

Overall design synopsis:

The study design, number of participants, study treatments and duration are described below.

Brief summary:

This is a randomized, multicenter, Phase 3, open-label study evaluating SC versus IV administration of isatuximab in combination with pomalidomide and dexamethasone (IsaPd) in RRMM patients (study participants) who have received at least 1 prior line of therapy including lenalidomide and a PI. The randomization will be stratified by 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). Eligible participants (approximately 534) will be randomized 1:1 into 1 of 2 study arms:

- Arm SC: Isatuximab SC at 1400 mg with device injector (N = 267).
- Arm IV: Isatuximab IV 10 mg/kg (N = 267).

The efficacy co-primary analysis will be conducted on the Intent-to-Treat (ITT) population, defined as all participants who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the interactive response technology (IRT). Participants will be included in a treatment arm as randomized, regardless of whether participants receive any study drug or receive a different study drug from which they were randomized. The PK co-primary analysis will be conducted on the Per Protocol-PK (PP-PK) population defined as all randomized participants who 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.

After the first 5 cycles, a home administration by an HCP may be proposed to the participants in the SC arm on D15 from Cycle 6 onwards. Visits at Day 1, on the other hand, from C6 onwards will always be outpatient visits at clinic. The decision to propose at home administration on D15 will be based on the absence of infusion reaction (IR) at C4 and C5, the hematology test at Day 1 of each corresponding cycle and the Investigator's judgement. Participant willingness and ability to adhere to the requirements of home administration need to be taken into account before initiating it.

Myeloma response and progression will be determined by the Independent Review Committee (IRC) based on central laboratory M protein analysis and central radiology review using IMWG 2016 criteria.

The cut-off date for the primary analysis is approximately 6 months after the Last Patient In (LPI), which includes analysis on the primary endpoints and secondary endpoints when applicable. There will be an update of PFS and OS analysis approximately 15 months after LPI, and then the cut-off date for final OS analysis will be approximately 30 months after LPI.

Number of participants:

Approximately 534 participants will be randomized to investigational intervention for 267 randomized participants in Arm SC and 267 randomized participants in Arm IV.

Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Study arms and duration:

Study interventions

Investigational Medicinal Products

Isatuximab SC (Arm SC):

- Formulation: The drug product is presented as a solution in a vial containing 10 mL (as extractable volume) at a concentration of 140 mg/mL.
- Route of administration: SC, using investigational device injector. The volume to be injected at each administration will be injected at a single site in the periumbilical region.
- Each cycle will be 28 days in duration.
- Dose regimen (Cycle 1): Isatuximab will be administered at the nominal dose of 1400 mg SC weekly for 4 weeks during Cycle 1 (Days 1, 8, 15, and 22).
- Dose regimen (Cycle 2 and onwards): Isatuximab will be administered at the nominal dose of 1400 mg SC on Day 1 and Day 15 of each subsequent cycle.
- From Cycle 6 onwards, the Day 15 administration may be performed at home by an HCP.

Isatuximab IV (Arm IV, per its currently approved dose, schedule, and infusion method):

- Formulation: The drug product is presented as a concentrate for solution for IV infusion in vials containing 20 mg/mL (500 mg/25 mL and 100 mg/5 mL).
- Route of administration: Intravenous with a fixed-volume infusion method.
- Each cycle will be 28 days in duration.
- Dose regimen (Cycle 1): Isatuximab will be administered at the dose of 10 mg/kg IV weekly for 4 weeks during Cycle 1 (Days 1, 8, 15, and 22).
- Dose regimen (Cycle 2 and onwards): Isatuximab will be administered at the dose of 10 mg/kg on Day 1 and Day 15 of each subsequent cycle.

Pomalidomide (both arms):

- Route of administration: Oral.
- Dose regimen: 4 mg on Days 1 to 21 of each cycle. Pomalidomide will be taken at the time that is the most convenient for the participants prior to or after isatuximab administration, preferably at the same time every day.

Dexamethasone (both arms):

- Route of administration: Oral.
- Dose regimen: 40 mg (or 20 mg for participants ≥75 years) on Days 1, 8, 15, and 22 of each cycle.

Dexamethasone will also have the intent of premedication for IRs. On the day of co-administration with isatuximab, dexamethasone will be given prior to isatuximab as part of premedication.

Auxilliary Medicinal Products (Premedication)

At least 15 to 30 minutes (but no longer than 60 minutes) prior to isatuximab administration (regardless of route):

- Montelukast 10 mg orally (or equivalent, Cycle 1 only).
- Acetaminophen/paracetamol 650 to 1000 mg orally.
- Diphenhydramine 50 mg orally (or equivalent: eg, cetirizine, promethazine, dexchlorpheniramine, according to the approval availability) or Diphenhydramine 25-50 mg IV (or equivalent). Intravenous route is preferred for at least the first 4 IV isatuximab infusions.

The order of premedication administration is the following:

- Montelukast, dexamethasone, acetaminophen/paracetamol, and then diphenhydramine.
- Dexamethasone oral (PO) will also be given in the same dose as stated in Section 6.1.1.
    - Methylprednisolone (or equivalent):100 mg IV if dexamethasone is discontinued earlier than isatuximab and premedication is still needed.

- Participants who do not experience IRs after 4 consecutive administrations of isatuximab may have their need for subsequent premedication reconsidered at the Investigator's discretion, except montelukast that should be administered only on Cycle 1.

Device

The (investigational) isatuximab injector device is a sterile, single-use, disposable, elastomeric, user filled wearable injector. The (investigational) isatuximab injector device includes an adhesive backing to secure it to the injection site during administration. Injection sites with the device are permitted only on the abdominal region. At the end of dosing, the injection needle retracts into the device housing and the device enters a locked-out state to prevent reuse. Further instructions are provided in the study pharmacy manual.

Duration of study intervention

Before the final OS analysis cutoff date, participants will be allowed to continue therapy until disease progression, unacceptable adverse events (AEs), participant request to discontinue treatment or any other reason, whichever is first. After the final OS analysis cutoff date, participants will be allowed to continue therapy until disease progression, unacceptable adverse events (AEs), participant request, study treatment is commercially available and reimbursed in the participant's country, switch to a long-term safety study, or any other reason, whichever is first.

Statistical considerations:

Sample size calculation

A total sample size of 534 participants (randomization ratio 1:1, ie, 267 randomized 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 C_{trough} at steady state (corresponding to predose at C6D1). For the co-primary efficacy endpoint of ORR, the non-inferiority test for non-unity null according to Farrington and Manning (1990) 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% confidence interval [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 is 1.02 for SC arm over IV arm. For the PK co-primary endpoint of C_{trough} at steady state (corresponding to predose at C6D1), assuming C_{trough} 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 population, 534 randomized participants will provide at least 86% power to show the lower bound of the 90% CI of the geometric mean ratio of C_{trough} at steady state is at least 80% (a non-inferiority margin of 80%). Calculations were made based on SAS 9.4 (1).

Main analysis populations

Intent-to-treat (ITT) population

The ITT population is the randomized population. All participants who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the IRT will be included in this population. Participants will be analyzed 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.

This population will be used for the analysis of the co-primary efficacy endpoint.

All efficacy analyses will be performed on this population.

Safety Population

The safety population will include ITT participants who have received at least 1 dose or a part of a dose of the study intervention. All analyses using this population will be based on the treatment actually received.

All safety analysis will be performed on this population.

PP-PK population

The PP-PK population will include 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 population will be used for the analysis of the co-primary PK endpoint.

CT4W-PK population

The CT4W - PK population for CT4W endpoint will include 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 population will be used for the analysis of the CT4W PK endpoint.

Primary analysis

The number and proportion of participants who achieve ORR per IRC assessment will be calculated for each group. The relative risk of Isa-SC + Pd relative to Isa-IV + Pd and its two-sided 95% CI using Farrington and Manning method will be provided. If the lower bound of the 95% CI is not less than a non-inferiority margin of 0.839, the non-inferiority of efficacy Isa-SC + Pd relative to Isa-IV + Pd will be concluded.

For the co-primary PK endpoint of C_{trough} at steady state (ie, C6D1 predose), summary statistics such as geometric means, coefficient of variation, median and range will be provided for treatment group. The ratio of the geometric means of Isa -SC + Pd relative to Isa-IV + Pd and corresponding two-sided 90% CI will be provided be provided 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 will be concluded if the lower bound of the 90% CI for the geometric mean ratio of C_{trough} at steady state is at least 80% (a non-inferiority margin of 80%).

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

Analysis of key secondary endpoints

If the co-primary endpoints are significant, the key secondary endpoints will be tested by hierarchical testing in the order of VGPR or better rate, CT4W, incidence rate of IRs, and the percentage of participants who reported satisfied or very satisfied with the injection method used to administer the study medication.

VGPR or better rate per IRC will be summarized for the ITT population in the same way as for ORR endpoint. The non-inferiority test for non-unity null according to Farrington and Manning (1990) will be 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 is 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 will be concluded.

The PK endpoint of CT4W will be summarized for the PP-PK population for CT4W in the same way as for the C_{trough} at steady state endpoint. The non-inferiority of Isa- SC + Pd relative to Isa-IV + Pd on CT4W will be concluded if the lower bound of the 90% CI for the geometric mean ratio of CT4W is at least 80% (a non-inferiority margin of 80%).

Incidence rate of IRs will 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 will be provided.

Percentage of participants who reported satisfied or very satisfied with the injection method used to administer the study medication based on the PESQ at C5D15 visit will be compared between treatment arms on the ITT population using the stratified Cochran–Mantel–Haenszel (CMH) method.

Analysis of other secondary endpoints

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 will be presented by treatment arm. The Kaplan-Meier PFS curves will also be provided. The Hazard Ratio (HR) estimated from the Cox proportional hazards model as well as its associated 95% CI will be provided too.

The analysis for PFS2, OS, DOR, and time-to-response (TTR) will be similar to that described for PFS per IRC assessment.

PK concentrations (C_{trough} and C_{eoi} - Isa-IV+Pd arm for C_{eoi} only-) will be summarized per arm with descriptive statistics. PK parameters and derived exposure will be summarized and provided in a separate report.

Number (and percentage) of participants experiencing TEAEs by primary system organ class and preferred term will be summarized by National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade (all grades and ≥Grade 3) for the safety population. The same summaries will be prepared for treatment related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, serious TEAEs and TEAEs with fatal outcome and ISRs. Second primary malignancies as an adverse event of special interest (AESI) will be reported throughout the study.

Hematology and biochemistry results will be graded according to NCI CTCAE v5.0. Number (and percentage) of participants with laboratory abnormalities (ie, all grades and ≥Grade 3) using the worst grade during the on-treatment period will be provided for the safety population.

Number of successful injections with investigational isatuximab injector device divided by total number of actual injections will be assessed.

Participant expectations at baseline, participant experience and satisfaction and assessment of treatment, and Health Resource Utilization and Productivity Questionnaires will be descriptively summarized.

Participant's health-related quality of life (influenced by both disease and treatment) will be assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma Module 20 (EORTC QLQ-MY20) via a comparison of change scores in C30 (individual symptom change scores) and MY20 (disease- and treatment-related summary scores) from baseline to follow-up between treatment arms. In addition, responder analyses will be conducted 1) for those who improve and 2) for those who deteriorate, utilizing the Clinically Important Differences (CIDs) for all individual symptom scores (C30) and disease- and treatment-related summary scores (MY20) for both treatment arms.

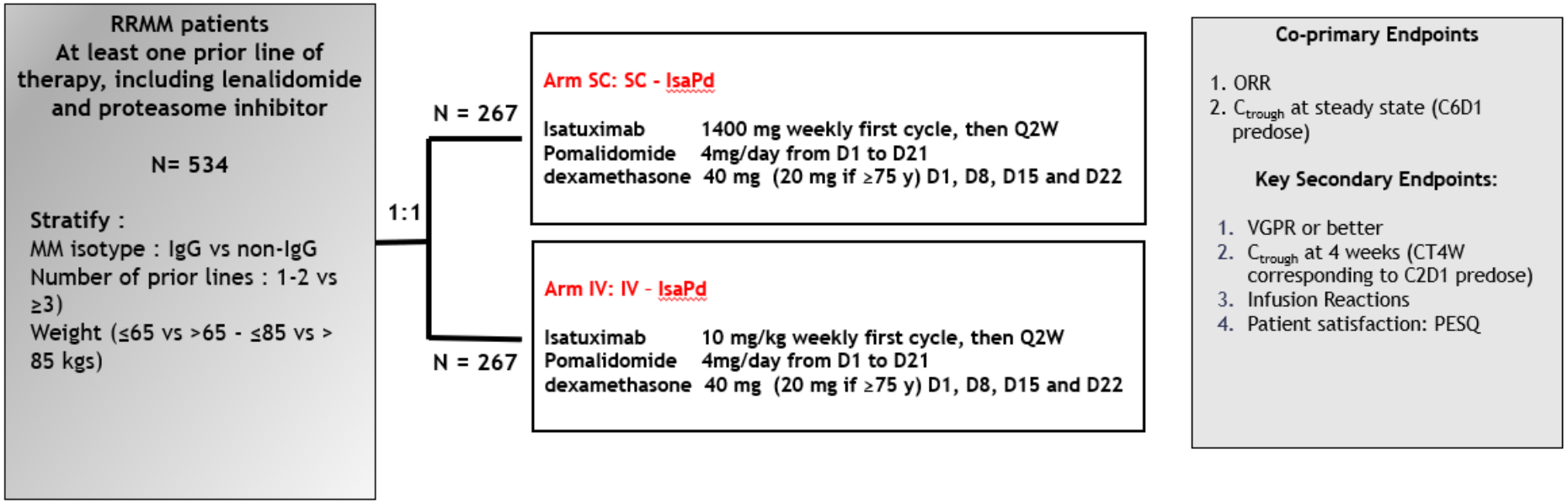
Health status (EQ-5D-5L, including Visual Analogue Scale [VAS]) will be assessed via a comparison of EQ-5D-5L health status change scores from baseline to follow-up between treatment arms. In addition, responder analyses will be conducted 1) for those who improve and 2) for those who deteriorate, utilizing the CIDs for health status VAS scores for both treatment arms.

Data Monitoring/Other committee: Yes

A Data Monitoring Committee (DMC) has been appointed for this study. The Data Monitoring Committee (board) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for harms. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. The data monitoring committee specific roles and interaction with the Sponsor will be described in the DMC charter.

1.2 SCHEMA

Figure 1 - Graphical study design



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

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1 - Schedule of activities

Evaluation/ Procedure[a]	Screening/Baseline	Cycle 1[ee]				Cycle 2[ee]		Subsequent cycles[ee]		End of treatment	Follow-up[d]	Notes
	Days -28 to -1	D1[c]	D8	D15[c]	D22	D1[c]	D15[c]	D1[c]	D15[c]	D30 (±5) after last study treatment administration or before the next therapy		D = Day
Informed consents[e]	X											
Training participants on ePRO technology		X										
Contraceptive counseling[f]	X	X										
Inclusion/exclusion criteria	X											
Randomization[b]	X											
Hepatitis B and C and HIV serologies[g]	X											As clinically indicated
Demography, medical/surgical and disease history[h]	X											
Performance status (ECOG)	X	X				X		X		X		ECOG = Eastern Cooperative Oncology Group
Prior/concomitant medication	Continuously throughout the study period (and within 21 days before first IMP administration)											
Isatuximab administration and administration data		X	X	X	X	X	X	X	X			
Pomalidomide[i]		D1 to D21				D1 to D21		D1 to D21				

Evaluation/ Procedure[a]	Screening/Baseline	Cycle 1[ee]				Cycle 2[ee]		Subsequent cycles[ee]		End of treatment	Follow-up[d]	Notes
	Days -28 to -1	D1[c]	D8	D15[c]	D22	D1[c]	D15[c]	D1[c]	D15[c]	D30 (±5) after last study treatment administration or before the next therapy		D = Day
Dexamethasone (before isatuximab when co-administered) [i]		D1, 8, 15, and 22				D1, 8, 15, and 22		D1, 8, 15, and 22				
Patient expectations Questionnaire (PEQ)[j]		X										
Patient experience and satisfaction Questionnaire (PESQ) and Patient's assessment of treatment (PAT) Questionnaire [k]			X	X	X	X	X	on D1 of Cycles 3 and 4	C5 up to EOT	X		
HRUPQ questionnaire		X	X	X	X	X			X	X		
EORTC QLQ-C30 and QLQ-MY20, EQ-5D-5L Questionnaires		X				X			X	X		
IADL and ADL questionnaires		X										
Physical examination[l]	X	X				X		X		X		
Weight (height at baseline)[m]	X	X	X	X	X	X	X	X		X		
Vital signs (HR, Temperature, RR or SPO2, BP)[n]	X	X	X									
Hematology[o]	X	X	X	X	X	X	X	X	up to C5	X		
Serum chemistry[p]	X	X	X	X		X		X		X		

Evaluation/ Procedure[a]	Screening/Baseline	Cycle 1[ee]				Cycle 2[ee]		Subsequent cycles[ee]		End of treatment	Follow-up[d]	Notes
	Days -28 to -1	D1[c]	D8	D15[c]	D22	D1[c]	D15[c]	D1[c]	D15[c]	D30 (±5) after last study treatment administration or before the next therapy		D = Day
PT/INR, PTT	X	As clinically indicated								X		PT/INR = prothrombin time/international normalized ratio PTT = partial thromboplastin time
Urinalysis[q]	X	As clinically indicated								X		
Thyroid function tests (TSH, and free T4)[r]	X	Once a year until EOT or as clinically indicated								X		TSH = thyroid-stimulating hormone EOT = end of treatment
Antibody screening test[s]	X					X						Antibody screening test: Blood typing and complete blood phenotyping and antibody screening
Pregnancy testing [FCBP][t]	X	X	X	X	X	X		X		X	X	FCBP = female of childbearing potential
AE/SAE reporting[u]	Continuously through the study period[v]										X (related AEs, all ongoing SAEs, second primary malignancy)	AE = adverse event SAE = serious adverse event

Evaluation/ Procedure[a]	Screening/Baseline	Cycle 1[ee]				Cycle 2[ee]		Subsequent cycles[ee]		End of treatment	Follow-up[d]	Notes
	Days -28 to -1	D1[c]	D8	D15[c]	D22	D1[c]	D15[c]	D1[c]	D15[c]	D30 (±5) after last study treatment administration or before the next therapy		D = Day
Local tolerability at injection site after isatuximab SC administration– participant assessment using diary[w]		Continuously throughout up to Cycle 9/D1										
Local tolerability at injection site after isatuximab SC administration – investigator assessment[x]		Continuously throughout the study period up to EOT visit										EOT = end of treatment
12 lead ECG	X	As clinically indicated								X		ECG = electrocardiogram
Extramedullary disease (plasmacytoma)[y]	X	If present at baseline									if EOT without progressive disease	EOT = end of treatment FAMT= Further Anti-Myeloma Therapy
Bone disease[z]	X	As clinically indicated									if EOT without progressive disease	FAMT= Further Anti-Myeloma Therapy
Bone marrow (BM) aspiration/biopsy for determination of % of plasma cells (local data)[aa]	≤21 days	As clinically indicated										

Evaluation/ Procedure[a]	Screening/Baseline	Cycle 1[ee]				Cycle 2[ee]		Subsequent cycles[ee]		End of treatment	Follow-up[d]	Notes
	Days -28 to -1	D1[c]	D8	D15[c]	D22	D1[c]	D15[c]	D1[c]	D15[c]	D30 (±5) after last study treatment administration or before the next therapy		D = Day
Myeloma-specific Lab tests (centralized)[bb]	X	X				X		X		X	If EOT without progressive disease assessment	
Bone marrow aspiration for cytogenetics assessment (central data)[cc]	X											
Bone marrow aspiration for MRD assessment (central data)[dd]	X	At time of confirmed CR or VGPR, 12 months after C1D1 and 12 months after first MRD negativity										CR = complete response MRD = minimal residual disease VGPR = very good partial response
Bone marrow aspiration for genomic and genetic profiling (central data)	X										At time of progression	
PK (isatuximab)		See PK/ADA Flowchart (Table 2 and Table 3)										
Immunogenicity (ADA)		See PK/ADA Flowchart (Table 2 and Table 3)										
Other	Follicle-stimulating hormone and estradiol (as needed in women of non childbearing potential only)											

Abbreviations: ADA = Anti-Drug Antibody; AEs = Adverse events; AESI = Adverse events of special interest; ALT = Alanine Aminotransferase; ANC = Absolute Neutrophil Count; anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; AP = Alkaline Phosphatase; AST = Aspartate aminotransferase; BMA = Bone marrow aspiration; BP= blood pressure; BUN = Blood urea nitrogen; C = Cycle; CBC = Complete blood count; CR = Complete response; CD38 = Cluster of differentiation 38; CT = Computed tomography; D = Day; DNA= deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-c30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-MY20 = Quality of Life Multiple Myeloma module; EQ-5D-5L= The European Quality of Life Group Questionnaire with 5 Dimensions and 5 Levels; EOT= end-of-treatment; FAMT= Further Anti-Myeloma Therapy; FCBP = Female of childbearing potential; FPG = Fasting plasma glucose; FISH= fluorescent in Situ Hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HRUPQ = healthcare resource utilization and productivity questionnaire; IAT = Indirect antiglobulin test; IFE= immunofixation; IgM = immunoglobulin M; IMWG= International Myeloma Working Group; INR = International Normalized Ratio; IR = Infusion reactions; IRT= Interactive Response Technology; ISR = Injection site reactions; IV = Intravenous; LDH= Lactate dehydrogenase; MDRD = Modification of Diet in Renal Disease; MRD = Minimal residual disease; MM = Multiple myeloma; MRI = Magnetic resonance imaging; PCR = polymerase chain reaction; PD= Progressive Disease; PAT = patient's assessment of treatment; PEQ = patient expectations questionnaire; PEQ-BL = patient

expectations questionnaire at baseline; PESQ = patient experience and satisfaction questionnaire; PET = Positron emission tomography; PK = Pharmacokinetic; PR = Partial response; PS = Performance status; PT = Prothrombin time; PTT = partial thromboplastin time; RNA= ribonucleic acid; RR= respiratory rate; sCR = stringent complete response; SC=Subcutaneous; SGOT = Serum glutamate-oxalate transferase; SGPT = Serum glutamate-pyruvate transferase; sFLC = Serum free light chain; SAE= serious adverse event; SPEP = Serum M-protein immunoelectrophoresis; TSH = Thyroid stimulating hormone; VGPR = Very good partial response; UPEP = Urine M-protein immunoelectrophoresis.

a **Evaluation:** Assessments to be performed prior to study treatment/premedication administration unless otherwise indicated. Results should be reviewed by the Investigator.

b **Randomization**: To take place once the consented participant has completed all the necessary screening procedures and is deemed eligible (based on assessments including myeloma specific results from central laboratory (see footnote "bb") and hematology/biochemistry local laboratory results) for randomization by the investigator or designee. All eligible participants must be randomized by contacting the Interactive Response Technology (IRT). Every effort should be made to start treatment within 3 working days of randomization.

c **Day 1 and Day 15 (28-day cycle [±3 day]):** Day 1 of Cycle 1 refers to the day the participants receive the first dose of study treatment administration. Day 1 of Cycle 2 corresponds to D29 of Cycle 1. Day 1 of each subsequent cycle corresponds to Day 29 (±3 day) of the previous cycle. Day 8 and Day 22 window (±1 day).

d **Follow-up**: Participants who discontinue study treatment due to disease progression will be followed every 3 months (12 weeks) (±7 days after last study treatment administration) for further antimyeloma therapy, second primary malignancies, PFS2, and survival until death, or final OS analysis cut-off date, whichever occurs first. Participants who discontinue the study treatment prior to documentation of PD will be followed up every 4 weeks until disease progression (even for participants who would initiate further antimyeloma therapy without PD), and then after confirmation of disease progression, every 3 months (12 weeks) for further anti-myeloma therapies, secondary malignancies, PFS2, and survival, until death or the final OS analysis cut-off date, whichever comes first. The information on the further antimyeloma therapy will consist of drug name, start and stop date, best overall response, and date of progressive disease.

e **Informed consent:** Informed consent should be signed before any study-specific procedures. It can be signed more than 28 days prior to inclusion. Screening time indicates in which time frame exams used to support eligibility have to be done prior to inclusion.

f **Contraceptive counseling**: Contraceptive counseling is to be done before initiation of each cycle prior to pomalidomide dispensing.

g **Hepatitis B and C and HIV serologies**: Screening with serological tests for hepatitis B, and C to be done prior to randomization/enrollment (HBsAg, anti-HBs, anti-HBc [total and IgM], anti-HCV, HCV RNA level) if not performed within 1 year. Participants with anti-HBc positive (HBsAg positive participants being ineligible), HBV DNA testing by PCR will also be done at baseline. In case HBV vaccination will be started before first study treatment administration, anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination. HIV serology will be tested at screening only for participants of countries where required as per local regulations.

h **Demography:** Includes age, gender, and race. **Medical/surgical history:** Includes relevant history of previous/associated pathologies other than multiple myeloma (MM) including smoking status. **Disease history:** Includes date of initial diagnosis, stage and extent of the disease, previous MM anti-tumor therapy (type and response to), disease status at inclusion, time on treatment, and duration of response.

i **Pomalidomide/Dexamethasone administration data:** Participants will be asked to maintain a diary to record the doses of pomalidomide/dexamethasone (except those administered by the study nurse/Investigator).

j **Patient Expectations Questionnaire (PEQ):** Patient Expectations Questionnaire (PEQ-BL) will be completed on Cycle 1/D1 by the participant at the site prior to discussing their health/disease status, and prior to study treatment administration or other study related procedures. The time estimated to complete this questionnaire is 5 minutes (Appendix 15, Section 10.16).

k **Patient experience and satisfaction Questionnaire (PESQ) and Patient's assessment of treatment (PAT) Questionnaire:** Patient Experience and Satisfaction Questionnaire-Follow-Up (PESQ-FU) will be completed on Cycle 1/D8, D15, D22, Cycle 2/D1, D15, Cycle 3/D1, Cycle 4/D1 and on Day 15 from Cycle 5 onwards. The overall patient experience and satisfaction questionnaire-end of treatment (PESQ-EOT) and PAT will be completed at the EOT visit by the participant at the site prior to discussing their health/disease status, or other study-related procedures. The time estimated to complete this questionnaire is 5 to 10 minutes (Appendix 15, Section 10.16).

l **Physical examination:** To be performed at screening, prior to study treatment administration on Day 1 of Cycle 1, and then on Day 1 of each subsequent cycle (a flexibility of a maximum of 24 hours before IMP administration is allowed), and at the EOT visit. Consists of examination of major body systems including neurological, digestive, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, and lymphadenopathy.

m **Weight:** Weight will be assessed for participants in both arms on screening, at each administration of Cycle 1 and 2, at D1 of subsequent cycles, and at EOT.

n **Vital signs:** Heart rate, temperature, respiratory rate (or pulse oximetry for at-home administration), and blood pressure to be assessed pre-administration, one hour after start of first administration and, for the IV arm only, 30 minutes after the start of the subsequent infusions. On site, vital signs are to be assessed at end of infusion/injection up to Cycle 5, and as clinically indicated. If at-home administration, vital signs are to be taken systematically just before and at the end of injection.

o **Hematology:** Complete blood count (CBC) to be performed weekly at Cycle 1, at D1 and D15 from Cycle 2 to Cycle 5 and at D1 only from Cycle 6 onwards, and to be reviewed by the Investigator within 1 working day before the day of dosing. If Grade 4 neutropenia is observed, the assessment of neutrophil count will be done every 2 to 3 days until ANC ≥0.5 $\times$ 10^9/L and at least weekly thereafter until ANC ≥1.0 $\times$ 10^9/L; platelet count can be assessed weekly or until ≥50 000/mm^3.

p **Serum chemistry:** To be performed and reviewed by the Investigator within 1 working day before the day of dosing. **Chemistry includes:** Fasting glucose, albumin, total protein, aspartate aminotransferase (AST) (serum glutamate-oxalate transferase [SGOT]), alanine aminotransferase (ALT) (serum glutamate-pyruvate transferase [SGPT]), bilirubin (total and direct), alkaline phosphatase (AP), lactate dehydrogenase (LDH), sodium, potassium, chloride, venous bicarbonate/carbon dioxide (if assessed only on arterial blood, should be done only if clinically indicated), total calcium, magnesium, phosphate, uric acid, urea/blood urea nitrogen (BUN), serum creatinine, and estimated glomerular filtration rate (MDRD equation – Appendix 2 [Section 10.2]).

q **Urinalysis:** Quantitative or alternatively semi-quantitative urinalysis at baseline (including red blood cells, protein, glucose, pH, ketones, bilirubin, and leukocytes) , and qualitative urinalysis (dipstick) after start of study treatment (including blood, protein, glucose, pH, ketones, bilirubin, and leukocytes).

r **Thyroid function tests** (Thyroid stimulating hormone [TSH], and free T4): To be performed at baseline and once a year thereafter until EOT or as clinically indicated, and at EOT. Free T3 to be done only if clinically relevant.

s **Antibody screening test:** Blood typing and complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S, s is recommended, if not available follow site's standard) if not already done, and antibody screening (indirect Coomb's test, indirect antiglobulin test [IAT]) to be obtained prior to Cycle 1/D1 study treatment administration. The IAT to be repeated at Cycle 2/D1; if the test is not performed at this visit, it can be done at the next blood sampling. Results of IAT will be recorded in the eCRF, including those performed prior to any red blood cells transfusion during study treatment. Red blood cells transfusions are to be recorded in the eCRF. During the study treatment the transfusion service should follow the recommendations issued in the AABB bulletin in case of red blood cells transfusion is needed. The web link to the AABB bulletin will be indicated on the study participant card (Appendix 13, Section 10.14]). Blood type card will be kept by the participant with the study card and the blood bank needs to be informed that the participant is receiving a treatment with an anti-CD38 and a potential interference with the indirect Coombs test is possible.

t **FCBP:** A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has achieved menarche at some time point, 2) has not undergone a hysterectomy or bilateral oophorectomy and bilateral salpingectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months. Serum or highly sensitive urine pregnancy tests for FCBP must be performed within 10 to 14 days and again within 24 hours of initiation of study treatment. Repeat pregnancy test every week for the first 4 weeks and then every 28-days while on therapy and during interruptions in therapy (or every 14 days in case of irregular menstrual cycles) and for at least 28 days after discontinuation of pomalidomide (14 and 28 days in case of irregular menstrual cycles), and monthly up to 5 months following isatuximab discontinuation, whichever occurs last. All participants must be counseled before initiation of each cycle prior to pomalidomide dispensing about pregnancy precautions, risks of fetal exposure and other risks. All participants enrolled into this study, must be registered in and must comply with all requirements of the Global Pregnancy Prevention Plan (GPPP) (if pomalidomide was provided by Sponsor) or the country specific risk management plan (if commercial pomalidomide is used).

u **Adverse event/Serious AE reporting:** All AEs, including AEs of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of any study treatment. After the 30-day follow-up, all ongoing related AEs or new related AEs, and all ongoing SAEs regardless of causal relationship are to be followed up to resolution or stabilization. In addition, second primary malignancies newly diagnosed during the entire study, including the post-treatment period, should be reported as AEs or SAEs, regardless of their causal relationship and followed up until resolution or stabilization. Severity will be graded according to NCI-CTCAE v5.0.

v Participants will stay at the site after isatuximab administration for at least 4 hours on Cycle 1/D1 in both SC and IV arms,1 hour after the end of injection for the following Cycle 1 administrations (SC arm only) and per investigator judgement subsequently, if not longer for any other reason (eg, PK sampling) and will be monitored closely for IRs and Injection site reactions (ISRs). The HCP will stay at least 30 minutes with the participant after the first at-home administration, and per clinical judgement for the subsequent at-home administrations.

w **Local tolerability at injection site after isatuximab SC administration– patient assessment using diary:** A participant diary will be used in order to document any type of injection site reaction beyond clinic stay. Participants will fill out the questionnaire at home up to Cycle 9/Day 1. These data will support the Investigator to assess retrospectively the local tolerability at injection site and report ISRs, if needed (Section 10.16).

x **Local tolerability at injection site after isatuximab SC administration – Investigator assessment:** Local tolerability at injection site will be assessed during clinical stay using eCRF hourly (relative to the start of administration) for duration of 4 hours at Cycle 1/D1, 1 hour after the end of injection for the following Cycle 1 administrations and at end of injection from Cycle 2 onwards. In case of at-home administration, for the first isatuximab injection performed at-home, an additional assessment should be performed 30 min after the end of the injection. Any swelling (unless it lasts longer than 24 hours) as a result of the injection of the isatuximab solution volume is not to be reported as an AE/adverse event of special interest (AESI).

y **Soft tissue plasmacytoma assessment (extramedullary disease OR paramedullary disease with a soft tissue lesion of diameter ≥2 cm)**

- If known soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline, repeated every 12 weeks (±1 week) until progressive disease (PD) from C1D1 (even for participants who would initiate further anti-myeloma therapy without PD), and if clinically indicated. From two years after randomization, the radiological assessment will be done every 6 months (±1 month). Assessment to be done until PD (even if further anti-myeloma therapy is started without PD as per protocol), or final cut-off date, whichever occurs first.
- If suspected soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline and if plasmacytoma confirmed on the exam to be repeated as indicated above.
- To be done in case of suspicion of progression or if clinically indicated in a participant with no previous positive image for soft tissue plasmacytoma.
- The bone component of paramedullary disease with a soft tissue lesion of diameter ≥2 cm will not be used for disease response assessment as per IMWG.

- Paramedullary (paraskeletal) plasmacytoma (bone plasmacytoma extending beyond the bone cortex into the surrounding tissues) with soft tissue lesions of diameter <2cm will be collected but will not be used for disease response assessment as per IMWG. No follow-up with repeated imaging is needed, except if clinically indicated.
- PET-CT should be the preferred option whenever possible.
- Note: For bone lesion assessment and soft tissue plasmacytoma, the same modality (low-dose whole body CT scan; CT scan, PET-CT scan, or MRI) should be used throughout the study for each individual participant when radiological follow-up is needed.
- All imagings will be sent for central review. Intravenous contrast is recommended if not medically contra-indicated. Participants who have contra-indication to CT scan with IV contrast may have MRI exams performed instead.

z **Bone disease (lytic or focal, depending on the method)**: Whole-body low-dose CT scan, PET-CT scan or MRI at baseline (within 28 days prior to randomization), once a year (±1 month) from C1D1, and anytime during the study if clinically indicated until PD (even if further anti-myeloma therapy is started without PD as per protocol), or final cut-off date, whichever occurs first. PET-CT should be the preferred imaging modality whenever possible.

aa **Bone marrow aspiration/biopsy for determination of % of plasma cells (local)**: Bone marrow aspiration (BMA) or biopsy is required at screening/baseline (within 21 days prior to study treatment administration) for determination of % of plasma cells. Repeat bone marrow aspirate or biopsy to confirm CR or stringent complete response (sCR), if CR or sCR is suspected.

bb **Myeloma-specific laboratory tests (centralized)**:

- β2-microglobulin at baseline only.
- Serum M-protein immunoelectrophoresis (SPEP) and immunofixation: SPEP to be performed at screening, C1D1 (predose, baseline for response assessment), prior to each cycle thereafter and at end of treatment (if last tests were >4 weeks or if disease progression was not confirmed on the last test). After baseline, immunofixation (IFE) to be done if SPEP shows no measurable monoclonal protein. For subjects with suspected isatuximab interference on serum IFE, the SEBIA HYDRASHIFT 2/4 isatuximab IFE test will be performed to specifically measure the endogenous M-protein. Subjects that meet all other IMWG criteria for CR, and for whom negative immunofixation is confirmed after using the HYDRASHIFT isatuximab test, will be considered complete responders. This will define the final CR rate as per IMWG criteria.
- Urine M-protein (24-hour urine) immunoelectrophoresis (UPEP) and immunofixation: UPEP to be performed at screening, C1D1 (predose, baseline for response assessment), prior to each cycle thereafter and at end of treatment (if last tests were >4 weeks or if disease progression was not confirmed on the last test). If urine M-protein is negative (UPEP and IF) at baseline, UPEP assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc), and to confirm CR and Very good partial response (VGPR) on blood laboratory parameters. After baseline, immunofixation to be done if UPEP shows no measurable monoclonal protein in participants whose disease is evaluable in urine.
- If urine M-protein is measurable or detectable or IF is positive at Cycle 1 Day 1, urine M-protein assessment should be done prior to study treatment administration in all subsequent cycles and at EOT (if last tests were >4 weeks or if disease progression was not confirmed on the last test).
- If urine M-protein is negative (UPEP and IF) at screening and Cycle 1 Day 1, this assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc), and to confirm CR and VGPR on blood laboratory parameters.
- After Cycle 1 Day 1, urine immunofixation is to be done only if urine M-protein is not detected in UPEP.
- Serum free light chain (sFLC) (quantification and ratio involved/uninvolved): To be performed at screening, C1D1 (predose) and prior to each cycle thereafter and at EOT (if last tests were >4 weeks or if disease progression was not confirmed on the last test).
- Immunoglobulins (IgG, IgA, IgM, IgD, and IgE): To be performed at screening, baseline and prior to each cycle thereafter and at EOT (if last tests were >4 weeks or if disease progression was not confirmed on the last test), (after baseline, IgD or IgE only if the heavy chain component of the disease is known to be E or D).
- Additional blood samples will be collected at all time points at which M-protein is assessed from Cycle 1 onwards, to evaluate new M-protein measurement methods for disease response assessment (such as mass spectrometry), (central laboratory).
- For participants who discontinue therapy for reasons other than progression, MM labs will be repeated every month during the follow-up period until progression (even if further anti-myeloma therapy is started without PD as per protocol).

cc **Bone marrow aspiration for cytogenetics assessment (central):** At screening, bone marrow aspirate will be collected for FISH (including, but may not be limited to, del[17p], t[4;14], t[14;16]), 1q21+ analyses in central laboratory.

dd **Bone marrow aspiration for Minimal Residual Disease (MRD) assessment:** To be performed at screening and at the time of maximum confirmed response of either CR or VGPR. For participants with CR without previous documentation of VGPR, bone marrow for MRD assessment will be collected at time of confirmation of CR (ie, at the second time point showing CR). For participants with VGPR, when VGPR is confirmed, a first bone marrow aspirate for MRD assessment will be collected as per investigator judgement based on kinetic of M protein decrease and/or if a plateau phase is reached (as an example, plateau is reached when there is a variation of less than 20% over 12 weeks). Bone marrow will also be collected:

- For participants in VGPR/CR at a fixed timepoint of 12 months after C1D1 (could not be collected if another BMA was collected in the previous 2 months period.
- For participants in VGPR/CR having achieved MRD negativity, 12 months after first MRD negativity.

ee Within a cycle, the treatment window is ±1 day for each of every week (QW) IMP administrations and ±3 days for each of every 2 weeks (Q2W) IMP administrations. Between cycles, the treatment window is ±3 days if 4-week cycle.

Table 2 - PK and ADA flowchart - Arm SC

Procedure		Intervention period													FUP
		C1									C2 to C5		C6, C7 and C8	C9 then every 3 cycles (C9, C12, C15…)	
		D1		D2	D5	D8	D15	D22		D23	D26	D1	D15	D1	D1	90 (±7) days after last study treatment administration
Isatuximab	SC administration	X				X	X	X				X	X	X	X	
	RNT (h) Ref. SOI	SOI[a]	8 h	24 h	96 h	SOI[a]	SOI[a]	SOI[a]	6 h	24h	96h	SOI[a]	SOI[a]	SOI[a]	SOI[a]	
	Time window	(-4h, SOI)	±1 h	±5 h	±5 h	(-4h, SOI)	(-4h, SOI)	(-4h, SOI)	±1 h	±5 h	±5 h	(-4h, SOI)	(-4h, SOI)	(-4h, SOI)	(-4h, SOI)	
	PK sample ID[b]	P00	P01	P02	P03	P04	P05	P06	P07	P08	P09	P00	P01	P00	P00	PF00
	ADA Sample ID[b]	AB00					AB01					AB00		AB00	AB00	ABF00

Abbreviations: ADA = Anti-Drug Antibody; C = Cycle; D = Day; P = Plasma; AB = Antibody in Plasma; FUP = Follow-up period; PK = Pharmacokinetic; RNT = Relative Nominal time; SC = subcutaneous; SOI = Start of Injection.

a Samples collected strictly before start of injection.

b PK and ADA samples will be samples as per PK and ADA flowchart or up to the primary cut-off date, whichever comes first.

Note: The sampling time points for PK and ADA may be reduced during the course of the study based on the updated knowledge of isatuximab behavior, upon notification from the Sponsor.

Table 3 - PK and ADA flowchart - Arm IV

Procedure		Intervention period																	FUP
		C1								C2			C3		C4 to C5			C6, C7 and C8	C9 then every 3 cycles (C9, C12, C15…)	
		D1			D3	D8	D15		D22	D1		D15	D1	D15	D1		D15	D1	D1	
Isatuximab	IV administration	X---------X				X	X---------X		X	X---------X		X	X	X	X---------X		X	X	X	90 (±7) days after last study treatment administration
	RNT (h) Ref. SOI	SOI[a]	EOI[c]	EOI+1 h	48h	SOI[a]	SOI[a]	EOI[c]	SOI[a]	SOI[a]	EOI[c]	SOI[a]	SOI[a]	SOI[a]	SOI[a]	EOI[c]	SOI[a]	SOI[a]	SOI[a]	
	Time window	(-4h, SOI)	±10 min	±10 min	±24 h	(-4h, SOI)	(-4h, SOI)	±10 min	(-4h, SOI)	(-4h, SOI)	±10 min	(-4h, SOI)	(-4h, SOI)	(-4h, SOI)	(-4h, SOI)	±10 min	(-4h, SOI)	(-4h, SOI)	(-4h, SOI)	
	PK sample ID[b]	P00	P01	P02	P03	P04	P05	P06	P07	P00	P01	P02	P00	P01	P00	P01	P02	P00	P00	PF00
	ADA Sample ID[b]	AB00					AB01			AB00			AB00		AB00			AB00	AB00	ABF00

Abbreviations: ADA = Anti-Drug Antibody; C = Cycle; D = Day; EOI= End of Infusion; P = Plasma; FUP = Follow-up period; AB = Antibody in plasma; PK = Pharmacokinetic; RNT = Relative nominal time; SOI = Start of infusion.

a Samples collected strictly before start of infusion.

b PK and ADA samples will be samples as per PK and ADA flowchart or up to the primary cut-off date, whichever comes first.

c Actual EOI sample should be taken when the pump beeps (end of fusion) after flush.

Note: The sampling time points for PK and ADA may be reduced during the course of the study based on the updated knowledge of isatuximab behavior, upon notification from the Sponsor.

2 INTRODUCTION

2.1 STUDY RATIONALE

Isatuximab has so far been administered primarily by IV route. Based on clinical efficacy, safety, PK simulations, and PK/pharmacodynamic (PDy) analyses, the dose selected for isatuximab IV in combination with approved MM therapies is 10 mg/kg QW × 4 administrations followed by 10 mg/kg Q2W.

The combination of IV isatuximab with pomalidomide and dexamethasone has demonstrated clinical efficacy with a statistically significant and clinically meaningful improvement in PFS, as well as an acceptable and manageable safety profile in the ICARIA-MM (NCT02990338) Phase 3 trial (2). In 2020, FDA and EMA approved this combination for the treatment of adults with RRMM who have received at least two prior therapies including lenalidomide and a PI. A trend in OS benefit with approximately 7 months improvement in median OS was shown in an updated analysis (3).

Isatuximab IV administration is approved in most countries with the fixed-volume infusion method allowing the IV infusion to be given during 75 minutes from the 3rd infusion onwards. A SC administration within several minutes allows for a shorter duration of administration compared to the currently approved IV route, optimizing the convenience of administration and minimizing the time the participant spent in healthcare facility, which is particularly relevant in the context of the current COVID-19 pandemic and in line with recommendations of hematology/myeloma societies (4, 5, 6). The SC administration of isatuximab is also intended to:

- Decrease the incidence of infusion-reactions due to the slower absorption of SC administration compared to IV.
- 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.
- Improve long term treatment adherence to maintain optimal disease control.
- Reduce health resource utilization and thus overall healthcare cost.

Aiming to enhance comfort and quality of life of the participants, SC administration of isatuximab is considered as a desirable alternative to the approved IV isatuximab administration, in particular for the long duration of treatment required in MM.

Among the approved treatments for MM, Velcade (bortezomib) is approved for administration by IV as well as SC route. More recently, in 2020, FDA and EMA approved the combination of daratumumab and hyaluronidase-fihj (Darzalex-Faspro) administered subcutaneously for both newly diagnosed and RRMM participants. Approval of Darzalex-Faspro was based on the evidence from the Phase 3 COLUMBA Study (MMY3012) and the supportive Phase 2 PLEIADES Study (MMY2040) (7, 8). Data from COLUMBA study demonstrated that Darzalex-Faspro efficacy and PK was non-inferior to IV daratumumab, and both studies demonstrated that Darzalex-Faspro resulted in fewer IRs and offered a reduced treatment burden.

In the COLUMBA trial, a greater satisfaction of the participants with their cancer therapy in the DARA SC arm was also suggested, compared to those in the DARA IV group (9).

Device-mediated SC administration can offer a number of benefits to both HCPs and patients, including controlled delivery and simplified user interface, and could ultimately be used by a qualified HCP in the outpatient setting or at patient's home.

Triplet regimens should be used as the standard therapy for patients with multiple myeloma (10, 11). A triplet is defined as a regimen combining two novel agents (PIs, immunomodulatory drugs, or monoclonal antibodies) with a steroid (12). At first relapse, prior therapies should be taken into consideration when selecting treatment and a monoclonal antibody-based regimen in combination with an immunomodulatory drug and/or PI should be considered (12, 13). In the 2021 IMWG guidelines, pomalidomide plus bortezomib and dexamethasone is one of the 3 preferred options for lenalidomide-refractory patients at first relapse, while several pomalidomide-based regimens, including combinations with carfilzomib, daratumumab or ixazomib are considered as other options (13). The increasing use of lenalidomide in frontline and thus the increased prior exposure to lenalidomide and PI at the moment of first relapse, with the standard of care shift of pomalidomide use towards second line, especially in lenalidomide-refractory patients, leads to the proposal of a study population of patients with RRMM who have received at least one prior line of therapy.

In the EQUULEUS MMY1001 trial, daratumumab combined with pomalidomide and dexamethasone was administered in participants with at least two prior lines of therapy including lenalidomide and bortezomib showing an ORR of 60% (14). In the APOLLO trial, the same combination administered with SC daratumumab in participants with at least one prior line of therapy including lenalidomide and a PI resulted in an ORR of 69% without any unexpected new safety signals (15). Isatuximab, in combination with carfilzomib and dexamethasone, has demonstrated efficacy and safety in MM participants who have received at least one prior line of therapy in the Phase 3 IKEMA trial (16). A similar efficacy and safety profile for the isatuximab, pomalidomide and dexamethasone combination is expected in participants at first relapse compared to second relapse and beyond.

The EFC15951 Study is proposed to evaluate SC administration of isatuximab versus IV, in combination with pomalidomide and dexamethasone using an Investigational device injector in participants with MM who have received at least one prior line of therapy including lenalidomide and a PI.

2.2 BACKGROUND

2.2.1 Isatuximab description

Isatuximab is a naked IgG1, mAb that selectively binds to the human cell surface antigen molecule classified as CD38. Cluster of differentiation 38 is expressed in a number of hematological malignancies from B-lymphocyte, T-lymphocyte, and myeloid origin and is expressed in 98% of MM patients.

The biological mechanisms by which isatuximab can induce the killing of CD38-positive tumors that have been demonstrated in tumor cell lines are:

1. Antibody-dependent cellular-mediated cytotoxicity.
2. Antibody-dependent cellular phagocytosis.
3. Complement-dependent cytotoxicity.
4. Induction of apoptosis (proapoptosis).
5. Activation of natural killer (NK) cells.

No significant cytokine release, cellular activation, or depletion was induced by isatuximab in-vitro assays with normal human peripheral blood mononuclear cells, despite some induction of apoptosis in purified NK cells.

2.2.2 Nonclinical data

In vivo antitumor activity of isatuximab was demonstrated in several implanted SC or injected IV implanted hematological tumor models. As a single agent, antitumor activity was observed in MM, non-Hodgkin's lymphoma, and acute lymphocytic leukemia tumor models.

In ex vivo primary patient tumor samples, isatuximab has demonstrated a direct proapoptotic effect in MM samples and acute myeloid leukemia samples.

In Good Laboratory Practice (GLP) cross-reactivity studies with normal human tissues, isatuximab was bound specifically to lymphoid tissues (spleen, thymus, lymph node, and tonsil), BM, pituitary gland (endothelial cells), prostate gland (glandular epithelial cells), and infiltrating or resident round cells (macrophages and/or lymphocytes) of the innate immune system including Kupffer cells in the liver. In preliminary non-GLP tissue cross-reactivity studies using a different isatuximab batch and different mAb concentrations, additional staining had also been observed in the brain (astrocytes) and lung (bronchial epithelium). Staining of all nonlymphoid tissue elements was interpreted as evidence of cross-reactivity that may possibly indicate potential unintended off-target sites.

Isatuximab is specific for human CD38 protein. In the absence of a relevant animal species for toxicity testing, only a repeat-dose IV (once weekly for 3 weeks) study was conducted in cynomolgus monkeys (a non-pharmacologically reactive species) in order to evaluate potential non-targeted and non-specific general toxicity. In this cynomolgus monkey toxicity study, no compound-related changes were noted in any parameters evaluated and the no-observed adverse effect level was 100 mg/kg/week (highest dose tested).

The local tolerance of isatuximab after a single IV injection (intended clinical route), as well as after single intra-arterial, intramuscular, SC, or paravenous injection (unintended routes that might occur accidentally), was assessed in female New Zealand White rabbits (a non-pharmacologically reactive species). Isatuximab produced no compound-related clinical signs or body weight changes and there were no compound-related macroscopic or microscopic findings at the injection sites for any route of administration at concentrations up to 5 mg/mL. In addition, isatuximab did not produce compound-related macroscopic or microscopic changes at the injection sites following once weekly IV infusion for 3 weeks in cynomolgus monkeys up to 20 mg/mL (maximum concentration tested).

The local tolerance of isatuximab in its clinical SC formulation has been tested in female minipigs (a nonpharmacologically reactive species). The single SC infusion of 12.9 mL isatuximab (140 mg/mL, SC formulation) to minipigs equivalent to a total dose of approximately 1800 mg/minipig at flow rates of 0.5, 1, and 2 mL/min was overall clinically well tolerated. Erythema and hemorrhage at injection sites were noted on the day of infusion, only, and were similar for the 3 SC flow rates as well as for isatuximab and saline. Swelling at injection site was more evident for isatuximab infused at 1 and 2 mL/min compared with 0.5 mL/min and was considered related to a physical phenomenon (large volume injected in a short period of time). It declined at 4 hours and had disappeared at 24 hours following administration. There were no compound-related microscopic findings at the examination of skin biopsies of SC injection sites sampled 7 and 28 days following each injection at all administration rates tested.

Finally, plasma compatibility and the hemolytic potential of isatuximab in human whole blood were tested in vitro at concentrations up to 2.5 mg/mL. No hemolytic effect or plasma incompatibility was observed.

2.2.3 Clinical data

At the cut-off date of 01 March 2021 the clinical development program with isatuximab IV consists of Phase 1/2/3 studies of isatuximab as a single agent or in combination with other therapies. A total of 1760 participants have been exposed to isatuximab so far.

2.2.3.1 Isatuximab IV in combination with pomalidomide and dexamethasone

The overall safety profile of isatuximab, well characterized by clinical studies, is predictable and manageable. Infusion reactions have been reported as the most common adverse reactions consequent to the IV administration of isatuximab (whether administered as a single agent or in combination with other anticancer agents), and therefore is an identified risk. These adverse reactions, whether acute or delayed, may be serious and systemic and may include anaphylactic reactions.

The combination of isatuximab IV with pomalidomide and dexamethasone has been evaluated in a completed Phase 1b Study (TCD14079) and a completed Phase 3 Study (EFC14335). Following the results of the EFC14335 Study, IsaPd was approved in the United States, European Union (EU), Canada, Japan, Russia, and Australia for its use in adult patients with MM who have received at least 2 prior therapies including lenalidomide and a PI.

In Study TCD14079 (Pd in RRMM; Part A), 45 participants were treated. Three dose levels of isatuximab were evaluated: 5 mg/kg (n = 8), 10 mg/kg (n = 31) and 20 mg/kg (n = 6). The median age of participants was 67 years (range: 42 to 82 years). The median time from initial diagnosis to first dose was 4.3 years (range: 1.0 to 15.8 years). Median number of lines was 3 (minimum to maximum: 2 to 10) with 13 (28.9%) participants having received 3 or more prior lines of treatment.

Overall, the therapy of isatuximab in combination with pomalidomide and dexamethasone in participants with RRMM was well tolerated up to the highest planned isatuximab dose (20 mg/kg). Three dose limiting toxicities (DLTs) were reported, one at each dose level: Grade 4 neutropenia, Grade 4 neutropenic infection, and Grade 3 confusional state. All the DLTs resolved

with pomalidomide dose omission or reduction and did not lead to treatment discontinuation. The isatuximab maximal tolerated dose (MTD) was not reached when isatuximab was administered with pomalidomide and dexamethasone. As no MTD was reached in the dose escalation cohort, isatuximab recommended dose of 10 mg/kg QW × 4, followed by 10 mg/kg Q2W was chosen based on PK/PDy modeling and simulations from the Phase 1 Study TCD11863 (assessing isatuximab in combination with lenalidomide and dexamethasone).

The ORR was 62.2% (28 out of 45 participants) in total including 2 participants achieving a complete response (CR)/stringent complete response (sCR) (4.4%); very good partial response (VGPR) was reported in 10 participants (22.2%), and PR in 16 participants (35.6%). The 10 mg/kg group had an ORR of 64.5%.

EFC14335 (ICARIA-MM) was a randomized, open-label, multicenter Phase 3 trial evaluating isatuximab in combination with approved doses of pomalidomide and dexamethasone (IsaPd) versus pomalidomide and dexamethasone in RRMM (2). The primary objective of this Phase 3 trial (NCT02990338) was PFS. Key secondary objectives were ORR and OS. Progression free survival and ORR were analyzed based on the assessment of an Independent Review Committee using central laboratory data for M-protein and central radiology review.

Participants with RRMM who received ≥2 prior lines, including lenalidomide and a PI, were refractory to last therapy, and had adequate bone marrow, kidney, and hepatic function, could be enrolled. Prior exposure to pomalidomide was not allowed. Participants in the Isatuximab (IsaPd) arm received Isa 10 mg/kg IV weekly for first 4 weeks, then every 2 weeks. Both arms received approved schedules of pomalidomide and dexamethasone (4 mg per os [PO] days 1 to 21; 40 mg [20 mg if >75 yrs] PO or IV weekly) every 28 days until progression or unacceptable toxicity.

Three hundred and seven participants were enrolled (154 IsaPd, 153 Pd). Overall, the median age was 67 years (range 36 to 86) and 19.9% of the population was ≥75 years of age, the median prior lines of therapy was 3 (2 to 11); estimated glomerular filtration rate was <60 ml/min in 33.9% participants; 92.5% were refractory to lenalidomide, 72.6% were refractory to both lenalidomide and PI, 75.9% to PI and 91.2% were refractory to lenalidomide at their last line immediately before their enrolment in the trial. Over the half of participants (56.4%) had received prior stem cell transplant; and 19.5% participants had high-risk cytogenetics.

At median follow-up of 11.6 months, the addition of isatuximab to pomalidomide and dexamethasone significantly improved PFS. Median PFS was significantly longer in the IsaPd arm (11.53 months, 95% CI: 8.936 to 13.897) than in the Pd arm (6.47 months, 95% CI: 4.468 to 8.279), respectively. The stratified HR was 0.596 (95% CI: 0.436 to 0.814) characterizing a reduction of 40.4% in risk for disease progression or death with IsaPd compared to Pd. All sensitivity analyses for PFS showed consistent results with the primary analysis. All PFS subgroup analyses showed consistent benefit with HRs in the ranges of 0.5 and 0.6, including elderly participants, renal impaired, heavily pretreated, and high-risk cytogenetics. The ORR was significantly better in IsaPd (60.4%) versus Pd (35.3%), p<0.0001. The depth of response, as measured by the VGPR or better rate, was improved with IsaPd (31.8%) compared to Pd (8.5%), p<0.0001. Minimal residual disease negativity (NGS,10^{-5}) was seen in 5.2% IsaPd versus 0% Pd participants (ITT analysis). At analysis date, OS was immature (99 events) but a trend to OS improvement in IsaPd versus Pd was observed (HR 0.687; 95% CI 0.461-1.023). The median treatment duration was 41 weeks on IsaPd versus 24 weeks on Pd.

An updated analysis of the ICARIA-MM trial confirmed a trend in overall survival benefit, with a median OS of 24.6 months in the IsaPd arm versus 17.7 months in the Pd arm, (HR 0.76; 95% CI 0.58-1.01) (3).

Grade ≥3 AEs were observed in 86.8% IsaPd versus 70.5% Pd participants; 7.2% IsaPd and 12.8% Pd participants discontinued treatment due to AEs; 7.9% IsaPd and 9.4% Pd participants died due to AEs. The addition of isatuximab to the Pd regimen was characterized by reversible IRs, which were reported in 38.2% (2.6% Grade 3 to 4) of the cases and an increase in neutropenia and infection rates. Grade ≥3 infections were seen in 42.8% of the participants in IsaPd arm versus 30.2% in Pd arm, Grade ≥3 neutropenia in 84.9% and 70.1%, respectively. Febrile neutropenia was reported in 11.8% IsaPd and 2.0% Pd participants. No difference in anemia and thrombocytopenia, and no difference in thrombo-embolic events was seen between arms.

These data from the Phase 3 and the Phase 1 study provide evidence of the efficacy and safety of IV IsaPd and support planned investigation of SC isatuximab in this combination. Details are provided in the most recent Investigator's Brochure (IB).

2.2.3.2 Isatuximab SC in combination with pomalidomide and dexamethasone

TCD15484 is an ongoing multi-center, open-label, Phase 1b study to assess the safety, PK, and efficacy of SC isatuximab administered QW for 4 weeks (Cycle 1) and then Q2W in subsequent cycles in combination with pomalidomide and dexamethasone (IsaPd).

The study includes the following cohorts of participants:

- Cohort 1
  - Cohort 1a: Participants receiving 1000 mg dose of isatuximab by SC route using an infusion pump (SC-IP) with a flow rate of 0.8 mL/min in combination with pomalidomide/dexamethasone.
  - Cohort 1b: Participants receiving 10 mg/kg dose of isatuximab by IV route in combination with pomalidomide/dexamethasone.
- Cohort 2
  - Cohort 2a: Participants receiving 1400 mg dose of isatuximab by SC-IP with a flow rate of 0.8 mL/min in combination with pomalidomide/dexamethasone.
  - Cohort 2b: Participants receiving 10 mg/kg dose of isatuximab by IV route in combination with pomalidomide/dexamethasone.
- Cohort 3: Participants receiving isatuximab by SC route at the recommended Phase 2 dose (RP2D) using an On Body Delivery System (OBDS), an (investigational) wearable injector device (SC-OBDS) in combination with pomalidomide/dexamethasone.

In Cohorts 1 and 2, participants were randomized with a 2:1 ratio to SC-IP or IV route. After determination of the RP2D based on Cohorts 1 and 2 results using an infusion pump for the SC administration of isatuximab, the participants were included in an expansion cohort, Cohort 3, using the OBDS.

As of the cut-off date of 16 May 2022, a total of 56 participants have been treated in the TCD15484 Study from October 2019 to August 2021:

- 12 participants in the 10 mg/kg IV cohort.
- 12 participants in the 1000 mg SC with infusion pump (1000 mg SC-IP) cohort.
- 10 participants in the 1400 mg SC with infusion pump (1400 mg SC-IP) cohort.
- 22 participants in the 1400 mg SC with the (investigational) injector device (SC-OBDS) cohort.

Due to the sequential nature of the enrollment, the median follow-up duration was higher in the IV, 1000 mg SC-IP, and 1400 mg SC-IP cohorts (24.4 months, 28.7 months, and 22.7 months, respectively) compared to the SC-OBDS cohort (10.1 months). At the time of the analysis, 33 participants discontinued treatment: 8 participants in the IV cohort, 9 participants in the 1000 mg SC-IP cohort, 7 in the 1400 mg SC-IP cohort, and 9 in the SC-OBDS cohort. The main reason for discontinuation was disease progression (26 participants). There was a trend for lower pomalidomide relative dose intensity (RDI) in the 1400 mg SC-IP cohort (69.2%) versus the IV, SC 1000 mg and the SC-OBDS cohorts (93.5%, 87.8%, and 85.4%, respectively). Pomalidomide reduction was mainly due to neutropenia.

One DLT was reported in each SC-IP cohort (Grade 4 neutropenia in the 1000 mg SC-IP cohort and Grade 3 pulmonary infection in the 1400 mg SC-IP cohort). According to the protocol, DLTs were not assessed in the isatuximab IV cohorts. DLTs reported with Isa-SC were consistent with the DLTs reported in the dose-escalation study of isatuximab IV in combination with Pd (Study TCD14079) in which one DLT was reported at each dose level (5 mg/kg: Grade 4 neutropenia; 10 mg/kg: Grade 4 neutropenic infection; and 20 mg/kg: Grade 3 confusional state).

The incidence of all-causality Grade ≥3 TEAEs was comparable (≥90%) in all cohorts. There were 2 TEAEs leading to death (sudden death not related to treatment or disease and bacterial meningitis) in the SC-OBDS cohort. Bacterial meningitis was the only adverse event leading to definitive treatment discontinuation in the study.

Grade ≥3 infections were reported in 3 (25%) participants in both IV and 1000 mg SC-IP cohorts, 4 (40%) in the 1400 mg SC-IP cohort, and 8 (36.4%) participants in the SC-OBDS cohort, including 1 case of Grade ≥3 Covid-19 in the 1400 mg SC-IP and 3 in the SC-OBDS cohorts.

Grade ≥3 laboratory neutropenia was observed in 10 (83.3%) patients of the IV cohort, 11 (91.7%) in the 1000 mg SC-IP cohort, 9 (90%) in the 1400 mg SC-IP cohort, and 20 (90.9%) in the SC-OBDS cohort.

Febrile neutropenia occurred in 1 (8.3%) patient in the IV cohort, none in the 1000 mg SC-IP cohort, 2 (20%) in the 1400 mg SC-IP cohort and 1 (4.5%) in the SC-OBDS cohort.

Infusion reactions occurred in less than 10% of the patients, with a single episode of IR (all Grade 2) in each of the IV, 1000 mg SC-IP, and 1400 mg SC-IP cohorts. These episodes occurred at the first administration only and lasted 1 (IV and 1400 mg SC-IP cohorts) to 2 days (1000 mg SC-IP cohort). No IR was observed in the SC-OBDS cohort.

Patients with at least 1 ISR were 6 (50%) in the 1000 mg SC-IP, 6 (60%) in the 1400 mg SC-IP and 5 (22.7%) in the SC-OBDS cohorts, experiencing 23, 46, and 7 episodes of ISR, respectively. The local tolerability profile in the SC-OBDS cohort was very good: the 7 episodes of ISR were all Grade 1, corresponding to 5 injection site erythema, 1 injection site hemorrhage, and 1 injection site induration, and representing 1.7% of the OBDS injections (7 out of 404 administrations).

The median duration of OBDS injection was 10 minutes at first and subsequent administrations, and all injections were successfully completed with no interruption.

In general, the incidence of TEAEs in any arm of Study TCD15484 compared favorably to the incidence of TEAEs in the IsaPd arm of the ICARIA-MM trial. Importantly, there was no new safety signal observed in Isa-SC arms compared to the known safety profile of IsaPd established with ICARIA-MM and TCD14079 studies.

With a shorter duration of follow-up of the SC-OBDS cohort (10 months versus ≥22 months in the other cohorts), the ORR was 66.7% in both IV and 1000 mg SC-IP cohorts, 80.0% in 1400 mg SC-IP cohort and 72.7% in the SC-OBDS cohort. At least VGPR rate was similar across all cohorts (40% to 50%). The CR rate was 16.5% in the IV cohort, 25% in the 1000 mg SC-IP cohort, 20% in the 1400 mg SC-IP cohort, and 22.7% in the SC-OBDS cohort. Overall, ORR, at least VGPR rate and CR rates are consistent with the ICARIA-MM trial.

Saturation of the CD38 receptors on bone marrow plasma cells was reached for all cohorts: mean CD38 receptor occupancy of 76.0% (range: 68.2% to 86.1%) for 10 mg/kg isatuximab IV, 79.8% (range: 74.7% to 84.2%) for 1000 mg SC-IP, 80.5% (range: 78.6% to 83.2%) for 1400 mg SC-IP, and 78.1% (range: 64.2% to 85.4%) for SC-OBDS. These data demonstrated that when administered SC, isatuximab saturates its target receptor similarly to when administered IV.

After the first Isa-SC administration, the median time to reach maximum concentration (C_{max}) was approximately 95 hours. The C_{max} and area under the plasma concentration time curve over the first week (AUC_{1week}) were comparable after the first 1000 mg and 1400 mg Isa-SC dose whichever the Isa-SC delivery method used (IP or OBDS) and were lower than those observed after 10 mg/kg IV administration (Table 4) which is in agreement with the slow absorption observed for the SC administration route. Similar results were observed after the seventh Isa-SC administration in the QW/Q2W regimen, with comparable area under the plasma concentration time curve over two weeks of dosing (AUC_{2weeks}) after 1000 mg and 1400 mg SC doses.
A moderate interpatient variability was observed for exposure after the first Isa-SC administration (total coefficient of variation [CV] for C_{max}, AUC_{1week} or C_{trough} of 33% to 52%) or after the seventh Isa-SC administration (total CV for C_{max}, AUC_{2weeks} or C_{trough} of 38% to 65%) with the IP and remained of the same extent when using the OBDS (total CV for C_{max}, AUC_{2weeks} or C_{trough} of 33% to 52%). The total variability appeared to be slightly higher for the 1400 mg SC-OBDS cohort versus 1400 mg SC-IP cohort but it remained comparable to the one observed for 1000 mg SC-IP cohort.

Previous population PK analysis (POH0503) with IV data has shown that participants with less aggressive disease at baseline are expected to have lower linear clearance (CL) and therefore higher exposure; similarly, non-IgG participants have higher exposure than the IgG participants. The unbalanced covariates distribution between the SC cohorts explains the comparable exposure between these cohorts with participants from the 1000 mg SC-IP cohort having less

advanced disease, lower tumor burden (higher albumin, lower β2 microglobulin level, International Staging System [ISS] stage, M-protein level and bone marrow plasma cell [BMPC]) than the 1400 mg SC cohorts. The covariates distribution between 1400 mg cohorts (IP and OBDS) was similar with the exception of body weight. For the weight, the distribution was similar between participants of 1000 mg SC-IP and 1400 mg SC-OBDS cohorts, but patients in the 1400 mg SC-IP cohort were heavier.

The mean (±standard error [SE]) C_{trough} over time after IV and SC isatuximab QW/Q2W show comparable C_{trough} profiles after 1000 mg and 1400 mg SC which were higher than those observed after 10 mg/kg IV. Relative to first administration, the accumulation ratio based on C_{trough} ranged from 2.65 (1400 mg SC-OBDS) to 3.64 (1000 mg SC-IP) for Cycle 2 Day 1 (fifth administration) and from 2.83 (1400 mg SC-OBDS) to 4.04-fold (1000 mg SC-IP) for Cycle 4 Day 1 (ninth administration) after the SC administration (1000/1400 mg with IP or OBDS). Accumulation was comparable to that observed after IV administration, with accumulation ratio of 3.96 for Cycle 2 Day 1 and of 3.60 for Cycle 4 Day 1.

It is important to note that individual CT4W values (best PK predictor of efficacy) after 1000 mg SC-IP and 1400 mg SC-IP or OBDS QW/Q2W regimens were similar or higher than those observed in patients treated by IV route at 10 mg/kg QW/Q2W, with comparable inter-patient variability (Table 4).

Table 4 - Mean (CV%) isatuximab PK parameters after the 1st and 4th SC administration at 1000 mg or 1400 mg QW/Q2W and after the IV administration at 10 mg/kg in TCD15484 – non compartmental analysis

Study	Dose/Route	Number of patients	C_{max} (µg/mL)	t_{max} [a] (h)	CT1W (µg/mL)	AUC_{1week} (µg.h/mL)	CT4W (µg/mL)
TCD15484*	1000 mg SC-IP	12	119 (48)	91.90 (46.20-168.00)	101 (44)[b]	15200 (52)[b]	339 (26)[c]
	1400 mg SC-IP	10	104 (33)	92.60 (68.40-168.00)	92.3 (31)[d]	12900 (36)	338 (36)[e]
	1400 mg SC-OBDS	22	145 (49)	95.10 (46.90-192.00)	128 (46)	17400 (49)	326 (46)[f]
	1400 mg SC (OBDS+IP)	32	132 (49)	94.70 (46.90-192.00)	118 (46)[g]	16000 (48)	330 (42)[h]
TCD15484*	10 mg/kg IV	12	234 (29)	3.63 (3.33-11.30)	56.8 (48)[b]	19300 (28)	235 (40)[d]

CT4W were used in descriptive statistics calculation even if patients did not receive the 4 doses at Cycle 1.
Abbreviations: AUC_{1week} = area under the plasma concentration time curve over the first week; C_{max} = maximum concentration; C_{trough} = predose concentration during repeated dosing; CT1W = C_{trough} at 1 week; CT4W = C_{trough} at 4 weeks; t_{max} = time to reach C_{max}; NR = No Result.
a Median(min-max),
b N = 11,
c N = 8,
d N = 9,
e N = 6,
f N = 13,
g N = 31,
h N = 19,
*based on NCA analysis.

2.2.3.3 Pomalidomide

Pomalidomide is a thalidomide analogue indicated, in combination with dexamethasone for participants with MM who have received at least 2 lines of therapies including lenalidomide and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Pomalidomide is an IMiD with multiple cellular effects that inhibit MM cell growth and survival blocking the stromal support from the bone marrow (BM) microenvironment that can promote myeloma cell growth; in addition, pomalidomide has potent immunomodulatory effects that enhance the immune response to myeloma cells by stimulating NK cell and by inhibiting regulatory T cells. Pomalidomide has been approved following the data reported in Study MM-003 (17) where pomalidomide plus low-dose dexamethasone was compared with high-dose dexamethasone.

In Study MM-003, the most common Grade 3 to 4 hematological AEs in the pomalidomide plus low-dose dexamethasone arm were neutropenia (48%), anemia (33%), and thrombocytopenia (22%); Grade 3 to 4 non-hematological AEs included pneumonia (13%), bone pain (7%), and fatigue (5%). After a median follow-up of 10 months, the ORR in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone was 31% and 10% respectively, the PFS was 4 months and 1.9 months.

Please refer to US or EU labeling for additional details.

2.2.3.4 Injector device

In addition to TCD15484, a version of the wearable injector device has been used in clinical trials with other medicinal product(s). [redacted]

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of isatuximab may be found in the IB.

2.3.1 Risk assessment

Table 5 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion reactions including anaphylactic reactions (identified risk) and cytokine release syndrome	Infusion reactions have been reported as the most common adverse reactions consequent to the IV administration of isatuximab (either as a single agent or in combination with other anticancer agents); this is consistent with the results from clinical studies and from extensive postmarketing experience acquired with other therapeutic mAb proteins. Extensive clinical experience with approved mAbs, in fact, indicates that mild to moderate IR (either allergic, or consisting of cytokine release, which mimics hypersensitivity reactions) are very common, particularly during the first infusion; the cytokine release syndrome associated with mAbs consists of a pseudo allergic Type B (nonimmunoglobulin E mediated) reaction. The infusion reactions with IV isatuximab are most commonly at the first administration, are not dose dependent, and the participants do not appear to sustain sequelae. Infusion reactions generally do not cause therapy discontinuation and tend not to recur at subsequent administrations of isatuximab. Occasionally, these adverse reactions may be serious and systemic (as with anaphylactic reactions, which have been reported throughout the isatuximab IV program). Infusion reactions, however, are most frequently of Grade 1/2 severity and are manageable (for more details on infusion reactions refer to the most recent IB). Similar reactions are expected after SC administration of isatuximab. To allow assessment of these reactions after isatuximab SC versus IV the common term of IRs will be used for this type of reactions after administration of either isatuximab SC or IV.	To minimize the incidence and severity of IRs, and as it is done in the isatuximab IV program, all the participants treated with isatuximab SC should routinely receive primary prophylactic treatment. See Section 6.1.2. Participants who do not experience an IR during the first 4 isatuximab administration may have their need for subsequent premedication reconsidered at the Investigator's discretion, except for montelukast which should be administered only on Cycle 1. Details for management of IRs and ISRs after isatuximab SC administration are provided in the Section 6.5.5.
Infections (identified risk)	Isatuximab modulation of lymphoid and myeloid cells due to CD38 expression on normal immune cells, effect of other medications like dexamethasone. Bone marrow suppression with risk of neutropenia.	Exclusion of trial participants with active infections. Close monitoring of clinical and laboratory parameters. Prophylactic use of antibiotics, antivirals, antifungals, and G-CSF as needed.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Neutropenia (identified risk)	Risk of bone marrow suppression is systematically considered with anti-cancer therapies. Multiple myeloma is a malignancy that primarily affects the bone marrow. Clinical manifestations of infections and febrile neutropenia can be life-threatening.	Exclusion of patients with ANC<1000 µL (1×10^9/L). The use of G-CSF is not allowed to reach this level. Close monitoring of blood cell count at each cycle. Prophylactic use of antibiotics, antivirals, antifungals, and G-CSF.
Interference with blood bank serologic tests (identified risk)	CD38 protein is weakly expressed on the surface of red blood cells. Because of this, anti CD38 antibodies in participants' plasma can lead to pan reactivity and thus interfere with various blood bank serologic tests. ABO/RhD typing is not affected by anti CD38 antibodies.	Before the first isatuximab infusion, conduct blood type and screen tests on isatuximab - treated participants. If treatment with isatuximab has already started, inform the blood bank that the participant is receiving isatuximab and isatuximab interference with blood compatibility testing can be resolved using dithiothreitol treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices. An antibody screen test (indirect Coomb's test) should be done before each red blood cell transfusion while on isatuximab treatment. See Appendix 13 Section 10.14). In all isatuximab studies, participant blood will be typed and screened before (if not already done) the first administration of the drug and a card with blood type will be carried by the participant throughout the study.
Second primary malignancies (potential)	CD38 antigen is expressed on normal immune cells; suppression of immune system (with its ability to detect and destroy cancer cells) may increase risk of malignancies. Overall incidence of SPMs with isatuximab in ICARIA study was 3.6% (6 in Isa arm versus 1 in control).	Monitoring and measurement of secondary cancers. Collect information on baseline characteristics, individual treatments, time to development, clinical characteristics, history of SPMs observed.
Viral reactivation (potential)	Participants with MM undergoing immunosuppressive drug therapy are at high risk of viral reactivation including hepatitis and herpes zoster reactivation.	Screening with serological tests for hepatitis B (HBV) and hepatitis C (HCV) has to be done prior to enrollment if not performed within 1 year. In case of viral reactivation during study treatment, the treatment will be held, specialist consulted for initiation of anti-viral treatment, and monitoring of the participant. Antiviral prophylaxis (such as herpes zoster prophylaxis) can be considered during treatment.
Subcutaneous Isatuximab		
Injection-site reaction	Although no Grade >1 ISRs were reported in the Phase 1 trial with SC isatuximab, the potential of the risk remains.	Monitoring of ISRs. Diary will be provided to patients to report potential ISRs during the first 9 cycles in the SC-arm.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study procedures		
Bone marrow aspirate/biopsy	Bone marrow aspirate is part of standard procedures for MM disease assessment.	Sites with MM expertise will be selected.
Other		
Not applicable.		

Abbreviations: ANC = Absolute Neutrophil Count; CD38 = Cluster of differentiation 38; G-CSF = granulocyte-colony stimulating factor; HBV = hepatitis B virus; HCV = hepatitis C virus; IB = investigators brochure; IR = Infusion reactions; ISR = Injection site reactions; IV = Intravenous; mAb = monoclonal antibody; MM = Multiple myeloma; RBC = red blood cell; SC = Subcutaneous; SPM = second primary malignancies.

2.3.2 Benefit assessment

All participants in the trial will receive a combination of isatuximab, pomalidomide and dexamethasone. The combination of IV isatuximab with pomalidomide and dexamethasone has demonstrated clinical efficacy with an acceptable and manageable safety profile in the ICARIA-MM (NCT02990338) Phase 3 trial. Device-mediated SC administration can offer a number of benefits to both HCPs and patients, including controlled delivery and simplified user interface, and could ultimately be used by a qualified HCP in the outpatient setting or at patient's home.

2.3.3 Overall benefit: risk conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with study intervention are justified by the anticipated benefits that may be afforded to participants with RRMM.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 6 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Demonstrate the efficacy non-inferiority between isatuximab SC and isatuximab IV in combination with Pd.	• Overall response rate (ORR): defined as the proportion of participants with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) according to the 2016 IMWG criteria assessed by Independent Review Committee (IRC).
• Demonstrate the pharmacokinetic (PK) non-inferiority between isatuximab SC and isatuximab IV in combination with Pd.	• Observed concentration before dosing (C_{trough}) at steady state (corresponding to predose at C6D1).
Secondary	
Key Secondary	
• Assess efficacy of isatuximab SC compared to isatuximab IV in combination with Pd.	• Very Good Partial Response or better rate: defined as the proportion of participants with sCR, CR, and VGPR according to the 2016 International Myeloma Working Group (IMWG) criteria assessed by IRC.
• Demonstrate the pharmacokinetic (PK) non-inferiority between isatuximab SC and isatuximab IV in combination with Pd.	• Observed concentration before dosing (C_{trough}) at 4 weeks (ie, CT4W corresponding to predose at C2D1).
• Assess safety of isatuximab SC and IV in combination with Pd.	• Incidence rate of infusion-reactions (IRs).
• 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.
Other Secondary	
• Assess efficacy of isatuximab SC compared to isatuximab IV in combination with Pd.	• Duration of response (DOR): defined as the time from the date of the first response to the date of first occurrence of progressive disease (PD) as determined by IRC or death from any cause, whichever happens first. DOR is determined only for participants who have achieved a response (PR or better). In the absence of PD or death before the analysis cut-off date, the DOR will be censored at the date of the last valid disease assessment performed prior to initiation of a further anti-myeloma treatment or the analysis cut-off date, whichever is earlier. Patients with two or more consecutive missed assessments prior to PD or death will be censored at the last valid disease assessment.
	• Time to first response (TT1R): defined as the time from randomization to the date of first IRC determined response (PR or better) that is subsequently confirmed.

Objectives	Endpoints
	• Time to best response (TTBR): defined as the time from randomization to the date of first occurrence of IRC determined best overall response (PR or better) that is subsequently confirmed. • Progression free survival (PFS): defined as the time from the date of randomization to the date of first documentation of progressive disease as determined by IRC or the date of death from any cause, whichever comes first. Responses will be determined according to IMWG criteria. Progression based on paraprotein will be confirmed based on two consecutive assessments. PFS will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first. Patients with two or more consecutive missed assessments prior to PD or death will be censored at the last valid disease assessment. Details censoring rule will be provided in SAP. • Overall survival (OS): defined as the time from the date of randomization to death from any cause. Participants without death prior to the analysis cut-off date will be censored at the last date the participant was known to be alive or the cut-off date, whichever is first. • PFS2: defined as time from the date of randomization to the date of first documentation of PD (as assessed by investigator) after initiation of further anti-myeloma treatment or death from any cause, whichever happens first. Same censoring rule applies as in the PFS endpoint.
• Assess safety of isatuximab SC and IV and local tolerability of isatuximab SC in combination with Pd.	• Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs). Treatment-emergent adverse events (AEs) are defined as AEs that develop, worsen, or become serious during the treatment period. The treatment period is defined as the time from first dose of study treatment up to 30 days after last dose of study treatment. • Laboratory parameters. • Injection site reactions (ISRs) – SC arm only. • Adverse events and laboratory parameters will be graded using NCI CTCAE v5.0.
• Characterize PK of isatuximab SC and IV in combination with Pd.	• PK concentrations.
• Assess the delivery performance of the (investigational) device injector.	• Number of successful injections with (investigational) isatuximab injector device defined as completion of administration per provided instructions for use with no use errors or technical issues, divided by the total number of injections.

Objectives	Endpoints
• Assess the potential immunogenicity of isatuximab SC and IV in combination with Pd.	• Incidence of participants with anti-drug antibodies (ADA) against isatuximab.
• Assess the clinical outcome of isatuximab SC and IV in combination with Pd.	• Patient expectation at baseline and experience/satisfaction with Isatuximab will be assessed using the patient expectation (PEQ), the patient experience and satisfaction (PESQ) and the Patient's Assessment of Treatment (PAT) questionnaires. • Health Resources Utilization will be assessed using the Health Resource Utilization and Productivity Questionnaire (HRUPQ). • Health-related quality of life will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) myeloma module with 20 items (QLQ-MY20) and EORTC quality of life questionnaire with 30 questions (QLQ-C30). • Health status will be assessed using the European Quality of Life Group questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L).
• Explore chromosomal abnormalities [mainly but not limited to t(4;14), t(14;16), del(17p), and 1q21+], and potential association with clinical outcomes.	• Impact of abnormal cytogenetic subtypes on participant outcome.
Exploratory	
• Assess Minimum Residual Disease (MRD) negativity rate of isatuximab SC compared to isatuximab IV in combination with Pd.	• Minimum residual disease (MRD) negativity rate: Defined as the proportion of participants for whom MRD is negative; threshold for negativity will be at least 10^-5. • MRD negative CR rate (MRD[-]CR): defined as the proportion of participants with best overall response as sCR/CR and for whom MRD is negative; threshold for negativity will be at least 10^-5.
• Explore PK and Pharmacodynamics (PDy) relationship.	• Relationship between isatuximab PK exposure and safety endpoints of interest may be investigated as well as between isatuximab PK exposure and efficacy endpoints (eg, ORR, VGPR) if possible (SC arm only).
• Explore genomic and genetic profiling at screening and at disease progression.	• Characterization of bone marrow (BM) genomic and genetic profiles to explore mechanism of drug resistance.
• Explore new methods for measuring serum M Protein such as mass spectrometry.	• Impact of new serum M-protein measurement methods on disease response assessment.
• Explore frailty and potential association with clinical outcome.	• Impact of frailty on participant clinical outcome.

For China, please see Section 10.8 for details.

Primary estimands defined for co-primary endpoints are summarized in Table 7 below.

For all these estimands, the comparison of interest will be the comparison of isatuximab- IV + Pd versus isatuximab- SC + Pd.

Table 7 - Summary of primary estimands for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: Demonstrate the efficacy and PK non-inferiority between isatuximab SC and isatuximab IV in combination with Pd				
Co-Primary endpoint	ORR [stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR)].	ITT	While not initiating new anti-cancer therapy Regardless of IMP discontinuation (treatment policy strategy).	This endpoint will be analyzed by calculating the relative risk between the SC and IV arm and its two-sided 95% CI using Farrington-Manning method and compare its lower CI limit with the pre-defined margin. In absence of confirmed PR or better, participants will be considered as non-responders, whatever the reason (including participants with missing or non-evaluable best overall response).
Co-primary endpoint	C_{trough} at steady state (corresponding to predose at C6D1).	PK-PP	(Principal Stratum strategy) Doses, administration scheme, sample collection, processing and result, time window of collection and adequate documentation.	The point estimate (ratio of geometric means for C_{trough} at steady state of SC/IV) together with its two-sided 90% CI will be calculated. The lower bound of the 90% CI will be compared with 80%. Participants who do not have all administrations up to C5D15 (one dose omission permitted at C1 only) and PK sample collected out of the prespecified time window are not included into the analysis population.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study are considered well established and relevant in a hemato-oncology setting, and suitable steps have been built into each of these assessments to ensure their reliability and accuracy.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a randomized, multicenter, Phase 3, open-label study evaluating SC versus IV administration of isatuximab in combination with pomalidomide and dexamethasone in adult RRMM patients (study participants) who have received at least 1 prior line of therapy including lenalidomide and a PI.

The randomization will be stratified by 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). Eligible participants (approximately 534) will be randomized 1:1 into 1 of 2 study arms:

- Arm SC: Isatuximab SC at 1400 mg with device injector (N = 267).
- Arm IV: Isatuximab IV 10 mg/kg (N = 267).

Isatuximab IV and SC will be administered weekly for 4 weeks (Cycle 1) and on Day 1 and Day 15 of each subsequent cycles, in combination with pomalidomide and dexamethasone.

SC administration of isatuximab will be done using an investigational isatuximab injector device (on body delivery system) (Section 6.1.3).

IV administration of isatuximab will be done by IV infusion with appropriate rate (refer to Table 8, Section 6.1.1.1.1).

Pomalidomide will be administered from Day 1 to Day 21 of each 28 days cycles and dexamethasone will be administered every week.

Before the final OS analysis cutoff date, participants will be allowed to continue therapy until disease progression, unacceptable adverse events (AEs), participant request to discontinue treatment or any other reason, whichever is first. After the final OS analysis cutoff date, participants will be allowed to continue therapy until disease progression, unacceptable adverse events (AEs), participant request, study treatment is commercially available and reimbursed in participant's country, or any other reason, whichever is first.

The efficacy co-primary analysis will be conducted on the ITT population, defined as 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 will be included in a treatment arm as randomized, regardless of whether participants receive any study drug or receive a different study drug from which they were randomized. The PK co-primary analysis will be conducted on the Per Protocol-PK (PP-PK) population defined as all randomized participants who 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.

4.2 AT HOME ADMINISTRATION

Home administration may be possible where permitted by national and local regulations.

After the first 5 cycles, at home administration by an HCP may be proposed to the participants in the SC arm on D15 from Cycle 6 onwards. Visits at Day 1, on the other hand, from C6 onwards will always be outpatient visits at clinic. The Investigator is responsible for approving a participant's initiation with home injections and is still responsible for all study procedures and participant's safety even when delegating infusion responsibilities to the home care company during this clinical study.

The decision to propose at home administration on D15 will be based on the absence of IR at C4 and C5, the hematology test at Day 1 of each corresponding cycle and the Investigator's judgement. Participant willingness and ability to adhere to the requirements of home administration need to be taken into account before initiating it.

D15 at home administration will be preceded immediately prior administration by a questionnaire comprising heart rate, systemic blood pressure, pulse oximetry, oral temperature, and appearance of novel clinical symptoms (Section 6.4.1, Section 8.4.2.1). At-home administration will require full completion of the questionnaire (filling of the questionnaire should be recorded) while participant should be addressed to investigator site if he or she does not meet all the criteria. Reason for non-administration at-home (including data from the questionnaire) should be recorded.

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.3.1 Rationale for the overall design

Randomized blinded clinical trials remain the cornerstone of evidence-based practice. However, due to the presence of a SC formulation and an IV formulation of isatuximab, participant blinding is not feasible. This trial was designed to prove the non-inferiority of SC isatuximab compared to intravenous formulation in combination of pomalidomide and dexamethasone in terms of ORR and C_{trough} at steady state.

4.3.2 Rationale for co-primary endpoints

4.3.2.1 ORR

Achieving deep responses is associated with long-term outcomes in patients with MM (18, 19, 20, 21).

The association between depth of response and PFS in RRMM has been evaluated using results from 102 clinical trials (22). Regression analysis indicated a correlation between the overall response rates (ORR) and median PFS ($R^2 = 0.5$). Another meta-analysis including 7 recent Phase III trials in RRMM demonstrated a strong correlation between ORR and PFS ($R^2 = 0.84$) (23).

In the ICARIA-MM study, that enrolled RRMM participants who had received at least two prior lines of therapy, the ORR were 60.4% versus 35.3% (p<0.0001) in the IPd and Pd arms, respectively, with a median PFS higher in the IPd versus Pd arm (11.5 versus 6.5 months, p=0.001, respectively).

In the IKEMA study, that included RRMM participants who had received 1 to 3 prior lines of therapy, the ORR was numerically higher in the IKd arm compared to the Kd arm (86.6% and 82.9%, respectively)

A margin that corresponds to retaining 40% of the demonstrated clinical effect of CD38+Pd over Pd was chosen because the control arm, Pd, is an efficacious standard of care regimen for RRMM participants (24, 25).

Therefore, retaining 40% of the demonstrated clinical benefit of CD38+Pd over Pd results in promising efficacy results for the Isa-SC+Pd combination. If the study demonstrates an ORR of 60.4% in the Isa-IV+Pd arm of Study EFC15951, which is observed ORR in ICARIA-MM study, then it takes an observed Isa-SC+Pd arm's ORR of 58.8% or higher to claim non-inferiority. This difference represents less than 2% between the two arms and is considered to be a clinically acceptable difference. In addition, the use of the proposed effect retention is aligned with the FDA Guidance for Industry "Non-Inferiority Clinical Trials to Establish Effectiveness" (November 2016), including:

- The pharmacological effect of Isa-SC is similar to Isa-IV, as shown in the TCD15484 study.
- Isa-SC has some important advantages over Isa-IV including the reduction in the frequency of IRs due to the slower SC absorption and the shorter duration of injection (10 minutes) allowing to minimize the time the participant spent in healthcare facility. Overall, the increased convenience of the delivery method aims to improve the long- term treatment adherence and maintain optimal disease control.

4.3.2.2 C_{trough} at steady state (Cycle 6 D1)

C_{trough} at steady state (C6D1 [predose]) was selected based on Health Authorities feedback.

4.4 JUSTIFICATION FOR DOSE

4.4.1 Justification for intravenous isatuximab, pomalidomide and dexamethasone

Oral pomalidomide, dexamethasone and intravenous isatuximab will be used at the dose reported in the ICARIA trial (NCT02990338) and as per recommended posology in the summary of products characteristics (SmPC) or Package Insert.

4.4.2 Justification for subcutaneous dosing of Isatuximab

As previously stated in Section 2.2.3.2, in Study TCD15484 efficacy was comparable between the Isatuximab IV and SC arms. In addition, in the Isatuximab SC arm there were no new safety signal, in comparison to the IV arm. The determination of the SC dosing is therefore based on the PK parameters.

The PK analyses (NCA and population PK modelling) from Study TCD15484 based on the first two dose escalation cohorts showed comparable exposure between SC cohorts despite the dose increase (1000 versus 1400 mg) due to unbalanced covariates in the 2 cohorts (see Section 2.2.3.2). As a consequence, the SC bioavailability of isatuximab is likely to be close to that observed for the 1400 mg SC cohort (ie, 60-65%) as participants from IV and SC 1400 mg cohorts were generally similar in terms of influential PK covariates.

In order to select the SC dose, trial simulations were performed to further establish the comparability of CT4W between isatuximab SC and IV and predict the probability of success as there is a strong relationship between CT4W and efficacy, and there was no apparent relationship between drug exposure in the therapeutic dose range and adverse events of interest. Model based simulations were conducted using a previously developed structural/covariate model (POH0503) (26) for IV isatuximab administration with the addition of SC population PK parameters (ie, the absorption rate constant Ka and the bioavailability F) derived from the popPK model built with data from TCD15484 only and available at the time of analysis. Different values were considered for typical F but the same arbitrary associated inter-individual coefficient of variability of 35% was used in all the simulations scenarios. Clinical trial simulations were performed to select a SC dose that would be non-inferior to IV 10 mg/kg dose (recommended dose for isatuximab IV). For this, a larger scale clinical trial compared to TCD15484 was considered with 1000 replicate trials for each dose scenario (eg, SC doses of 1000 mg, or 1400 mg QW/Q2W with different values for F and to be compared to IV dose of 10 mg/kg QW/Q2W). For each trial, 85 participants for a given SC dose of interest and 43 participants for 10 mg/kg IV were resampled from the subgroup of 198 participants from Studies TCD14079 Part A and EFC14335 that were included in the previous population PK analysis POH0503. The outcome of each individual trial is considered positive if the lower bound of the 90% CI for the ratio of the geometric means (SC/IV) is at least 0.80. Then, the probability of success calculated on 1000 trial replicates was derived for a given SC dose scenario. Considering the SC bioavailability would be in the range of 60-65%, trial simulations show a probability of success of at least 90% for a 1400 mg SC dose whereas the PoS was below 50% for a lower dose (ie, 1000 mg).

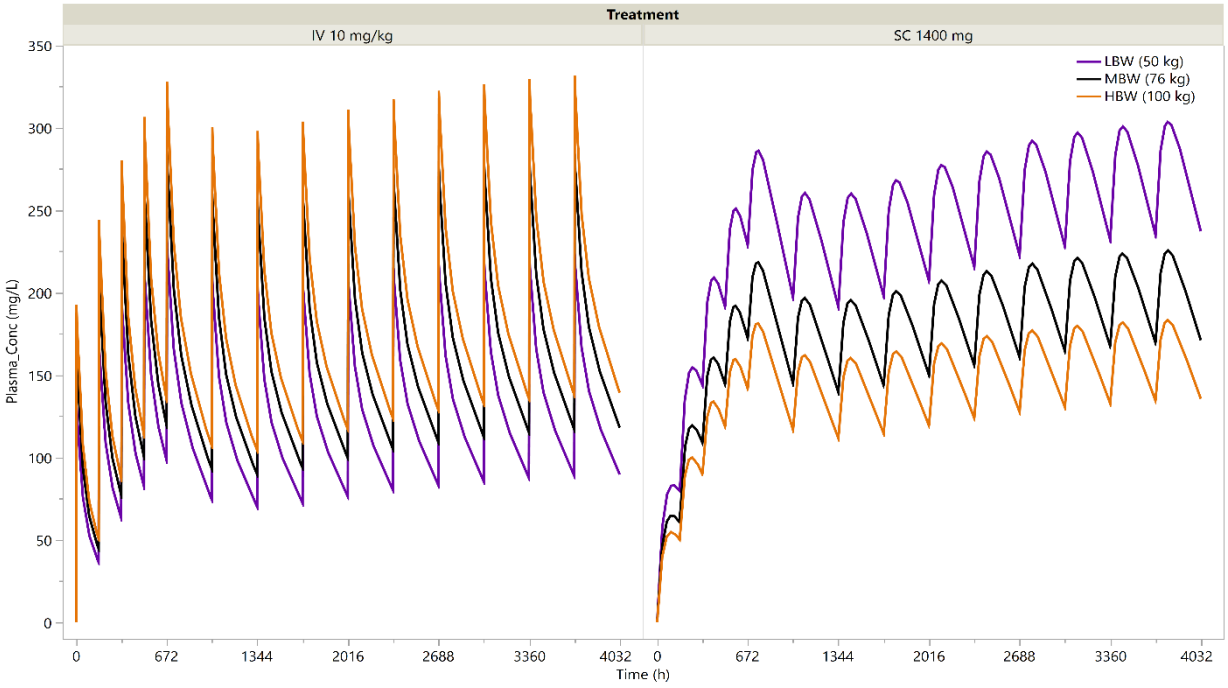
In addition, isatuximab exposure-driven tumor growth inhibition modeling, with serum M-protein as a surrogate for tumor growth, was performed using data from participants who had evaluable serum M-protein at baseline and at least one on treatment assessment in Study TCD15484 (n = 23). Serum M-protein profiles were simulated with the model for IV 10 mg /kg, SC 1000 mg, and SC 1400 mg QW/Q2W regimens using individual PK/PD parameters. Predicted change of serum M-protein from baseline at Week 8 and time to progression (TTP) defined as the time up to an increase of serum M-protein greater than 25% with absolute increase greater than 5 g/L compared to the Nadir (criterion based on only M-protein predictions) were used for comparison of the different doses/route of administration. SC 1400 mg dose resulted in deeper reductions in serum M-protein at Week 8 compared to SC 1000 mg and IV 10 mg/kg, with predicted median% change of baseline [5-95th percentile] of -85.6 [-98.5;-58.1], -77.8 [-96.6;-48.8] and -79.5 [-97.2; -41.6], respectively, translating into a longer time to progression.

Further simulations based on the POH0503 typical population model parameters and including SC parameters, were performed to evaluate the impact of extreme body weights on drug exposure after SC flat dosing. Flat SC dosing results in a higher exposure in lower weight participants

compared to higher weight participants. Compared to a typical participant with median weight (76 kg), a 50 kg participant (5th percentile of body weight) would have 27-33% higher exposure and a 100 kg participant (95th percentile of body weight) would have 15-18% lower exposure at 1400 mg SC (Figure 2). The trend was reversed for isatuximab IV given as body weight-based dose, where higher exposure is observed at higher body weight. In addition, the simulated C_{max} for the lower body weight typical participant (50 kg) for SC was comparable to the C_{max} in the higher body weight typical participant (100 kg) for IV route, but, in general, the C_{max} values for the overall population would be lower for SC route. Overall, flat SC dosing resulted in generally comparable variability as body weight based IV dose, thus supporting the choice of a flat SC dose.

In conclusion, the PK and PK/PD modeling and simulations support the choice of a flat SC dose of 1400 mg in combination therapy.

Figure 2 - Simulated isatuximab plasma concentration-time profiles for participants with low (5th percentile), median or high (95th percentile) body weight after flat SC dose of 1400 mg - Comparison with body weight based IV dose of 10 mg/kg



For SC, F was set to 0.625 and ka to 0.0105.
Body weight distribution POH0503 database: 5th percentile :51 kg, median 76 kg and 95%:110 kg.
Icaria population: Low Body Weight (<50 kg): 2.7% of total; High Body Weight (≥100 kg): 6.0% of total.

4.5 DURATION OF STUDY PARTICIPATION

The participant will be considered in the study from informed consent signature until death, consent withdrawal, or the overall survival (OS) analysis cut-off date (approximately 30 months after LPI), whichever comes first.

The duration of the study for a participant will include a period for screening of up to 28 days. A cycle duration is 28 days. All AEs occurring after informed consent signature will be reported up to 30 days after last study treatment administration.

After study treatment discontinuation, participants will return to the study site 30 days after the last dose of study treatment for end of treatment (EOT) or before further anti-myeloma therapy initiation, whichever comes first (Section 7).

Related AEs and all SAEs regardless of relationship to the study treatment ongoing at the time of study treatment discontinuation will be followed during the follow-up period until resolution or stabilization. During the follow-up period, all (serious or non-serious) new AEs related to study treatment and any second primary malignancy will be collected and followed up until resolution or stabilization.

Participants who discontinue the study treatment due to PD will be followed up every 3 months (12 weeks ±7 days after last study treatment administration) for further anti-myeloma therapies, second primary malignancies, PFS2, and survival, until death or the final OS analysis cut-off date, whichever comes first. Participants who discontinue the study treatment prior to documentation of PD will be followed-up every 4 weeks until disease progression (even for participants who would initiate further anti-myeloma therapy without PD), and then after confirmation of disease progression, every 3 months (12 weeks) for further anti-myeloma therapies, second primary malignancies, PFS2, and survival, until death or the final OS analysis cut-off date, whichever comes first.

Before the final OS analysis cutoff date, participants will be allowed to continue therapy until disease progression, unacceptable adverse events (AEs), participant request to discontinue treatment or any other reason, whichever comes first. Participants still on treatment at the time of the final OS analysis cut-off date, and benefiting from the study treatment, can continue the treatment until disease progression, unacceptable AEs, participant wish to discontinue further study treatment, until study treatment is commercially available and reimbursed in participant's country, or for any other reason, whichever comes first. For cycles administered with products supplied by the Sponsor after the cut-off date, all ongoing SAEs (related or not) and all ongoing related non serious AEs at this cut-off date, all new related AEs (serious or not), product administration, and reason of EOT will continue to be collected.

4.6 END OF STUDY DEFINITION

The end of the study is defined as the last visit of the last participant in the study.

4.7 INTERIM ANALYSIS

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

4.8 TIMINING OF PLANNED ANALYSIS

The cut-off date for the primary analysis is approximately 6 months after the LPI, which includes analysis on the primary endpoint and secondary endpoints when applicable. An update of PFS and OS will be performed 15 months after LPI. The cut-off date for final OS analysis will be approximately 30 months after LPI.

4.9 STUDY COMMITTEES

Refer to Section 10.1.5 for Steering Committee and Data Monitoring Committee information.

An IRC blinded to treatment assignment will determine disease response and progression according to efficacy MM laboratory data (central laboratory results), local BM for plasma cell infiltration assessment as recorded in the electronic case report form (eCRF), and imaging as per IMWG criteria and in line with the IRC charter up to primary analysis.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all the following criteria apply:

Age

I 01. Participant must be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place), at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants must have a documented diagnosis of multiple myeloma.

I 03. Participants with measurable disease defined as at least one of the following:

- Serum M-protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis and/or,
- Urine M-protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis and/or,
- Serum free light chain (FLC) assay: Involved FLC assay ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).

I 04. Participants must have received at least 1 prior line of anti-myeloma therapy, which must include lenalidomide and a PI (bortezomib, carfilzomib or ixazomib) given alone or in combination.

Note: An induction treatment followed by ASCT and consolidation/maintenance is considered as one line of treatment.

I 05. Participants must have documented evidence of progressive disease on or after the last regimen.

I 06. Participants who received only one prior line of therapy must have progressed on or within 60 days after end of the lenalidomide therapy before signing the informed consent form (ICF), ie, lenalidomide refractory.

Weight

None.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 07. All

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

Male participants agree to practice true abstinence or agree to use contraception and refrain from donating sperm as defined in Appendix 4, Section 10.4 while receiving study treatment, during dose interruptions and at least 28 days after the last dose of pomalidomide or 5 months following the last dose of isatuximab, whichever occurs last, even if he has undergone a successful vasectomy.

b) Female participants

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and either is not a female of childbearing potential (FCBP) or agrees to practice complete abstinence or use contraception as described below.

(Note: A FCBP as defined in Appendix 10.4 [Section 10.4.2.1]).

A FCBP must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 to 14 days prior to and again within 24 hours of starting study treatment and must either commit to continue abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts study treatment, during dose interruptions and for at least 5 months following discontinuation of study treatment. An FCBP must also agree to ongoing pregnancy testing during the entire duration of treatment.

Informed Consent

I 08. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other Inclusion Criteria

I 09. Introduced as per Protocol Amendment 01: Country-specific requirement applicable for Norwegian clinical sites; see Appendix 8, Section 10.8 (Country-specific requirements).

a) Male participants that agree to not donate semen or sperm during therapy or for at least 4 weeks following discontinuation of pomalidomide or 5 months following discontinuation of isatuximab.

b) Participants that agree to not donate blood during therapy and for at least 3 months following discontinuation of pomalidomide.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Primary refractory multiple myeloma defined as: participants who have never achieved at least a minimal response (MR) with any treatment during the disease course.

E 02. Inability to tolerate thromboprophylaxis or excess risk of bleeding.

Prior/concomitant therapy

E 03. Participants with prior anti-CD38 treatment: a) administered less than 9 months before randomization or, b) Intolerant to the anti-CD38 previously received.

E 04. Prior therapy with pomalidomide.

E 05. Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone.

E 06. Prior allogenic HSC transplant with active graft versus host disease (GvHD) (GvHD any grade and/or being under immunosuppressive treatment within the last 2 months prior to randomization).

E 07. Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy.

Prior/concurrent clinical study experience

E 08. Received any other investigational drugs or prohibited therapy for this study within 28 days or 5 half-lives from randomization, whichever is shorter.

Diagnostic assessments

E 09. ECOG status >2.

E 10. Platelets <50000 cells/µL. Platelet transfusion is not allowed within 7 days before the screening hematological test.

E 11. ANC <1000 µL (1×10^9/L). The use of granulocyte-colony stimulating factor (G-CSF) within 14 days from the screening hematological test is not allowed to reach this level.

E 12. Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m^2 (modification of diet in renal disease MDRD Formula).

E 13. Total bilirubin >1.5 × upper limit of normal (ULN) (>3 × ULN if Gilbert syndrome).

E 14. Serum calcium (corrected for albumin) level above the ULN range (treatment of hypercalcemia is allowed and participants may enroll if hypercalcemia returns to normal with standard treatment).

E 15. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 × ULN.

E 16. Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy >Grade 1 (Version 5.0 of NCI-CTCAE).

E 17. 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.

E 18. Known intolerance or hypersensitivity to dexamethasone, to any of isatuximab SC formulation excipients (L-histidine; L-histidine hydrochloride monohydrate, L-arginine monohydrochloride, sucrose, polysorbate 80, and poloxamer 188), or to any of the components study therapy that are not amenable to premedication with steroids, or H2 blockers, that would prohibit further treatment with these agents.

E 19. Participants with:

a) Contraindication to dexamethasone, and/or,

b) Contraindication to pomalidomide, and/or,

c) ≥Grade 2 peripheral neuropathy.

E 20. Significant cardiac dysfunction; myocardial infarction within 12 months of randomization; unstable, poorly controlled angina pectoris.

E 21. Diagnosed or treated for another malignancy within 3 years prior to randomization with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low risk prostate cancer after curative therapy.

E 22. Known acquired immunodeficiency syndrome (AIDS)-related illness or known human immunodeficiency virus (HIV) disease requiring antiviral treatment, known active hepatitis A infection (defined as positive hepatitis A antigen or positive IgM), and current active or chronic hepatitis B (HBV) or hepatitis C (HCV) infection. Participants with chronic HBV or HCV disease that is controlled under antiviral therapy are allowed. HIV serology will be tested at screening for participants of countries where required as per local regulations. Hepatitis B and C serology will be tested at screening for all participants.

E 23. Malabsorption syndrome or any condition that can significantly impact the absorption of pomalidomide.

E 24. Active primary amyloid light-chain amyloidosis (evidence of end organ damage or receiving treatment for amyloidosis).

E 25. Concomitant plasma cell leukemia.

E 26. Daily requirement for corticosteroids (equivalent to >10 mg/day of prednisone) for more than 7 days (except for inhalation corticosteroids).

Other exclusions

E 27. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 28. Any country-related specific regulation that would prevent the participant from entering the study; see Appendix 8, Section 10.8 (country-specific requirements).

E 29. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6 [R2]).

E 30. Any severe acute or chronic medical condition which could impair the ability of the participant to participate in the study or interfere with interpretation of study results (eg, systemic infection unless specific anti-infective therapy is employed) or participant unable to comply with the study procedures.

E 31. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 32. Any specific situation during study implementation/course that may raise ethics considerations.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened during the open screening period, provided they meet at that time all inclusion and none of the exclusion criteria. A different participant identification number will be issued, while the other identification for this participant should be recorded as a screen failure. There is no requirement for a waiting period between a screen failure date and the rescreening date.

Screen failure participants can be re-screened, and all screening procedures will have to be re-started for these participants. There is no limitation in the number of times a participant will be screened.

All screening procedures must be repeated except for radiological disease assessment if it has been done in the 28 days prior to novel randomization.

In case the participant is a temporary screen failure, there is no need to have the participant reconsent (ie, sign a new ICF) if the participant ends up participating in the study. However, if the reason for temporary screen failure is a reason that might have altered the initial agreement given by the participant to participate in the study, the Investigator should ensure the willingness of the participant to continue or repeat some screening procedures and to confirm his/her participation in the trial. This oral agreement should be documented in the participant's chart. All tests outside of the protocol window should be repeated and entered to the additional pages.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Section 10.9 (Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency) should be considered for screening/enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified IMPs, AxMPs, and medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

6.1.1 Investigational medicinal products

6.1.1.1 Isatuximab

6.1.1.1.1 Isatuximab IV formulation

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

Isatuximab infusion rate are described in Table 8.

Table 8 - Isatuximab intravenous infusion rate

	Dilution volume	Initial rate	Absence of infusion-related reaction	Rate increment	Maximum rate
First infusion	250 mL	25 mL/hour	60 min	25 mL/hour every 30 minutes	150 mL/hour
Second infusion	250 mL	50 mL/hour	30 min[a]	50 mL/hour for 30 minutes then increase to 100 mL/hour	200 mL/hour
Third and subsequent infusion	250 mL	200 mL/hour			200 mL/hour

a Applicable to Grade ≥2 infusion reactions.

Regarding potential reduction of infusion rates due to IRs active comparator arm, the following steps are recommended:

- **First infusion:** in case of Grade 2 IR during first infusion, infusion could be restarted at one-half (12.5 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 25 mL/hour increments every 30 minutes, up to a maximum of 150 mL/hour, until the total volume is infused.
- **Second infusion:** in case of Grade 2 IR during second infusion, infusion could be restarted at one-half (25 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, up to a maximum of 200 mL/hour, until the total volume is infused.

- **Third and subsequent infusions:** in case of Grade 2 IR during third infusion, infusion could be restarted at one-half (100 mL/hour) of the infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, up to a maximum of 200 mL/hour, until the total volume is infused.

Please refer to the pharmacy manual for further details with regards to formulation.

6.1.1.1.2 Isatuximab SC formulation

Isatuximab will be administered weekly for 4 weeks (Cycle 1) and on Day 1 and Day 15 of each subsequent cycle, at the nominal dose of 1400 mg.

Isatuximab will be administered by an HCP (either on-site or, from Cycle 6, at-home for D-15, see Section 4.2) in the periumbilical region at a single site, using an investigational device injector; injection site will be rotated from one administration to the other.

See Table 9 for more detailed description of dose and method of administration.

6.1.1.2 Dexamethasone

Dexamethasone will be taken orally at a dose of 40 mg (or 20 mg for participant ≥75 years) on Day 1, 8, 15, and 22 (to be repeated every 28 days).

If a dose of dexamethasone is missed, it should be taken as soon as possible within the next 2 days. The dose per cycle must not exceed 160 mg (80 mg if the participant is ≥75 years old). Participants will be asked to maintain a diary to record the doses of dexamethasone taken orally (except those administered by the study nurse/ Investigator).

When administered on the same day as other investigational medicinal products (IMP)s, dexamethasone will be administered before all other IMPs.

Particular care is needed when treating participants with glaucoma (or family history of glaucoma) as well as when treating participants with ocular herpes simplex, because of possible corneal perforation, as prolonged use of corticosteroids may produce subcapsular cataracts and glaucoma, and may result in impaired vision including loss of vision. Investigators are recommended to refer to product SmPC of dexamethasone.

6.1.1.3 Pomalidomide

Pomalidomide will be taken orally at a dose of 4 mg on Days 1 to 21 (to be repeated every 28 days). Pomalidomide may be taken with water and should be swallowed whole. Participants are not permitted to break, chew, or open the capsules. Pomalidomide should be taken with or without food, preferably at the same time every day. Participants will be asked to maintain a diary to record the doses of pomalidomide (except those administered by the study nurse/Investigator). If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, the dose should not be made up and will be considered omitted (and will not be replaced). The next scheduled dose should be taken at the next scheduled time point.

Participants should be monitored for any new or worsening neurologic, cognitive or behavioral signs and symptoms.

If progressive multifocal leukoencephalopathy (PML) is suspected, study treatments should be put on hold immediately until a diagnosis of PML has been definitively excluded. If suspected, the Investigator should refer participant to a specialist and appropriate diagnosis testing should be initiated [Serial Magnetic resonance imaging (MRI) with contrast and cerebrospinal fluid analysis for John Cunningham Virus] [Please refer to PML diagnostic criteria by American Association of Neurology (AAN) (27)].

If PML is confirmed, pomalidomide should be discontinued and isatuximab and dexamethasone should be put on hold. [Please refer to PML diagnostic criteria by AAN (27)] Isatuximab and dexamethasone could be resumed after recovery of PML based on Investigator's judgement and after discussion with the Sponsor.

Table 9 - Study intervention(s) administered

Intervention label	Isatuximab IV	Isatuximab SC	Dexamethasone	Pomalidomide
Intervention name	Isatuximab IV	Isatuximab SC	Dexamethasone	Pomalidomide
Intervention description	Single use vial	Single use vial	Tablets	Capsules
Type	Drug	Drug	Drug	Drug
Dose formulation	Concentrate solution for IV infusion	Solution for Subcutaneous administration	Tablets	Hard capsules
Unit dose strength(s)	Concentration: 20 mg/mL Dosage presentation: 500 mg/25 mL or 100 mg/5 mL	140 mg/mL isatuximab,	4 mg 8 mg	1 mg 2 mg 3 mg 4 mg
Dosage level(s)	10 mg/kg QW (Cycle 1) 10 mg/kg Q2W (subsequent cycles)	1400 mg QW (Cycle 1) 1400 mg Q2W (subsequent cycles)	40 mg QW for participants <75 years of age 20 mg QW ≥75 years of age	4 mg on Day 1 to 21 in a 28-days cycle
Route of administration	IV	SC	Oral	Oral
Use	Active comparator	experimental	Active comparator	Active comparator
IMP	IMP	IMP	IMP	IMP
Packaging and labeling	Isatuximab (SAR650984) will be provided in 1 glass vial per box. The content of the labeling will be in accordance with the local regulatory specifications and requirements	Study Intervention will be provided in one glass vial per box. Each vial and box will be labeled as required per country requirement	Supplied as blisters containing 10 tablets each (1kit = 2 blisters of 10 tablets into a wallet) except for US where it is supplied in a child resistant bottle containing 100 tablets each	Supplied as blisters of 7 hard capsules each (1 kit = 3 blisters of 7 hard capsules into a wallet).
[Current/former name(s) or alias(es)]	Isatuximab, SAR650984	Isatuximab, SAR650984	Dexamethasone	Pomalidomide

6.1.1.4 Study arms

Table 10 - Study arm(s)

Arm title	Arm SC.	Arm IV.
Arm type	Experimental.	Active comparator.
Arm description	Participants will receive isatuximab SC 1400 mg QW (ie, on Day 1, 8, 15, and 22) in first cycle (28 days) then 1400 mg Q2W (ie, on Day 1 and Day 15) for subsequent 28-day cycles. Participants will receive in addition dexamethasone 40 mg QW (<75 years of age) or 20 mg (≥75 years of age) at Day 1, 8, 15, and 22 of every 28 days cycle, as well as pomalidomide 4 mg/day from Day 1 to Day 21 of every 28 days cycle.	Participants will receive isatuximab IV 10 mg/kg QW (ie, on Day 1, 8, 15, and 22) in first cycle (28 days) and then 10 mg/kg Q2W (ie, on Day 1 and Day 15) for subsequent 28-day cycles. Participants will receive in addition dexamethasone 40 mg QW (<75 years of age) or 20 mg (≥75 years of age) at Day 1, 8, 15, and 22 of every 28 days cycle, as well as pomalidomide 4 mg/day from Day 1 to Day 21 of every 28 days cycle.
Associated intervention labels	Isatuximab SC. Dexamethasone. Pomalidomide.	Isatuximab IV. Dexamethasone.. Pomalidomide

Abbreviations: IV = intravenous; QW = once a week; Q2W =once every 2 weeks; SC = subcutaneous.

6.1.2 Auxillary medicinal products

All participants will receive 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 do not experience IRs after 4 consecutive administrations of isatuximab may have their need for subsequent premedication reconsidered at the Investigator's discretion, except for montelukast which should be administered only on Cycle 1.

The standard premedication regimen will include, in this order:

- Montelukast (ATC code: R03DC03)10 mg PO (or equivalent; to be administered during Cycle 1 only).
- Dexamethasone (ATC code: H02AB02) PO will also be given in the same dose as stated in Section 6.1.1.
  - 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: eg, 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.

6.1.3 Devices

Dispensing devices have to be used for administration of isatuximab in the SC arm only.

Preparation and SC administration of isatuximab in the periumbilical region using the (investigational) isatuximab injector device will be performed by study staff. The (investigational) isatuximab injector device is a sterile, single-use, disposable, elastomeric, user-filled wearable injector. The device will be supplied in a blister package into a box. Both the blister package and the box will be labeled according to the local requirements.

The (investigational) isatuximab injector device includes an adhesive backing to secure it to the injection site during administration. Injection sites with the device are permitted only on the abdominal region. At the end of dosing, the injection needle retracts into the device housing and the device enters a locked-out state to prevent reuse.

The volume to be injected at each administration will be injected at a single site; injection site will be rotated from one administration to the next. The administration times including any pauses or stoppages will be recorded for all cohorts.

Further detailed instructions for preparation and administration using the (investigational) isatuximab injector device are provided in Pharmacy Manual. Study staff must be trained on proper use of the device prior to use.

All medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the Investigator throughout the study (see Section 10.7.4).

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

6.2.1 Responsibilities

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, or administer study intervention.

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the study treatment will be responsible for ensuring that the IMP/AxMP/device used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP/AxMP/device will be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of IMP/AxMP/device issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP/AxMP/device (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see pharmacy manual and Section 8.6.8).

A potential defect in the quality of IMP/AxMP/device may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP/AxMP/device and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/AxMP/device to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP/AxMP/device to be used other than as directed by this clinical trial protocol, or dispose IMP/AxMP/device in any other manner.

6.2.2 Treatment accountability and compliance

Administration of the IMP/AxMP/device will be supervised by the Investigator or Subinvestigator.

The person responsible for dispensing IMP/AxMP/device is required to maintain adequate records of the IMP/AxMP/device. These records (eg, drug movement form) include the date the IMP/AxMP/device is received from the Sponsor, dispensed for participant, and destroyed or returned to the Sponsor.

The packaging batch number (PR Nr) on the vial must be recorded on the drug accountability form.

The person responsible for IMP/AxMP/device administration to the participant will record precisely the date and the time of the IMP/AxMP/device administration to the participant.

For dexamethasone PO and pomalidomide PO, a participant diary will be used to document all oral dexamethasone or pomalidomide (if not administered at the site level).

6.2.3 Return and/or destruction of treatments

Partially used and used IMP/AxMP/device will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the Pharmacist). A detailed treatment log form of the destroyed study treatment will be established with the Investigator (or the Pharmacist) and countersigned by the Investigator and the Monitoring Team. Any study materials provided by the Sponsor (IMP and/or medical devices) must be retained for return to the Sponsor for investigation if subject to a product technical complaint (see Section 8.6.8).

The Investigator must not destroy the unused study treatment unless Sanofi provides written authorization.

6.2.4 Isatuximab subcutaneous formulation

All details of preparation and administration of isatuximab are provided in the Pharmacy Manual.

Storage of Isatuximab SC should be in a secure area with restricted access. Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F), is not to be frozen, and is to be protected from light. All containers must be kept in their box until use.

For at-home administration, isatuximab will be provided by the site on Day 1 and stored similarly (without the secure area) for D-15 administration.

For first at-home administration, the participant will be followed 30 min after the injection. Subsequent follow-up is left as per investigator judgment.

6.2.5 Isatuximab intravenous formulation

For participant with IV administration, the appropriate volume of isatuximab will be diluted in a 250 mL infusion bag of 0.9% sodium chloride solution or 5% dextrose solution. Please refer to the Pharmacy Manual for more information.

See Section 6.1.1.1.1 for more detailed description of dose and method of administration.

Storage of isatuximab IV should be in a secure area with restricted access in site. Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F), is not to be frozen, and is to be protected from light. All containers must be kept in their box until use. No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

6.2.6 Pomalidomide

Countries, where commercial supplies are desirable based on the country specific regulatory requirements, Pomalidomide from commercial supplies can be used. Otherwise, it will be re-labeled by the Sponsor according to Good Manufacturing Practice guidelines before supplies are provided by the study sites.

When commercial supplies will be used:

- Please refer to package insert or SmPC for further details as regards to formulation, storage, and handling procedures.
- When applicable the Pomalidomide Pregnancy Prevention Plan (Appendix 15, Section 10.15) or the country specific risk management plan (in countries where pomalidomide is not supplied by the Sponsor) has to be followed to ensure adherence of the pregnancy risk mitigation plan already in place in addition to the protocol requirements.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, pomalidomide may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company, where allowed by local regulations and agreed upon by the participant during the time the measures are applied.

Further details as regards to formulation, storage and handling procedures will be provided in Package Insert or SmPC of commercial study treatment.

6.2.7 Dexamethasone

Dexamethasone PO will be supplied and re-labeled by the Sponsor according to Good Manufacturing Practice guidelines before supplies are provided to the sites.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, dexamethasone may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company, where allowed by local regulations and agreed upon by the participant during the time the measures are applied.

Further details as regards to formulation, storage and handling procedures will be provided in Package Insert or SmPC of commercial study treatment.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Blinding rules

Potential bias will be reduced by the following steps:

- During the trial, administration of isatuximab SC or IV will be open-label, and no attempts will be made to blind administration. An IRT centralized randomization system will be used to prevent the investigators from knowing in advance the study intervention assignment, as the randomization is the best method to avoid bias.
- Despite the open-label administration of treatments, assessment of efficacy outcomes will be based on objectively collected data, which are radiological assessments for tumor response and central laboratory assessment that will be reviewed by an IRC blinded to study intervention arms.
- During the course of the study, an external independent statistician will perform unblinded safety and efficacy analyses for the data review of DMC. Access to these data and analyses will be restricted to the DMC members.
- Blinding rules for the Sponsor study team will be detailed in a separate document.

6.3.2 Randomization

All eligible participants will be randomly assigned to a treatment group (either SC or IV arm) in a 1:1 ratio using an IRT. Participant assignment to a treatment group will be 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).

After each participant has completed the necessary screening visit procedures, the corresponding baseline eCRFs have been completed and the participant is deemed eligible for randomization by the Investigator or designee based on the laboratory evaluations as defined in the study flow chart (Section 1.3), the study site will contact the IRT.

Study intervention will be dispensed at the study visits summarized in the schedule of activities (SoA).

WARNING: Randomization will be blocked if study treatment is not available at site level. A minimum of time will be required between screening registration call and study treatment delivery at site level. Please consider this time between screening call and randomization call, which is indicated in the IRT manual.

Study treatment should be initiated within 3 working days after randomization.

6.4 STUDY INTERVENTION COMPLIANCE

6.4.1 Subcutaneous isatuximab at-home administration

Subcutaneous at-home administration will be performed by an HCP, after completing the questionnaire allowing for at-home administration (including vital signs and novel symptoms). For at-home administration, filling of this questionnaire should be recorded and in case at-home administration is not performed, reason should be collected.

Participants randomized in the SC arm will receive a participant diary. The purpose of the diary is to report potential ISRs during the first 9 cycles in the SC-arm.

6.4.2 Dexamethasone and pomalidomide

Compliance to dexamethasone and pomalidomide will be assessed by direct questioning during the site visits and documented in the eCRF. Participants will be asked to maintain a diary to record the doses of pomalidomide/dexamethasone (except those administered by the study nurse/Investigator). Deviation(s) from the prescribed dosage regimen should be recorded.

6.5 DOSE MODIFICATION

Dose modifications are permitted according to the guidelines described in this section.

The participant may have a dose omitted for any IMP within a cycle if toxicity occurs and the participant does not recover within 3 days after the planned day of planned infusion/administration. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended (dose reduction/omission/delay appropriate to the most severe toxicity) should be followed. Within a cycle, the treatment window is ±1 day for each of QW IMP administrations and ±3 days for each of Q2W IMP administrations.

Cycle delays are permitted in case of toxicity (see Section 6.5.7). Cycle is considered delayed if Day 1 is performed more than 3 days after the planned Day 1 of this cycle. Once a dose of IMP has been decreased, intra-participant re-escalation back to the previous dose level is not permitted, except for dexamethasone dose reduction in a context of intercurrent condition neither related to dexamethasone adverse event nor related to multiple myeloma that might require a transient dose reduction. If a dose reduction is required, it is to be applied compared to the last dose level received by the participant.

Administration of the IMP will be discontinued in the event of an AE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

All changes to study treatment administration must be recorded in the eCRF. Participants will receive the next cycle of study treatment after recovery of the toxicity as described below. If one of the IMPs is permanently discontinued, the other IMPs can be continued until PD, unacceptable toxicity, or participant's wish to discontinue further study treatment. The end of study treatment in this case will be 30 days after the date of the last study treatment administration.

Recommendations for dose adjustments of IMPs due to AEs are described in Table 13, Table 14, Table 15 (SC arm) and Table 16.

6.5.1 Isatuximab

No dose reductions for isatuximab are permitted, but flow rate/infusion can be reduced, and dosing omissions are allowed in case of toxicity. Within a cycle, a delay of up to 3 days in cases of unresolved toxicity at the time of planned readministration is permitted; otherwise, the infusion is omitted.

6.5.2 Pomalidomide

Dose reduction steps for pomalidomide are shown in Table 11. One or several doses of pomalidomide can be omitted.

Table 11 - Dose reduction steps for pomalidomide

Starting dose of pomalidomide (PO)	First dose reduction	Second dose reduction	Third dose reduction
4 mg	3 mg	2 mg	1 mg

6.5.3 Dexamethasone

For participants ≥75 years old, dexamethasone will be administered at 20 mg on Days 1,8,15 and 22 of a 28-day cycle. One or several doses of dexamethasone can be omitted, or the dose of dexamethasone can be decreased to every other week (Table 12).

Table 12 - Dose reduction steps for dexamethasone

Starting dose of dexamethasone Days 1, 8, 15 and 22 (PO)	First dose reduction	Second dose reduction	Third dose reduction	Fourth dose reduction
40 mg	20 mg	12 mg	8 mg	Discontinue dexamethasone
20 mg	12 mg	8 mg	4 mg	Discontinue dexamethasone

6.5.4 Dose adjustments according to adverse events

Dose adjustments for participants treated with isatuximab, pomalidomide and dexamethasone combination in the case of hematological adverse reaction are shown in Table 13.

Table 13 - Guidelines for dose adjustments for hematologic toxicities - isatuximab/pomalidomide/dexamethasone combination

Adverse event	Recommended action		
	Isatuximab[a] (IV or SC)	Dexamethasone (PO)	Pomalidomide (PO)
Thrombocytopenia			
Thrombocytopenia Grade 3	Day 1 of cycle: delay until improvement ≥50 × 10^9/L[b] and administer at same dose level[c]. Within cycle: maintain full dose of study treatment as planned. SC injection of isatuximab: at-home administration at D-15 should not be performed prior alignment with the investigator site.		
Thrombocytopenia Grade 4 with or without bleeding	Day 1 of cycle: delay until improvement ≥50 × 10^9/L[b] and administer at same dose level[c]. Within cycle: delay isatuximab until bleeding is controlled and platelet recover ≥50 × 10^9/L and then administer full dose. If delay is >3 days omit isatuximab and dexamethasone until next planned administration. SC injection of isatuximab: at-home administration at D-15 should not be performed prior alignment with the investigator site. Further episodes: same recommendation.		Day 1 of cycle: delay Day 1 administration until recovery and pomalidomide decreased by one dose level[c]. Within cycle: hold pomalidomide until bleeding is controlled and platelet recover ≥50 × 10^9/L, and then re-start with 1 dose level decrease up to planned Day 21. Next cycle will be restarted with this one dose level decrease. second episode: same recommendation with decrease of pomalidomide by a second dose level. third episode: discontinue pomalidomide.
Neutropenia			
Neutropenia Grade 3	Day 1 of cycle: delay until recovery absolute neutrophil count ≥1.0 × 10^9/L and administer at same dose level[c]. Within cycle: maintain full dose as planned.		

Adverse event	Recommended action		
	Isatuximab[a] (IV or SC)	Dexamethasone (PO)	Pomalidomide (PO)
Neutropenia Grade 4[d]	Day 1 of cycle: delay until absolute neutrophil count recovery ≥1.0 × 10^9/L and administer at the same dose level[c]. Within cycle: Maintain same dose as planned. Further episodes: same recommendations.		Day 1 of cycle: delay Day 1 administration until recovery and restart pomalidomide decreased by one dose level or consider G-CSF use and keep same dose level. Within cycle: hold pomalidomide until neutrophil counts recover ≥0.5 × 10^9/L and then: • Re-start with 1 dose level decrease up to planned Day 21. Next cycle will be re-started with this one dose level decrease. • Or consider G-CSF use and keep same dose level. Second episode: same recommendations with decrease of pomalidomide by a second dose level. third episode: discontinue pomalidomide.
Febrile neutropenia and/or neutropenic infection	Day 1 of cycle: delay Day 1 administration until fever and infection recover and add G-CSF until ANC>1 × 10^9/L[c] Then administer Day 1 next cycle with isatuximab and dexamethasone at the same dose level and pomalidomide with dose recommendations below. Within cycle: omit isatuximab and dexamethasone, hold pomalidomide dose and add G-CSF until fever and infection have recovered and ANC>1 × 10^9/L. Then administer isatuximab and dexamethasone at the planned days at the same dose level and re-start pomalidomide up to planned Day 21 with dose recommendations below: • First episode, resume same dose pomalidomide with G-CSF or re-start with 1 dose level decrease. • Second episode, resume with action not done at first episode (same dose with G-CSF or 1 dose decrement pomalidomide). • Third episode, resume with one dose decrement of pomalidomide. • Fourth episode, stop pomalidomide.		

a Participants may have isatuximab dose omission within a cycle if certain toxicities do not recover within 3 days following the day of planned infusion (Section 6.5.1).

b For participants with plasma cells >50% of bone marrow nucleated cells at baseline, to initiate Cycle 2, platelet counts should be ≥30 000/mm^3 regardless response status at end of Cycle 1. During Cycles 2-4, platelet counts should be ≥30 000/mm^3, if last response is not better than SD, but if last response is PR or better during Cycles 2-4, D1 next cycle can be administered only if platelet counts ≥50 000/mm^3. For D1 administration beyond Cycle 4, platelet counts should be ≥50 000/mm^3.

c A dose delay of up to 14 days between cycles is permitted in order to recover to the participant´s baseline status. Beyond 14 days, the participant should be discontinued from study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment (see Section 6.5.7).

d If G4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 × 10^9/L and at least weekly thereafter until ANC ≥1.0 × 10^9/L.

IV: intravenous.

SC: subcutaneous.

PO: per os.

Dose adjustments for participants treated with isatuximab, pomalidomide and dexamethasone combination in the case of non-hematological adverse reaction are shown in Table 14.

Table 14 - Guidelines for dose adjustments for non-hematologic toxicities - isatuximab/pomalidomide/dexamethasone combination

Adverse event	Recommended action		
	Isatuximab[c]	**Dexamethasone[c]**	**Pomalidomide**
DVT/PE			
Grade 3	Day 1 of cycle: initiate appropriate anticoagulation therapy and when efficient anticoagulation administer cycle at full dose isatuximab and the same dose level of dexamethasone and pomalidomide[a]. Within cycle: maintain full dose isatuximab and the same dose level of dexamethasone as planned. For pomalidomide: • First episode: hold pomalidomide, initiate appropriate anticoagulation therapy and restart same dose pomalidomide when efficient anticoagulation. • Second episode: despite appropriate anticoagulation pomalidomide permanently discontinued.		
Grade 4	Day 1 of cycle: delay Day 1 administration until controlled and administer the full dose of isatuximab and the same dose level of dexamethasone[a]. Within cycle: delay isatuximab and dexamethasone until stabilization and resume without dose reduction at the next planned dates. If delay is >3 days omit isatuximab and dexamethasone until next planned administration.		Pomalidomide permanently discontinued.
Peripheral Edema Grade ≥3 (limiting function and unresponsive to therapy or anasarca), excluding infusion associated reaction	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Diuretics as needed, and decrease dexamethasone dose by 1 dose level. if edema persists despite above measures, decrease dose another dose level. If symptoms persist despite second reduction, dexamethasone permanently discontinued.	Day 1 of cycle or within cycle: maintain full dose pomalidomide as planned.
Allergic reaction/hypersensitivity			
Grade 2	Hold study treatment until <Grade 2, and participant clinically stable; then, resume study treatment at the same dose level for infusion reaction related to isatuximab[a]. For allergic reaction related to pomalidomide, refer to site local protocol. In case of D-15 at-home administration: transfer participant to investigator site.		
Grade ≥3	Permanent discontinuation of the drug responsible of the allergic reaction.		
Grade ≥3 Infections without concomitant neutropenia	Hold study treatment until systemic treatment of infection complete. Resume all at the same dose level.		
Herpes zoster	Hold study treatment until lesions are dry, then resume all at the same dose level.		

Adverse event	Recommended action		
	Isatuximab[c]	**Dexamethasone[c]**	**Pomalidomide**
Neuropathy			
Grade 2 with pain or Grade 3	Full dose isatuximab and same dose level of dexamethasone.		Hold pomalidomide until neuropathy improves to Grade ≤2 without pain. First episode: resume pomalidomide with a decrease of pomalidomide by 1 dose level. Second episode: resume pomalidomide with a decrease by a second dose level. Third episode: pomalidomide permanently discontinued.
Grade 4	Full dose isatuximab and same dose level of dexamethasone.		pomalidomide permanently discontinued.
Confusion or mood alteration Grade ≥2 (interfering with functions ±daily activities)	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above measures, dexamethasone permanently discontinued.	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned.
Gastrointestinal dyspepsia, gastric or duodenal ulcer, gastritis			
Grade 1-2 (requiring medical management)	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned.
≥Grade 3 (requiring hospitalization or surgery)	Hold study treatment until symptoms adequately controlled. Then, restart full dose isatuximab and same dose level of pomalidomide, and decrease dexamethasone by one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, dexamethasone permanently discontinued.		
Acute pancreatitis	Dexamethasone permanently discontinued. Day 1 of cycle: delay Day 1 until recovery[c] and re-start full dose isatuximab and same dose level of pomalidomide. Within cycle: hold all study treatment until recovery and re-start full dose isatuximab and same dose level of pomalidomide.		
Hyperglycemia ≥Grade 3	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned.

Adverse event	Recommended action		
	Isatuximab[c]	**Dexamethasone**[c]	**Pomalidomide**
Muscle weakness ≥Grade 2 (symptomatic and interfering with function ±daily activities)	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. If symptoms persist dexamethasone permanently discontinued.	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned.
Renal dysfunction eGFR <30 mL/min/1.73m^2 (MDRD formula)	Day 1 of cycle: delay Day 1 administration until eGFR returns to ≥30 mL/min[a]. Within cycle: hold study treatment until improvement to ≥30 mL/min. Then re-start full dose isatuximab, same dose level of dexamethasone and pomalidomide up to planned Day 21. If delay is >3 days, omit isatuximab and dexamethasone.		
Progressive multifocal leukoencephalopathy (PML)[d]	If PML is suspected Immediately put on hold all study treatments and refer the patient to a specialist[d].		
	If PML is confirmed Put on hold isatuximab and dexamethasone.		If PML is confirmed Pomalidomide must be permanently discontinued.
	If PML is recovered Isatuximab and dexamethasone can be resumed after recovery of PML based on Investigator's judgement and after discussion with the Sponsor.		If PML is recovered Pomalidomide must be permanently discontinued.
Any other drug related nonhematologic Grade 3-4 AE	Day 1 of cycle: delay Day 1 administration until recovery and apply same rules of dose modification than the rules below[a]. Within cycle: For isatuximab attribution, omit dose if the event has not recovered within 3 days. Resume at full dose when toxicity has improved to Grade 2 or less or to baseline grade. Second episode, isatuximab discontinuation. For dexamethasone attribution omit dose if the event has not recovered within 3 days. Resume with 1 dose level decrease when toxicity has resolved to Grade 2 or less or to baseline grade. Second episode, apply new dose reduction. Third episode, dexamethasone discontinuation. For pomalidomide attribution, hold dose. Resume with 1 dose level decrease when toxicity has improved to Grade 2 or less or recovered to baseline grade. Second episode, apply new dose reduction. Third episode, pomalidomide discontinuation.		

a A dose delay of up to 14 days between cycles is permitted in order to recover to the participant´s baseline status. Beyond 14 days, the participant should be discontinued from study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment (see Section 6.5.7).

b See Section 6.1.2 for IR management. Participants may have pomalidomide one or several dose omission at any moment during the cycle.

c Participants may have isatuximab and/or dexamethasone dose omission within a cycle if certain toxicities do not recover within 3 days following the day of planned infusion (see Section 6.5).

d See Section 6.1.1.3 for monitoring of PML and dose modification of study IMPs.

6.5.5 Management of infusion reactions and injection site reactions

Participants should receive premedications prior to isatuximab infusion as detailed in Section 6.1.2 to reduce the risk and severity of IRs commonly observed with mAbs. Infusion associated reactions (including, for example, NCI-CTCAE V5.0 terms "infusion related reaction" or "anaphylactic reaction") are defined as AEs related to product administration with onset typically within 24 hours from the start of the infusion.

Please refer to the current edition of the IB for IRs manifestations reported in participants treated with isatuximab.

Management of IR and injection sites reactions ISRs is described in Table 15 for SC injection and in Table 16 for IV injections.

Table 15 - Guidelines for management of injection sites reactions (ISRs) and infusion reactions (IRs) for Isatuximab subcutaneous administration NCI-CTCAE v5.0 criteria

Injection site reaction	Infusion reactions	Recommendation
Grade 1 Tenderness with or without associated symptoms (eg, warmth, erythema, itching).	**Grade 1** Mild transient reaction; infusion interruption not indicated; intervention not indicated.	**ISRs:** Continuation of isatuximab administration. Report AE. If the ISRs occurs during or in the 48 hours after at-home administration, subsequent 2 (D15 of subsequent cycle) administrations should be done at the investigator site.
		IRs: Continuation of isatuximab administration is per the judgment of the Investigator following close direct monitoring of the participant's clinical status. Report AE. Isatuximab administration may be stopped at any time if deemed necessary. If stopped, IR will be classified as Grade 2 as per NCI-CTCAE v5.0 definition.
Grade 2 Pain; lipodystrophy; oedema; phlebitis.	**Grade 2** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours).	**ISRs:** If during administration: Interrupt isatuximab administration and resume only with an administration with pauses after recovery to G1 or better. Report AE and AESI. In case the reaction occurs during the D-15 at-home administration, definitely stop the at-home injection and contact investigator site. If post-administration: Continue isatuximab treatment after recovery to G1 or better. Report AE and AESI.
		IRs: If during administration, interrupt isatuximab administration without possibility to restart the current injection. For subsequent cycles, give additional medication with IV diphenhydramine 25 mg IV (or oral equivalent) and/ or IV methylprednisolone 100 mg (or oral equivalent) and/or other supportive care as needed. Report AE.
Grade 3/4	**Grade 3/4**	**ISRs:** Definitive discontinuation of isatuximab administration. Report AE and AESI.

Injection site reaction	Infusion reactions	Recommendation
Grade 3: Ulceration or necrosis severe tissue damage operative intervention indicated. Grade 4: Life-threatening consequences; urgent intervention indicated.	Grade 3: prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: life-threatening consequences; urgent intervention indicated.	**IRs:** If during administration: Definitive stop of the current isatuximab administration. Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Report AE and AESI. In case of Grade 3, isatuximab administration may be resumed at the next planned administration at Investigator's discretion. If a Grade 3 IR occurs for a 3rd time, treatment with isatuximab will be definitively discontinued for that participant. In case of Grade 4, isatuximab will be permanently discontinued.

Table 16 - Guidelines for management of infusion reactions for isatuximab intravenous administration NCI-CTCAE v5.0 criteria

Infusion reaction grading (NCI-CTCAE V5.0 criteria	Recommendation
Grade 1: mild transient reaction; infusion interruption not indicated; intervention not indicated.	Continuation of isatuximab infusion is per the judgment of the Investigator following close direct monitoring of the participant's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IR will be classified as Grade 2 as per NCI-CTCAE definition.
Grade 2: moderate reaction; therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours).	Stop isatuximab infusion. Give additional medication with IV diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed only after participant recovery, at half the infusion rate before the interruption, and with close monitoring-, and may be increased subsequently, at the Investigator's discretion.
Grade 3 / 4: severe or life-threatening reaction; Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop isatuximab infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed until the resolution of the AE or until the AE improves to Grade 1. Only then, if previous Grade 3, the infusion may be restarted at the Investigator's discretion; if so, the infusion rate should be half of the initial infusion rate and it may be increased subsequently, at the Investigator's discretion. If the severity of an infusion-related AE returns to Grade 3 after the restart of the infusion, the same procedure described above may be repeated at the Investigator's discretion. If a Grade 3 infusion-related AE occurs for a 3rd time, treatment with isatuximab will be definitely discontinued for that patient. In case of Grade 4, isatuximab will be permanently discontinued.

6.5.6 Tumor lysis syndrome

Tumor lysis syndrome may occur and is a life-threatening event. The participants at greatest risk of TLS are those with high tumor burden prior to treatment. These participants should be monitored closely, and appropriate precautions should be taken (such as use of prophylactic uric acid lowering agents [eg, allopurinol or rasburicase], regular measurement of electrolytes).

Tumor lysis syndrome has to be managed according to site usual practice. Table 17 provides some parameters to be checked in case of TLS suspicion and high-level recommendations for TLS management. Abnormalities listed in Table 17 do not support TLS diagnosis exclusively and any differential diagnosis also needs to be assessed if appropriate.

After recovery, study treatment can be re-administered as planned at the same dose.

Table 17 - Management of tumor lysis syndrome

TLS main possible diagnosis criteria	Recommended action
Laboratory TLS: ≥2 simultaneous abnormalities within 3 days prior to and up to 7 days after treatment start: • Uric acid >8 mg/dL (>475.8 µmol/L). • Potassium >6.0 mmol/L. • Phosphate >4.5 mg/dL (>1.5 mmol/L). • Corrected calcium <7.0 mg/dL (<1.75 mmol/L), ionized calcium <1.12 mg/dL (0.3 mmol/L)[a].	Omit study treatment until all serum chemistries have resolved. Ensure adequate hydration, correct laboratory abnormalities, fluid overload, uric acid lowering agents (such as rasburicase), electrolyte, or acid-base deviation. Monitor TLS complications including renal functions. Reinstitute study treatment at full dose after resolution.
Clinical TLS: Laboratory TLS in addition to 1 of the following complications: • Acute kidney injury: Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hour for 6 hours. • Seizures, sudden death, cardiac dysrhythmia, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia. • Dysrhythmias probably or definitely caused by hyperkalemia.	

a The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4-albumin in grams per deciliter). Adapted from Howard et al.

6.5.7 Retreatment criteria

A new cycle of study treatment may begin on the scheduled Day 1 of a subsequent cycle if the following criteria are met.

- Absolute neutrophil count ≥1.0×10^9 /L.
- Platelet count ≥50×10^9 /L.
- Any other IMP-related AE that may have occurred in the previous cycle has recovered to Grade ≤1 or baseline severity (or according to the dose modifications shown in Section 6.5 of this protocol).

If these criteria are not met on the scheduled Day 1, Day 1 should be delayed until participants recover as defined above and if D1 delay is more than 3 days, the reason should be documented. If these criteria are not met within 14 days of the scheduled Day 1 (planned Day 1 Cycle n +1 corresponds to Day 29 cycle n), the participant should be discontinued from study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment. The Investigator must discuss the rationale with the Sponsor before a decision is taken.

A delay for participant's convenience should be avoided during the first cycles and a delay more than 14 days has to be discussed with the Sponsor before a decision is taken.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Participants still on treatment at the time of the final OS analysis cut-off date, and benefiting from the study treatment, can continue the treatment until disease progression, unacceptable AEs, participant wish to discontinue further study treatment, until study treatment is commercially available and reimbursed in participant's country, or for any other reason, whichever comes first.

6.7 TREATMENT OF OVERDOSE

For the study, IMP overdose is defined as any of the following conditions:

- Any administration of isatuximab IV or isatuximab SC at least 30% above the intended dose at each administration or dose administered in less than half the recommended duration of administration.
- Any administration of an oral IMP (pomalidomide and dexamethasone) at least twice the intended dose within the intended therapeutic interval. Of note, dexamethasone dose will be evaluated on a whole cycle.

AxMP overdose is defined as at least twice the intended dose within the intended therapeutic interval.

In case of accidental or intentional overdose with the IMP/AxMP, even if not fulfilling a serious criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the eCRF.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 5 months).
- Evaluate the participant to determine, if possible, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
- Obtain a plasma sample for PK analysis as soon as possible if requested by the Sponsor or Sponsor representative(s) (determined on a case-by-case basis).
- Document appropriately in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor or Sponsor representative(s) based on the clinical evaluation of the participant.

6.8 PRIOR AND CONCOMITANT THERAPY

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

A concomitant medication is any treatment received by the participant concomitantly to any study treatment(s). All treatments being taken by the participant 21 days prior to inclusion, at any time during the treatment period and up to 30 days after the last dose are regarded as prior and concomitant treatments respectively and will be reported on the appropriate pages of the eCRF.

Concomitant medications are allowed if not listed in prohibited medications and if these are considered necessary for the participant's welfare and are unlikely to interfere with the investigational product. They may be given at the discretion of the Investigator and recorded in the eCRF.

Antifungal and antiviral agents for prophylactic or therapeutic use can be administered as considered appropriate by the Investigator.

Hepatitis B vaccination could be considered, following Investigator’s discretion, for participants with negative HBsAg, total antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs) and HBV-DNA. At least 3 doses of vaccine will be administered at monthly intervals, the first one 1 to 2 weeks before start of study treatment. Anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination. Anti-HBs above 100 mU/mL will indicate a good seroconversion, between 10 and 100 mU/mL moderate seroconversion that can be limited in time, less than 10 mU/mL will indicate no response to vaccination.

If antiviral therapy for HBV or HCV was started before initiation of study treatment and participant was eligible for the trial, the antiviral therapy for HBV or HCV should continue throughout the treatment period as recommended by specialist. In case of trial testing combo, it should be checked that there is no drug-drug interaction with the drug associated with isatuximab.

In case of viral reactivation during study treatment (greater than 1 $\log_{10}$ IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in participants with resolved infection [ie, previous known history of acute or chronic hepatitis B or the presence of total anti-HBc with/without anti-HBs; HBsAg negative; undetectable serum HBV DNA; normal L-alanine aminotransferase levels]), study treatment will be held and a specialist consulted for initiation of anti-viral treatment and monitoring of the participant. Restart of the study treatment should be agreed among the Sponsor, Investigator, and specialist (hepatologist) if infection is controlled. Close monitoring of L-alanine aminotransferase and L-aspartate aminotransferase should be done every month, up to study treatment discontinuation. Hepatitis B virus DNA testing must be done as per specialist advice.

6.8.1 Antithrombic therapy

Pomalidomide increases the risk of venous thromboembolism. Anticoagulation prophylaxis is required after an assessment of each participant's underlying risk factors. Unless there is an excess risk of bleeding (those participants are to be excluded from the study; see exclusion criterion E2) all participants should receive prophylactic antithrombotic treatment. Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (eg, smoking, hypertension, and hyperlipidemia).

Aspirin prophylaxis is recommended for participants with standard risk. If aspirin is contraindicated, participants will receive another form of antithrombotic therapy according to hospital guidelines or physician preference. Participants with at least 1 risk factor (ie, history of prior venous thromboembolism, immobilization, and concomitant use of an erythropoiesis-stimulating agent) should use low-molecular weight heparin or alternatively a direct oral anticoagulant (factor Xa inhibitors, direct oral factor IIa inhibitors) or a vitamin K antagonist.

6.8.2 G-CSF prophylaxis

Prophylactic administration of G-CSF in a participant who is experiencing recurrent neutropenia, or therapeutic use in participants with serious neutropenic complications (such as tissue infection, sepsis syndrome or fungal infection) may be considered at the Investigator's discretion, consistent with the American Society of Clinical Oncology guidelines (2006) (28) in order to decrease the risk of neutropenia specially in participants with baseline extensive BM involvement and/or low neutrophil count (29).

6.8.3 Antibiotic prophylaxis

Neutropenia is one of the most common adverse events of pomalidomide. A high rate of Grade 3/4 neutropenia (>80%) was observed in the isatuximab plus pomalidomide and dexamethasone arm of the ICARIA trial, with a quarter of participants experiencing a neutropenic complication (2). Antibiotic prophylaxis is thus recommended at start of treatment, with fluoroquinolone as the preferred option per NCCN (Prevention and Treatment of Cancer-Related Infections, Version 2.2016) guidelines for the participants with an intermediate risk of infection (MM and anticipated neutropenia) (30). However, Ciprofloxacin and Clinafloxacin which are strong inhibitors of Cytochrome P450 Family 1 Subfamily A Member 2 (CYP1A2) should be avoided. Investigators may consider other appropriate antibiotic prophylaxis. Although there is no specific NCCN guidelines on duration of prophylaxis when MM treatment is ongoing, 3 months of antibiotic prophylaxis is recommended at diagnosis for MM participants at high-risk of infections (31).

6.8.4 Prohibited concomitant therapy

Concurrent treatment with any other antimyeloma therapy not specified in the protocol, including immunotherapy, targeted therapy, biological therapies and curative radiotherapy, as well as any other investigational drug, is prohibited. However, palliative radiotherapy may be given to control

pain. The irradiated area should be as small as possible and should never involve more than 20% of the BM in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical, biochemical, and radiological assessments of the tumor. The irradiated area cannot be used as a parameter for response assessment.

Drugs prohibited 28 days prior to randomization include:

- Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone.
- Prior allogenic HSC transplant with active GvHD (GvHD any grade and/or being under immunosuppressive treatment within the last 2 months prior to randomization).
- Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy.
- Any other investigational drugs or prohibited therapy for this study within 28 days or 5 half-lives from randomization, whichever is shorter.
- Concomitant systemic long-term corticosteroids, other than as part of the protocol-specified therapeutic regimen or for treatment of hypersensitivity reaction or for the treatment of adverse reactions, are prohibited. Any short-term corticosteroids are allowed to treat AEs.
- Additional glucocorticoids (or inhaled glucocorticosteroids whenever indicated), antihistamines, and analgesics, for the management of IRs are permitted.
- Live vaccines should be avoided up to 90 days after last dosing of study IMPs. However, given the increased risk of infection, non-live vaccines on routine vaccinations are recommended for the participants and their contacts. Prophylactic vaccination is recommended for influenza A and B virus, pneumococci and *Haemophilus influenzae*.
- Avoid co-administration of strong inhibitors of CYP1A2:
  - Bai-zhi.
  - Clinafloxacin.
  - Ciprofloxacin.
  - Enoxacin.
  - Fluvoxamine.
  - Oltipraz.
  - Rofecoxib.
  - Vemurafenib.

6.8.5 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The study treatment should be continued whenever possible. Any study treatment discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible.

Pregnancy in the female participants will lead to definitive treatment discontinuation in all cases.

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1.1 Permanent discontinuation

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the study treatment at any time during the study, or from the participant not to be re-exposed to the study treatment whatever the reason. In rare instances, it may be necessary for a participant to permanently discontinue study intervention.

If one of the study treatments is prematurely permanently discontinued, then other drug(s) can be continued until disease progression or unacceptable toxicity or participant's wish to discontinue further study treatment. During this period the participant will remain in the study and continue being assessed per SoA. If all study treatments are permanently discontinued, the visit will be treated as the last dosing day with the IMPs, with subsequent relevant assessments per SoA.

In case of permanent treatment discontinuation due to disease progression, follow up will be every 3 months for further antimyeloma therapy, second primary malignancies, PFS2, and survival until death, or final OS analysis cut-off date, whichever occurs first. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1.1 List of criteria for permanent discontinuation

The participants may withdraw from study treatment if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

Isatuximab, pomalidomide, and/or dexamethasone can be discontinued permanently.
The participant will remain on study treatment until the last study treatment is discontinued.
The reason for permanent discontinuation will be captured in the appropriate eCRF page.

All efforts should be made to document the reason for discontinuation of treatment with the study treatment:

- At the participant's request, at any time and irrespective of the reason (consents withdrawal). Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical records check. Participants requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. The Investigator should make every effort to re-contact the participant, to identify the reason why he/she decided to withdraw, and to determine his/her health status, including at least his/her vital status.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as:
  - Disease progression.
  - Unacceptable AE.
  - Poor compliance to the study protocol.
  - Any other reason such as intercurrent illness that prevents further administration of study treatment (will be specified).
- Pregnancy in a female participant.
- Participant is lost to follow-up.

If participants are clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, the participant will be maintained on treatment for the maximum period of time defined in Section 1.3.

Participants who have been withdrawn from the study treatment cannot be re-included in the study. Their inclusion and treatment number must not be re-used.

7.1.1.2 Handling of participants after permanent intervention discontinuation

Participants will be followed up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever occurs last.

If possible, and after the permanent discontinuation of treatment, the participants will complete the evaluations scheduled for the EOT and follow-up visits as detailed in the SoA (Section 1.3). All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs (Section 8.6) or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.9). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.3 Rechallenge

Re-initiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely if the selection criteria for the study are still met (refer to Section 5).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or whitout providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an end-of-treatment visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent, as per applicable clinical regulation(s).
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study. The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study treatment should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent. Participants who discontinue study treatment will not be replaced.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 244 mL per participant in Cycle 1 to 3 and will be lower in subsequent cycles.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements [see Appendix 9 (Section 10.9)].

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9 (Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

8.1 ADMINISTRATIVE [AND GENERAL/BASELINE] PROCEDURES

Not applicable.

8.2 EFFICACY ASSESSMENTS

The primary and secondary efficacy endpoints will be determined by IRC based on central laboratory M-protein analysis, local BM for plasma cell infiltration assessment as recorded in the electronic case report form (eCRF) and central radiology review according to IMWG criteria (Section 10.10, Appendix 10). IRC will be blinded to treatment assignment. Please see the schedule of activities for more information (Section 1.3).

The following myeloma-specific lab tests will be performed at screening (for eligibility) and again within 24 hours prior to the start of study treatment administration at Cycle 1/Day 1 (baseline for response assessment) and then Day 1 of every cycle during treatment up to progression and for participants who discontinue study treatment for reasons other than progression, every 4 weeks during follow-up until PD:

- M-protein quantification (serum and 24-hour urine, protein immunoelectrophoresis, and immunofixation) by central laboratory. After Cycle 1/Day 1, immunofixation will be done in case of undetectable M-protein (serum and urine).
- Serum free light chain levels by central laboratory.
- Quantitative immunoglobulins (IgG, IgA, IgM, IgD, and IgE) by central laboratory.

Other examinations for disease assessment will be done as below:

- Bone marrow aspiration (BMA) (or biopsy as clinically indicated) for quantification of percentage plasma cells is required at screening/baseline (within 21 days prior to study treatment administration). Repeat BM aspirate or biopsy to confirm CR or sCR if CR or sCR is suspected (local laboratory).
- Bone marrow aspiration for MRD assessment: At screening, at time of maximum confirmed CR or VGPR, 12 months after C1D1 and 12 months after first MRD negativity.
- Bone marrow aspiration for cytogenetics assessment: At screening, bone marrow aspirate will be collected for Fluorescent in Situ Hybridization (FISH) (including, but may not be limited to, del[17p], t[4;14], t[14;16]), 1q21+) analyses in central laboratory.
- Bone marrow aspiration for genomic and genetic profiling at screening and at time of progression (central laboratory).
- Bone imaging: Whole-body low-dose (WBLD) computed tomography (CT) scan, Positron emission tomography-Computed tomography (PET-CT) scan or MRI at baseline (within 28 days prior to randomization), once a year (±1 month) from C1D1, and anytime during the study if clinically indicated, until PD (even if further anti-myeloma therapy is started without PD as per protocol), or final cut-off date, whichever occurs first. PET-CT should be the preferred imaging modality whenever possible.
- Soft tissue plasmacytoma assessment (extramedullary disease OR paramedullary disease with a soft tissue lesion of diameter ≥2 cm):
  - If known soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline, repeated every 12 weeks (±1 week) until progressive disease (PD) from C1D1 (even for participants who would initiate further anti-myeloma therapy without PD), and if clinically indicated. From two years after randomization, the radiological assessment will be done every 6 months (±1 month). Assessment to be done until PD (even if further anti-myeloma therapy is started without PD as per protocol), or final cut-off date, whichever occurs first.
  - If suspected soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline and if plasmacytoma confirmed on the exam to be repeated as indicated above.

- To be done in case of suspicion of progression or if clinically indicated in a participant with no previous positive image for soft tissue plasmacytoma.
- The bone component of paramedullary disease with a soft tissue lesion of diameter ≥2 cm will not be used for disease response assessment as per IMWG.
- Paramedullary (paraskeletal) plasmacytoma (bone plasmacytoma extending beyond the bone cortex into the surrounding tissues) with soft tissue lesions of diameter <2 cm will be collected but will not be used for disease response assessment as per IMWG. No follow-up with repeated imaging is needed, except if clinically indicated.
- PET-CT should be the preferred option whenever possible.

Note: For bone lesion assessment and soft tissue plasmacytoma, the same modality (whole-body low-dose CT scan; CT scan, PET-CT scan, or MRI) should be used throughout the study for each individual participant when radiological follow-up is needed.

Intravenous contrast is recommended if not medically contra-indicated.

In case of both serum and urine M-protein become below level of eligibility on efficacy laboratory performed on Cycle 1/Day 1, please refer to the IMWG Response Criteria (Appendix 10, Section 10.10) for assessment of progression and overall response.

8.3 PHARMACOKINETICS

Blood samples will be collected for the measurement of isatuximab concentration as described in the PK/ADA flowcharts (Section 1.3). The actual date and time of each sample will be recorded. Instructions for the collection and handling of PK samples will be provided by the Sponsor or Sponsor's designee in a separate laboratory manual. These samples will be tested by the Sponsor or Sponsor's designee. Pharmacokinetic samples may be used for additional testing of analytical method performance such as incurred sample reproducibility. These data will not be included in the study report but will be kept on file.

Descriptive statistics on C_{trough}, and C_{eoi} - Isa-IV+Pd arm for C_{eoi} only-) such as the mean, standard deviation, coefficient of variation, geometric mean, median, and range will be provided by treatment Arms (Isa-SC+Pd or Isa-IV+Pd) as well as C_{trough} ratio (SC/IV) over time.

For the co-primary endpoint observed C_{trough} at steady state, ie, C_{trough} corresponding to predose at C6D1, see Section 9.2.2.

For the key secondary PK endpoint, observed CT4W, ie corresponding to predose at C2D1, see Section 9.2.3.1.

In addition, isatuximab concentrations will be used for population PK analysis by non-linear mixed effects modeling. Data from other studies might be added for model development. The population PK analysis will involve an estimation of inter-individual PK variability, the determination of the population PK parameters estimates and possibly the quantitative evaluation of potential effect of participant characteristics on the main PK parameters. More

precisely the impact of body weight on exposure will be assessed for justification of the flat dosing across body weight. Empirical Bayesian estimation of individual exposure parameters such as C_{max}, C_{trough}, and area under the curve (AUC) will also be computed. Those individual exposure parameters will then be investigated as predictive factors for clinical outcomes including safety and efficacy endpoints, if possible. Additional details of the analysis plan and the results will be provided in separate documents.

8.4 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Participants will stay at the site between 1 and 4 hours after each administration in Cycle 1. For subsequent cycles, participant's surveillance will be left at the Investigator's judgement.

For the first at-home administration, the HCP administering the SC formulation of isatuximab will stay for 30 minutes to ensure safety of the administration.

8.4.1 Body weight and Physical examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Body weight (kg) for all the participants will be recorded in eCRF. Physical examination consists of an examination of major body systems including neurological, digestive, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, and lymphadenopathy.

Only clinically relevant findings will be reported in the eCRF as AEs.

8.4.2 Vital signs

The following vitals will be measured at site: heart rate, body temperature, respiratory rate (RR), and blood pressure (BP).

Note: Vital signs are assessed pre-administration, one hour after start of first administration and, for the IV arm only, 30 minutes after the start of the subsequent infusions. On site, vital signs are to be assessed at end of infusion/injection up to Cycle 5, and as clinically indicated.

8.4.2.1 At-home administration

For at-home administration, the following vital signs will be measured systematically just before and at the end of SC injection:

- Heart rate.
- Systemic blood pressure.
- Body temperature.
- Pulse oximetry (SPO2).

Normal parameters are described in Table 18. These are given as a guide but might be adapted by the investigator based on the clinical history and participant basal values.

In case of abnormal parameters, investigator should be called prior to D-15 injections and if deemed appropriate by the investigator, the participant should be transferred to the investigator site.

Table 18 - Normal values for at-home administration*

Vital sign	Normal range
Heart rate	[50-100] bpm.
Systolic blood pressure	≥90 mmHg (or no lower than 20mmHg below the participant normal value).
Diastolic blood pressure	≥50 mmHg.
Body temperature	Oral temperature <38°C (or equivalent with other measurement).
Pulse oximetry	SPO2 ≥95% or below the participant normal value in the context of prior chronic respiratory disease.

* Given as a guide, should be adapted to the participant medical history.

8.4.3 Electrocardiograms

A 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (Section 1.3).

8.4.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. See Appendix 3 (Section 10.3) for abnormal laboratory results reporting. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.

8.4.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female participant with an early undetected pregnancy.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted weekly during Cycle 1, and then on D1 of each cycle from Cycle 2, ie monthly at intervals during intervention (at study visits and if needed, at home in between visits).
- Pregnancy testing (urine or serum as required by local regulations) must be conducted corresponding with the time frame for female participant contraception in Section 5.1 Inclusion criteria.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator, or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Refer to Section 10.4.3 for duration of pregnancy testing.

8.4.6 Suicidal ideation and behavior risk monitoring

Not applicable.

8.4.7 Assessment of local tolerability

Local tolerability at injection site after SC administration of isatuximab will be assessed during clinical stay using eCRF hourly (relative to the start of administration) for duration of 4 hours at Cycle 1/D1, 1 hour after the end of injection for the following Cycle 1 administrations and at end of injection from Cycle 2 onwards (Section 1.3). In case of at-home administration, for the first isatuximab injection performed at-home, an additional assessment should be performed 30 min after the end of the injection.

Table 19 - Summary of assessment timelines for local tolerability

On site administration	Cycle 1 Day 1: End of Injection (EoI), 1h, 2h, 3h, 4h Cycle 1 Day 8 & Cycle 1 Day 15: EoI, 1h Cycle 2 and subsequent cycles: EoI.
At-home administration	1st injection from Cycle 6: EoI, 30 min Rest of cycles: EoI.

Any swelling (unless it lasts longer than 24 hours) as a result of the injection of the isatuximab solution volume is not to be reported as an AE/ AESI.

8.4.8 Assessment of frailty

Frailty in multiple myeloma patient will be evaluated using functional assessments, at Cycle 1 Day 1. This will be done using the Katz index of independence in activities of daily living (ADL) (32) and the Lawton instrumental activities of daily living scale (IADL) (33).

8.5 PATIENTS REPORTED OUTCOMES

Patient-reported outcome (PRO) measures to be included are the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire with 30 questions (QLQ-C30), the EORTC myeloma module with 20 items (QLQ-MY20), the EQ-5D-5L, the Health Resource Utilization and Productivity will be assessed using the HRUPQ, the Patient Expectations Questionnaire at baseline (PEQ-BL), the Patient Experience and Satisfaction Questionnaires during treatment Follow-Up and at the End Of Treatment (PESQ-FU and PESQ-EOT) and the PAT. All questionnaires are described in this section and presented in Appendix 16 (Section 10.16).

All questionnaires have been designed for self-completion. All PROs are in electronic form (electronic patient-reported outcomes [ePRO]) and will be completed by the patient (study participant) using either the study mobile phone provided or the patient's own device. Alternatively, a dedicated website could be proposed to collect PROs as a backup solution in case of unavailability of handheld devices. To minimize any bias, participants will fill out the ePROs before clinician assessments and discussion of their clinical condition, treatment plan, AEs, and any other related topics that could influence participant's perception and feelings prior to responding to the questions. Timing for each assessment is detailed in SoA section.

Since participants are to complete ePRO questionnaires on their own, there will be 20 minutes time allocated for training participants on ePRO technology at Cycle 1 Day 1 visit. Meanwhile, assistance will be provided if a participant needs longer time to learn or have training questions (eg, a refresher) during subsequent cycles. For the ePRO data it is mandatory that a key person (eg, research nurse) at each site is responsible for ePRO data collection, in order to optimize participant compliance and to ensure data completeness.

Compliance rates for completion will be generated based on number of assessments completed divided by number of assessments expected (per protocol). Reason for non-completion will be documented.

The planned statistical analysis of the PROs will be detailed in the SAP.

European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30)

The EORTC QLQ-C30 is a cancer-specific instrument that contains 30 items and provides a multi-dimensional assessment of HRQL (34, 35, 36). The validity and reliability of the EORTC QLQ-C30 has been established in various types of cancers (37). This instrument provides a comprehensive assessment of the principal HRQL dimensions identified as relevant by cancer patients (physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, global HRQL, impact of symptoms and of toxicities). The EORTC QLQ-C30 is one of the standard instruments used in oncology for the evaluation of new cancer therapies.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea and vomiting, and pain), a Global Health Status (GHS)/quality of life scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial scales). All of the scales and single-item measures range in score from 0 to 100. A higher score for a functional scale/GHS represents a higher/healthier level of functioning/HRQL, whereas a higher score for symptoms/items represents a higher level of symptomatology/problems.

The recall period for this instrument is 1 week.

European Organization for Research and Treatment of Cancer quality of life myeloma module (EORTC QLQ-MY20)

The EORTC QLC-MY20 is to be used in conjunction with the EORTC QLQ-C30 to assess symptoms and side effects due to the treatment or the disease which impact HRQL in participants with multiple myeloma (38, 39). This instrument contains 20 items in 4 independent subscales covering 2 functional domains (future perspective and body image) and 2 symptom scales (disease symptoms and side effects of treatment). Higher scores for disease symptoms and side effects of treatment indicate more symptoms and side effects and lower HRQL, whereas a high score for future perspective and body image represents better outcomes.

Both EORTC QLQ-C30 and EORTC QLQ-MY20 are reliable and valid measures of HRQL in cancer patients and the 2 instruments together (50 items) take approximately 15 minutes on average to complete. The instruments have been validated and used in many countries.

European Quality of Life Group measure with 5 dimensions and 5 levels per dimension (EQ-5D-5L)

The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health utility, and consists of 2 sections: descriptive and VAS. The descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the respondent's self-rated health on a 20 cm vertical, VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine' anchored from 0 to 100 respectively. This information can be used as a quantitative measure of health as judged by the individual respondents.

The EQ-5D-5L is designed for self-completion by participants. Response options are measured with a 5-point Likert scale with higher scores indicate better HRQL.

Health Resource Utilization and Productivity Questionnaire (HRUPQ)

Medical resource utilization and participant productivity will be collected from participants through the specific HRUPQ questionnaire developed for this study (initially adapted to early Phase TCD15484 and modified for EFC15951). The data collected include number, nature (emergency or routine) and duration of hospitalizations, emergency room visits and outpatient medical encounters and employment history. The HRUPQ contains 46 items and takes approximately 10-15 minutes to complete.

Patient expectation, experience and satisfaction questionnaires

Patient Expectations Questionnaire (PEQ-BL)

The PEQ-BL will be completed at baseline prior to study treatment administration or other study related procedures. This questionnaire has been designed to assess the expectations of the participants regarding both the treatment (side effects, worth taking) and the administration method (confidence, comfortability, pain, side effects, potential time-savings), as well as to

understand previous treatment experience from the participant (experience with injection methods for oncology medication). This questionnaire has been developed by Sanofi as internal measure and has been debriefed and adapted based on qualitative interviews with oncology participants.

This questionnaire contains 7 items and take approximately 5 minutes to complete.

Patient experience and satisfaction questionnaires (PESQ; PESQ-FU and PESQ-EOT)

The PESQ-FU has been designed to follow up on participant experience and satisfaction regarding the treatment (side effects, worth taking and overall satisfaction) and the administration method (confidence, comfortability, pain, side effects, potential time-savings and overall satisfaction). This questionnaire has been developed by Sanofi as internal measure and has been debriefed and adapted based on qualitative interviews with oncology participants. The PESQ-FU contains 9 items and take approximately 5 minutes to complete.

The PESQ-EOT has been designed to assess participant experience and satisfaction regarding the treatment (side effects, worth taking and overall satisfaction) and the administration method (confidence, comfortability, pain, side effects, potential time-savings and overall satisfaction). This questionnaire includes also additional items to assess participant preference on injection method (SC or IV) and location of administration (at home or at clinic). This questionnaire has been developed by Sanofi as internal measure and has been debriefed and adapted based on qualitative interviews with oncology participants. The PESQ-EOT contains 17 items and take approximately 5-10 minutes to complete.

Patient's Assessment of Treatment questionnaire (PAT)

In order to demonstrate from participant perspective that the overall benefits outweigh the disadvantages in the target patient population, Sanofi has developed an internal measure; the Patient Assessment of Treatment questionnaire (PAT). The PAT provides patient insights on the benefits and disadvantages of treatment, including an overall B/D ratio using a final question that provides a quantitative assessment of the patient's perceived B/D. The 4-item PAT is an internally developed non-disease specific and self-administered assessment. The PAT is a modification from the Sanofi developed Patients' Qualitative Assessment of Treatment (PQAT; initially developed for diabetes (40) and has been debriefed with oncology patients during qualitative interviews. This questionnaire contains 4 items and take approximately 2-3 minutes to complete.

Timing of Assessments

Cycle 1 Day 1 will serve as the baseline assessment for all participants. While on treatment, ePROs are to be completed prior to treatment on Day 1 of every cycle, and at the EOT visit. The time estimated to complete the EORTC QLQ-C30 and the EORTC QLQ-MY20 together is approximately 10 to 15 minutes. The time estimated to complete the EQ-5D-5L is approximately 5 to 10 minutes.

Since the participants are to complete ePRO questionnaires on their own, there will be 20 minutes time allocated for training participants on ePRO technology at Cycle 1 Day 1 visit. Meanwhile, assistance will be provided if a participant needs longer time to learn or have training questions (eg, a refresher) during consequent cycles. For the ePRO data it is mandatory that a key person (eg, research nurse) at each center be responsible for ePRO data collection, in order to optimize compliance of the participant and to ensure completeness of the data. The planned statistical analysis of the 3 ePROs will be detailed in the SAP.

8.5.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a cancer-specific instrument that contains 30 items and provides a multidimensional assessment of HRQL (34, 35, 36). The validity and reliability of the EORTC QLQ-C30 has been established in various types of cancers (37).

The EORTC QLQ-C30 provides a comprehensive assessment of the principal HRQL dimensions identified as relevant by cancer patients (physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, global HRQL, and impact of symptoms and of toxicities). The EORTC QLQ-C30 is one of the standard instruments used in oncology for the evaluation of new cancer therapies.

The QLQ-C30 is composed of 3 domains with multi-item scales. These include:

- Global health status (GHS)/quality of life (2 items).
- Functional scales:
  - Physical functioning (5 items).
  - Role functioning (2 items).
  - Emotional functioning (4 items).
  - Cognitive functioning (2 items).
  - Social functioning (2 items).
- Symptom scales/items:
  - Fatigue (3 items).
  - Nausea and vomiting (2 items).
  - Pain (2 items).
  - Dyspnea; Insomnia; Appetite loss; Constipation; Diarrhea; Financial impact (1 item each).

Scoring is based on 4-point Likert scales and 7-point numerical rating scales. All of the scales and single-item measures range in score from 0 to 100. A higher score for a functional scale/GHS represents a higher/healthy level of HRQL, whereas a higher score for symptoms/ items represents a higher level of symptomatology/problems. The recall period for this instrument is 1 week.

8.5.2 EORTC QLQ-MY20

The EORTC QLQ-MY20 is to be used in conjunction with the EORTC QLQ-C30 to assess symptoms and side effects due to the treatment or the disease which impact HRQL in participants with MM (38, 39).

It contains 20 items, 4 independent subscales covering 2 functional domains:

- Symptom scales:
  - Disease symptoms (6 items).
  - Side-effects of treatment (10 items).
- Function scale:
  - Future perspective (3 items).
  - Body image (1 item).

Scores are based on the 4-point Likert scale ranging from "Not at all" to "Very much", ranging by items from 0 to 100. Higher scores for Disease Symptoms and Side Effects of Treatment indicate more symptoms and side effects and lower HRQL, whereas a high score for Future Perspective and Body Image represents better outcomes.

These are reliable and valid measures of HRQL in cancer participants and the 2 EORTC instruments (QLQ-C30 and QLQ-MY20) together (50 items) take approximately 15 minutes on average to administer. The instruments have been validated and used in many countries.

8.5.3 EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health utility, and consists of 2 sections: descriptive and VAS.

The descriptive system consists of 5 dimensions:

- Mobility.
- Self-care.
- Usual activities.
- Pain/discomfort.
- Anxiety/Depression.

Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (ie, EQ-5D™ index score) to self-reported health states from a set of population-based preference weights. For the US general population, the possible EQ-5D™ index scores range from -0.11 (ie, 33333) to 1.0 (ie, 11111) on a scale where 0.0 = death and 1.0 = perfect health.

The VAS records the respondent's self-rated health on a 20 cm vertical VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine', anchored from 0 to 100 respectively. This information can be used as a quantitative measure of health as judged by the individual respondents.

The instrument is designed for self-completion by participants. Response options are measured with a 5-point Likert scale with higher scores indicate better HRQL. The EQ-5D™ produces 3 types of data for each respondent:

- A profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor.
- A population preference weighted-health index score based on the descriptive system.
- A self-reported assessment of health status based on the EQ-VAS.

8.6 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.6.6.

The definitions of unsolicited and solicited adverse events can be found in Appendix 3 (Section 10.3).

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Appendix 7 (Section 10.7). Device deficiencies are covered in Section 8.6.8.

AEs and ADEs will be reported by the participant.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, ADE or SADE and remain responsible for following up AEs and ADEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs, ADEs, SAEs and SADEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.6.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.6.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.6.3 Follow-up of AEs and SAEs

After the initial AE/ADE/AESI/SAE/SADE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, SADEs and AESI (as defined in Section 8.6.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.6.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information section of the Investigator's Brochure.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure / package insert (as applicable) and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.6.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 5 months after the last isatuximab administration.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant pregnancy or a female partner of male participants.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.6.4. While the Investigator is not obligated to actively seek this information in former study participants he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.6.6 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

- Infusion reactions Grade ≥3. Infusion reactions (for example, NCI CTCAE Version 5.0 terms "infusion related reaction", "allergic reaction", or "cytokine release syndrome") are defined as AEs related to isatuximab and/or to novel agent with onset typically within 24 hours from the start of the infusion.
- ISRs: Grade 2 or higher.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome of the pregnancy. The Investigator will collect follow-up information on the participant or pregnant female partner and the neonate. The information will be forwarded to the Sponsor. Follow-up will be up to 1 year after the delivery of a newborn. (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP/AxMP (see definition of an overdose in Section 6.7).
- Second primary malignancies are to be reported using the AE report form and must be considered as AESIs; these AEs must also be documented in the appropriate page(s) of the eCRF and participant's source documents. Diagnosis and tests completed as per standard clinical practice of the second primary malignancy must be provided at the time of reporting (eg, any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans, etc).

8.6.7 Medication errors or misuses of medicinal product

All reports of medication error or misuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

8.6.8 Guidelines for reporting product complaints

Any defect in the IMP/ AxMP/device must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.6.9 Medical device deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiencies that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 7 (Section 10.7).

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Appendix 7 (Section 10.7) of the protocol.

8.6.9.1 Time period for detecting medical device deficiencies

- SADEs, as well as medical device deficiencies that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate will be detected and documented during all periods of the study in which the medical device is used.
- SADEs as well as medical device deficiencies that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate will be reported during all periods of the study in which the medical device is used.

Similarly, any new finding in relation to an ADE or SADE will be detected, documented, and reported during all periods of the study in which the medical device is used.

- If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting medical device deficiency is provided in Appendix 7 (Section 10.7).

8.6.9.2 Follow-up of medical device deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.6.9.3 Prompt reporting of device deficiencies to Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the Sponsor by the Product Technical Complaint (PTC) form completed in the pharmacy manual.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.6.9.4 Regulatory reporting requirements for device deficiencies

- The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.
- Sponsor will retain medical devices subject to a complaint/deficiency for return to sponsor for investigation.

8.7 GENETICS

No congenital genetic testing is planned in this study; however, tumoral genetic and genomic analyses will be performed on bone marrow samples.

8.8 BIOMARKERS

Bone marrow and blood samples will be collected and analyzed at a central lab for the following biomarker analyses:

- Minimal residual disease will be assessed by next generation sequencing or any other validated technology in BM aspirates and correlated with parameters of clinical response. Bone marrow aspirate samples will be collected at screening for all participants and at the time of maximum confirmed response of either CR or VGPR, 12 months after C1D1 and 12 months after first MRD negativity.
- Characterization of tumoral genomic and genetic profiles to explore mechanism of drug resistance: Bone marrow aspirate samples will be collected at screening and at disease progression.
- Impact of new serum M-protein measurement methods (such as mass spectrometry) on disease response assessment: blood samples will be collected at all timepoints at which M-protein is assessed.

- Cytogenetics assessment: At screening, bone marrow aspirate will be collected for FISH analyses including, but may not be limited to, del[17p], t[4;14], t[14;16]), 1q21+,in central laboratory.
- Samples collected for biomarker analyses and their derivatives will be stored for a period of up to 5 years after last participant last visit for potential re-analyses for future research.

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies to isatixumab will be evaluated in plasma samples collected from all participants according to the SoA. Additionally, plasma samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Blood samples will be collected for assessing the presence of ADA against isatuximab in plasma from all participants as described in the PK/ADA flowcharts (Section 1.3).

Instructions for the collection and handling of PK/ADA samples will be provided by the Sponsor or Sponsor's designee in a separate laboratory manual. These samples will be tested by the Sponsor or Sponsor's designee.

Plasma samples will be screened for antibodies binding to isatuximab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to isatuximab and/or further characterize the immunogenicity of isatuximab by evaluating for their ability to neutralize the activity of isatuximab.

8.10 SPECIFICITIES REGARDING COVID-19 SITUATION AND VACCINATION

With regards to EFC15951 there are currently no specific restrictions on the use of vaccines authorized today by local regulatory health authorities to prevent COVID-19. Sanofi will continue to monitor vaccine authorizations moving forward and inform you if this position changes.

Participants being actively treated with daratumumab (another CD38 directed monoclonal antibody) and low-dose dexamethasone were successfully immunized for *S. pneumoniae* and *H. influenzae* (41) supporting the safety of continuing active treatment with isatuximab while undergoing vaccination for COVID-19. In addition, the half-life of isatuximab of 28 days (refer SARCLISA SmPC or package insert) is such that a short-term interruption of the administration schedule is not expected to substantially modify immune responsiveness.

Based on recommendations or statements from scientific societies, if at least one vaccine has been authorized by your national competent regulatory health authority(ies) to prevent COVID-19 and a participant in isatuximab study is both eligible, based on the local vaccination guidelines or recommendations, and willing to receive this authorized COVID-19 vaccine, the study participant should proceed with vaccination. Ultimately the decision for each individual participant will need to be made on a case-by-case basis and informed by sound clinical judgement and your local recommendations and guidelines.

There is no recommendation to alter the isatuximab administration schedule in light of the vaccination schedule. Other anti-myeloma agents administered during the study, in particular high dose steroids, may be considered to be temporarily held as per the official recommendations and investigator judgment.

With regards to COVID-19 vaccination, please report the following in the appropriate eCRF pages according to the revised CRF completion instructions:

1. Each COVID-19 vaccine injection.
2. Any observed adverse event following the administration of the COVID-19 vaccine during study treatment period phase.
3. COVID-19 antibody titers if measured after vaccination.

Please ensure that all the above steps are well documented in the participant's health records at the study site.

8.11 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization will be collected through the specific HRUPQ questionnaire. Protocol-mandated procedures, tests, and encounters are excluded. The data collected will include number, nature (emergency or routine) and duration of hospitalizations, emergency room visits and outpatient medical encounters.

8.12 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Coded study data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

For participants who consent to the storage and use of their data and remaining (leftover) and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions.

Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins, or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease, or its associated conditions.

Data protection – Processing of coded clinical data

The study participant will be provided with all mandatory details of the data processing in Section 2 of the core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in Section 2 of the Core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes. Biological samples for future use will be stored for a maximum of 25 years after the end of the study unless local regulations require a different retention period. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

9 STATISTICAL CONSIDERATIONS

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 20 - Populations for analyses

Population	Description
Intent-to-treat (ITT)	The intent-to-treat (ITT) population is the randomized population. All participants who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the IRT will be included in this population. Participants will be analyzed according to the treatment group allocated by IRT, regardless of whether the participants received any study treatment or receive a different study treatment from that to which they were randomized. This population will be used for the analysis of the co-primary efficacy endpoint.
Per Protocol-PK (PP-PK) population	The Per Protocol PK population will include all randomized participants who 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 population will be used for the analysis of the co-primary PK endpoint.
CT4W-PK population	The CT4W-PK population for CT4W endpoint will include 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 population will be used for the analysis of the CT4W PK endpoint.
Per Protocol population	The PP is defined as all treated subjects who have measurable disease at baseline and have no major protocol deviations with respect to eligibility. This population will be used for sensitivity analysis of ORR in the context of a non-inferiority design.
Safety	The safety population will include ITT participants who have received at least 1 dose or a part of a dose of the study intervention. All analyses using this population will be based on the treatment actually received. All safety analysis will be performed on this population.
Pharmacokinetic (PK)	The PK population will include all participants with at least 1 available isatuximab concentration post-baseline (whatever the cycle and even if dosing is incomplete) with adequate documentation of dosing and sampling dates and times. This population will be used for the analysis of PK secondary endpoints.
ADA	The immunogenicity population will include all participants from safety population with at least 1 ADA result (negative, positive or inconclusive) post-baseline.

Screened participants are defined as any participants who signed the ICF.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

9.2 STATISTICAL ANALYSES

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.2.1 General considerations

Myeloma response and progression will be determined by Independent Review Committee based on central laboratory M-protein analysis and central radiology review using IMWG 2016 criteria.

The following stratification factors will be used:

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

Primary and secondary endpoints will be analyzed by treatment arm.

Study treatment is defined as isatuximab (SC/IV) in combination with pomalidomide and dexamethasone. First dose of study treatment is defined as the first starting dose of any study intervention of isatuximab, pomalidomide or dexamethasone. Last dose of study treatment is defined as the last dose of any study intervention of isatuximab, pomalidomide, or dexamethasone.

For each of the safety parameters, the baseline will be defined as the last value or measurement taken up to the first dose of study treatment.

The observation period will be divided into 3 segments:

- The **pre-treatment** period is defined as the time the ICF is signed until the first dose of the study treatment administration.
- The **treatment-emergent (TE) period** is defined as the period from the first study treatment administration to the last study treatment administration +30 days.
- The **post-treatment period** is defined as the time starting 31 days after the last study treatment is administered to study closure or death, whichever comes first.

9.2.2 Primary endpoint(s) analyses

The number and proportion of participants who achieve ORR per IRC assessment will be calculated for each group. The relative risk of Isa-SC + Pd relative to Isa-IV + Pd and its two-sided 95% CI using Farrington and Manning method will be provided. If the lower bound of the 95% CI is not less than a non-inferiority margin of 0.839, the non-inferiority of efficacy Isa- SC + Pd relative to Isa- IV + Pd will be concluded. The odds ratio of ISA- SC+ Pd relative to Isa- IV + Pd with their 95% CI will also be provided.

For the co-primary PK endpoint of C_{trough} at steady state (corresponding to predose at C6D1), summary statistics such as geometric means, coefficient of variation, median and range will be provided for treatment group. The ratio of the geometric means of Isa-SC+ Pd relative to Isa- IV + Pd and corresponding two-sided 90% CI will be provided 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 will be concluded if the lower bound of the 90% CI for the geometric mean ratio of C_{trough} at steady state is at least 80% (a non-inferiority margin of 80%).

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

9.2.3 Secondary endpoint(s) analyses

9.2.3.1 Key Secondary Endpoints

VGPR or better rate per IRC assessment will be summarized for the ITT population in the same way as for ORR endpoint. The non-inferiority test for non-unity null according to Farrington and Manning (1990) will be 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 is 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 will be concluded.

The PK endpoint of CT4W will be summarized for the CT4W-PK population in the same way as for the C_{trough} at steady state endpoint. The non-inferiority of Isa- SC + Pd relative to Isa-IV + Pd on CT4W corresponding to predose at C2D1 will be concluded if the lower bound of the 90% CI for the geometric mean ratio of CT4W is at least 80% (a non-inferiority margin of 80%).

Incidence rate of IRs will 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 will be provided.

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 will be compared between treatment arms on the ITT population using the stratified CMH method.

9.2.3.2 Other Secondary Endpoints

The CR rate will be summarized in the same way as for 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 will be presented by treatment arm. The Kaplan-Meier PFS curves will also be provided. Additionally, the HR estimated from the Cox proportional hazards model as well as its associated 95% CI will be provided too.

The analysis for PFS2, OS, DOR, and TTR (TT1R and TTBR) as well as the impact of abnormal cytogenetic subtypes will be similar to that described for PFS per IRC assessment.

PK parameters and derived exposure will be summarized and provided in a separate report. PK concentrations (C_{trough} and C_{eoi} - Isa-IV+Pd arm for C_{eoi} only) will be summarized per arm with descriptive statistics.

Incidence of participants with ADA against isatuximab will be provided in a separate table.

Number (and percentage) of participants experiencing TEAEs by primary system organ class and preferred term will be summarized by NCI CTCAE (v5.0) grade (all grades and ≥Grade 3) for the safety population. The same summaries will be prepared for treatment related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, serious TEAEs and TEAEs with fatal outcome and ISRs. Second primary malignancies as AESI will be reported throughout the study.

Hematology and biochemistry results will be graded according to NCI CTCAE v5.0. Number (and percentage) of participants with laboratory abnormalities (ie, all grades and ≥Grade 3) using the worst grade during the on-treatment period will be provided for the safety population.

Number of successful injections with investigational isatuximab injector device will be assessed.

Participant expectations at baseline, participant experience, and satisfaction, assessment of treatment, and Health Resource Utilization and Productivity questionnaires will be descriptively summarized.

Participants' health-related quality of life (influenced by both disease and treatment) will be assessed by EORTC QLQ-C30 and EORTC QLQ-MY20 via a comparison of change scores in C30 (individual symptom change scores) and MY20 (disease- and treatment-related summary scores) from baseline to follow-up between treatment arms. In addition, responder analyses will be conducted 1) for those who improve and 2) for those who deteriorate, utilizing the CIDs for all individual symptom scores (C30) and disease- and treatment-related summary scores (MY20) for both treatment arms.

Health status (EQ-5D-5L, including VAS) will be assessed via a comparison of EQ-5D-5L health status change scores from baseline to follow-up between treatment arms. In addition, responder analyses will be conducted 1) for those who improve and 2) for those who deteriorate, utilizing the CIDs for health status VAS scores for both treatment arms.

9.2.4 Tertiary/exploratory endpoint analyses

Statistical analysis for exploratory endpoints will be described in the SAP.

9.2.5 Multiplicity adjustment

Both co-primary endpoints will need to achieve non-inferiority as specified in Section 9.2.2, 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 will be carried out. A hierarchical test procedure will be used to control the familywise Type I error rate at one-sided significance level of 0.025 meaning that testing of key secondary endpoints will be performed only if the non-inferiority for both co-primary endpoints are established and testing on subsequent endpoints will continue only if the null hypothesis for the previously tested endpoint is rejected. The hierarchical procedure for testing the key secondary endpoints comparing SC arm with IV arm will be 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.

9.2.6 Other/safety analysis

9.2.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened, or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

Summaries will be provided for all grades combined and for Grade ≥3 (including Grade 5). Missing grades, if any, will be included in the “all grades” category.

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with number (and percentage) of participants experiencing at least one event.

Deaths will also be analyzed.

9.2.6.2 Laboratory variables, vital signs, and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables, vital signs and ECG variables, the following analyses will be applied for each planned visit on safety population.

Clinical laboratory values will be analyzed after conversion into standard international units. (International units will be used in all listings and tables).

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE V5.0, when applicable. Number (and percentage) of participants with laboratory abnormalities (ie, all grades and by grade) using the worst grade during the treatment period will be provided for the safety population. Analyses will be performed according to PCSA.

For laboratory tests for which NCI-CTCAE v5.0 scale is not applicable, potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review.

The PCSA criteria will determine which patients had at least 1 PCSA during the treatment period, taking into account all evaluations performed during the treatment-emergent period, including nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level. For blood pressure/heart rate parameters, the incidence of PCSAs prior to study treatment administration at any cycle during the on-treatment period will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria

The incidence of PCSAs during and after isatuximab administration at any cycle during the treatment period in the SC arm will also be summarized.

For laboratory variables graded by NCI-CTCAE. The number (and percentage) of participants with abnormal laboratory tests at baseline will be presented by grade.

The number (and percentage) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (and percentage) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing.
- Abnormal.

9.2.6.3 Product complaints

Product complaints will be summarized in the safety population.

9.2.7 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9): Contingency measures for a regional or national emergency that is declared by a governmental agency.

9.3 INTERIM ANALYSES

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

9.4 TIMING OF PLANNED ANALYSIS

The cut-off date for the primary analysis is approximately 6 months after the LPI, which includes analysis on the primary endpoint and secondary endpoints when applicable. An update of PFS and OS will be performed approximately 15 months after LPI. The cut-off date for final OS analysis will be approximately 30 months after LPI.

9.5 SAMPLE SIZE DETERMINATION

A total sample size of 534 participants (randomization ratio 1:1, ie, 267 randomized 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 C_{trough} at steady state (corresponding to predose at C6D1). For the co-primary efficacy endpoint of ORR, the non-inferiority test for non-unity null according to Farrington and Manning (1990) 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 C_{trough} at steady state, assuming C_{trough} 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 population, 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 C_{trough} at steady state is at least 80% (a non-inferiority margin of 80%).

Calculations were made based on SAS 9.4 (1).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable.
  - The General Data Protection Regulation - (GDPR) and any other applicable data protection laws.
  - Any other applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, [IDFU] and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

- Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
  - The return of such information to the study participant (and/or his/her designated healthcare professional, if so, designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and,
  - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
  - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
  - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- As applicable, according to requirements of the Regulation No536/2014 of the European Parliament and the Council of the European Union

The Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal

Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

The ICF will be provided to the study participant in paper version. When feasible, an eConsent process may be used at global level and/or locally if permitted by country regulations.

- The Investigator or the Investigator's representative will explain the nature of the study including the risk and benefits to the potential participants, and answer all questions regarding the study, including what happens to the participants when their participation ends (post-trial access strategy for the study).
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the General Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by checkboxes in CSICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of

additional biological samples for storage and use for future research, and consent for performance of genetic analyses on biological samples. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9, Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including trial participants, Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

“Participant race and ethnicity will be collected in this study because they are expected to modify the drug response. They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and

detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers.
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 46 avenue de la Grande Armée - 75017 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committee's structure

10.1.5.1 Steering committee

The **Steering Committee** will include a chairman, investigators, and Sponsor's representatives.

The Steering Committee will be responsible for:

- Supervising the progress of the trial towards its overall objectives.
- Reviewing at regular intervals relevant information that may affect the study conduct.
- Discussing the implementation of the recommendations of the independent DMC.

10.1.5.2 Data monitoring committee

An independent **DMC**, consisting of 3 external independent members (2 physicians with MM expertise and 1 statistician), not associated with the conduct of the study or other study committees will meet regularly as specified in the DMC charter:

- Review the progress of the trial.
- Review the safety data.
- Advise the Sponsor on potential modifications or communications that may be necessary to ensure the participant safety or protect the scientific integrity of the trial. The Sponsor will make the final decision(s).

The DMC procedures will be detailed in the DMC charter and approved by the DMC members. The charter will be discussed during a kick-off meeting before the first participant in DMC members will then meet periodically.

Ad-hoc DMC meetings may also be held if a significant safety issue or issue deemed important for discussion arise on this or any other studies of isatuximab. After each meeting, the DMC will advise the Steering Committee and the Sponsor's representatives on recommendations regarding the continued safety of treating ongoing and future study participants, as well as the course of action regarding the conduct of the trial.

10.1.6 Dissemination of clinical study data and results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, euclinicaltrial.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials of participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance Drug Clinical Trial Registration and Information Disclosure "Management Practice (Trial Implementation)" requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTL)s will be pre-defined in the QTL specification document to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is permanently terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 21 will be performed by the local laboratories.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 21 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	Prothrombin time (PT)/international normalized ratio (INR) Partial thromboplastin time (PTT)
Clinical chemistry	
	Urea/Blood urea nitrogen (BUN) Creatinine • Estimated glomerular filtration rate (MDRD) (see Section 10.2.1) Glucose (fasting) Potassium Sodium Calcium Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase[a] Total and direct bilirubin Total protein Thyroid function test • Thyroid-stimulating hormone (TSH) • Free T3 • Free T4 Albumin Lactate dehydrogenase (LDH) Venous bicarbonate/carbon dioxide Uric acid Chloride Magnesium Phosphate
Routine urinalysis	• RBCs, protein, glucose, pH, ketones, bilirubin, and leukocytes by dipstick.
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b].
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only). • Serology (HIV antibody, hepatitis B (HBsAg, anti-HBs, anti-HBc total and IgM) and hepatitis C (anti-HCV, HCV RNA level). • Bone marrow aspirate or biopsy.

NOTES :

a If alkaline phosphatase is elevated, consider fractionating.

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.2.1 Modification of diet in renal disease (MDRD) equation

Estimated Glomerular filtration rate (mL/mins/1.73 m^2) = $175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times$ (0.742 if Female) $\times$ (1.212 if African-American).

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), or more severe than expected for the participant's condition), eg:

- Leading to IMP discontinuation or modification of dosing, and/or,
- Fulfilling a seriousness criterion, and/or,
- Defined as an AESI.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors and misuse with the IMP.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death.

b) Is life-threatening.

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization.

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect.

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm.
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse.
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE, and document this in the medical notes.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the investigator site file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Risk associated with pregnancy

The effects of isatuximab on reproductive toxicity, pregnancy and lactation have not been investigated in formal toxicity studies. Therefore, the effects of isatuximab on reproductive organs in males and females are unknown. However, isatuximab is an IgG antibody, it may cross into the placenta and possibly affect embryonal or fetal growth and development. Therefore, the following contraceptive measures are required for males and females of childbearing potential.

Pomalidomide is structurally related to thalidomide. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected. Therefore, a risk minimization plan to prevent pregnancy must be observed. All study participants must comply with the requirements of Pomalidomide Pregnancy Prevention Plan recommendations (Appendix 15, Section 10.15) or the country specific risk management plan in countries where pomalidomide is not supplied by the Sponsor.

10.4.2 Contraception guidance

10.4.2.1 Criteria for females of childbearing potential

This protocol defines a FCBP as a sexually mature female who:

- Has achieved menarche at some time point.
- Has not undergone a permanent sterilization method including:
  - Documented hysterectomy.

- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

- Has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 24 months of amenorrhea, a single FSH measurement is insufficient.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2.2 Contraception guidance for female subjects

- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
- Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study:
  - For at least 28 days before starting study treatment,
  - And throughout the entire duration of pomalidomide treatment,
  - And during dose interruptions,
  - And for at least 5 months after study treatment discontinuation.
- The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method.
- Highly effective contraception with low user dependency is preferred.
- A FCBP must be referred to a qualified provider of contraceptive methods if needed.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
• Intrauterine device (IUD).
• Intrauterine hormone-releasing system (IUS).
• Bilateral tubal occlusion.
• Azoospermic partner (vasectomized or due to a medical cause). *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[c] associated with inhibition of ovulation. - Intravaginal. - Transdermal. - Injectable.
• Progestogen-only hormone contraception associated with inhibition of ovulation. - Oral. - Injectable.
• Sexual abstinence.
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c A patient can use 'oral' combination if they have discontinued pomalidomide.
As per pomalidomide Summary of Product Characteristics (SmPC), combined oral contraceptive pills are not recommended because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone.

Note: Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.4.2.3 Contraception for male subjects

Male subjects with heterosexual partners of reproductive potential (FCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:

- Refrain from donating sperm,

  and

- At least 1 of the following conditions applies:
  - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle,

    or

  - Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects) while taking pomalidomide/isatuximab, during dose interruptions and for at least 28 days after the last dose of pomalidomide or 5 months following the last dose of isatuximab, whichever occurs last, even if he has undergone a successful vasectomy.

10.4.3 Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP, including FCBP who commit to complete abstinence, as outlined below.

10.4.3.1 Female participants

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to prescribing pomalidomide.

The first pregnancy test must be performed within 10 to 14 days prior initiation of pomalidomide, and the second pregnancy test must be performed within 24 hours prior pomalidomide administration.

The participant may not receive pomalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Pregnancy testing is also required weekly during 1st month of treatment and then every 28 days while on therapy (14 and 28 days in case of irregular menstrual cycles) and during interruptions in therapy (or every 14 days in case of irregular menstrual cycles) and for at least 28 days after discontinuation of pomalidomide (14 and 28 days for in case of irregular menstrual cycles), or monthly up to 5 months following isatuximab discontinuation, whichever occurs last.

10.4.3.2 Male participants

Females of childbearing potential, who have male partners receiving pomalidomide, must use highly effective contraception during his treatment and during dose interruptions and for at least 4 weeks after his last dose of pomalidomide or at least 5 months after his last dose of isatuximab, whatever occurs last.

Note: True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

10.4.4 Additional precautions during and after study participation

10.4.4.1 Female participants

At each visit, the Investigator must confirm with the FCBP that she is continuing to use a highly effective form of contraception (see definition above) at each visit during the time that birth control is required.

If pregnancy or a positive pregnancy test does occur in a study participant, pomalidomide and isatuximab must be immediately discontinued.

Pregnancy testing and counseling must be performed if a participant misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide and isatuximab treatment must be temporarily discontinued during this evaluation.

Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation of pomalidomide or 5 months after discontinuation of isatuximab, whichever occurs last.

10.4.4.2 Male participants

If pregnancy or a positive pregnancy test does occur in the partner of a male study participant during study participation, the Investigator must be notified immediately.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be up to 1 year following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Male participants should not donate semen or sperm during therapy or for at least 4 weeks following discontinuation of pomalidomide or 5 months following discontinuation of isatuximab.

10.4.4.3 Precautions related to pomalidomide

Female caregivers of childbearing potential should not touch the pomalidomide capsules or bottles unless they are wearing gloves.

Participants should be instructed never to give pomalidomide to another person.

Participants should not donate blood during therapy and for at least 3 months following discontinuation of study treatment.

Only enough pomalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

Any unused pomalidomide must be returned as instructed in the Pomalidomide Pregnancy Prevention Plan (Appendix 15, Section 10.15) or the country specific risk management plan in countries where pomalidomide is not supplied by the Sponsor.

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Not applicable.

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).

Both the Investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study (see Section 6.1.3) for the list of Sponsor medical devices).

10.7.1 Definition of medical device AE and ADE

Medical device AE and ADE definition

- A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2 Definition of medical device SAE, SADE and USADE

A medical device SAE is any adverse event that:

a) Led to death.

b) Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

SADE definition

- A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.
- Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3 Definition of device deficiency

Device deficiency definition

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.7.4 Recording and follow-up of medical device AE and/or SAE and device deficiencies

Medical device AE, SAE, and device deficiency recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as "severe" should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator’s Brochure (IB) and Product Information, for marketed products, as part of the assessment.
- The Investigator must review and provide an assessment of causality for each AE/SAE/device deficiency, and document this in the medical notes.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of medical device AE/SAE/device deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.7.5 Reporting of medical device SAEs

Medical device SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the Sponsor/medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in investigator site file.

10.7.6 Reporting of SADEs

SADE reporting to the Sponsor

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.
- The Sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in investigator site file.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

Upon a request from the Human Genetics Resource Administration of China (HGRAC) regulation, the Chinese sites will not participate to the collection (and analyses) of samples for exploratory endpoints.

Introduced as per Protocol Amendment 01: Country-specific requirement applicable for Norwegian clinical sites:

A) Male participants that agree to not donate semen or sperm during therapy or for at least 4 weeks following discontinuation of pomalidomide or 5 months following discontinuation of isatuximab.

B) Participants that agree to not donate blood during therapy and for at least 3 months following discontinuation of pomalidomide.

Per local regulations in France, Direct-to-Patient supply of isatuximab SC from the Site/Sponsor is allowed for home-based administration of isatuximab SC. Agreement from participant for Direct-to-Patient supply should always be sought in such situation.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

The decision for each individual participant to remain in the study should be made on a case-by-case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site.

When participants are already randomized and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.

When possible, the focus should be on IMP administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints (eg, disease assessments). The deviations from the study protocol (eg, treatment delay, omission, tests not performed) should be documented in the source document and collected in the appropriate pages of the eCRF.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety data.
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- The Direct-to-Patient supply of dexamethasone and pomalidomide from the site/sponsor where allowed by local regulations and agreed upon by participant. Contingencies implemented due to emergency will be documented.

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in

the SAP. For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

Appendices to be provided for studies conducted in European countries.

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (Article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

10.11 APPENDIX 11: IMWG RESPONSE CRITERIA

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG) (42). A confirmation assessment for disease response within 4 weeks is required in this protocol (either PR or better, or PD).

Table 22 - Adapted from updated International Myeloma Working Group response criteria

IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.
Standard IMWG response criteria	
Response	**IMWG criteria**
CR	• Negative immunofixation on the serum and urine and, • Disappearance of any soft tissue plasmacytomas.

	• <5% plasma cells in bone marrow aspirates and, • A normal FLC ratio of 0.26–1.65 is required for FLC disease only. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
sCR	CR as defined above plus: • Normal FLC ratio (0.26 to 1.65) and, • Absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells). **Two consecutive assessments of laboratory parameters are needed. No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or, • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h or, • ≥90% decrease in the sum of maximal perpendicular diameter compared to baseline in soft tissue plasmacytoma. • FLC only: a ≥90% decrease in the difference between involved and uninvolved FLC levels. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
PR	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h. • If serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
MR	≥25% but ≤49% reduction in serum M-protein and reduction in 24 h urine M-protein by 50%-89%, which still exceed 200 mg/24 h. In addition to the above listed criteria, if present at baseline, ≥50% reduction in size (SPD) of soft tissue plasmacytomas is also required. **No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
Stable Disease	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease. **No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
Progressive disease	Any one or more of the following criteria: Increase of ≥25% from lowest confirmed value in any one of the following criteria: • Serum M-protein (the absolute increase must be ≥0.5 g/dL). • Serum M-protein increase ≥1 g/dL if the lowest M-component was ≥5 g/dL. • Urine M-component (the absolute increase must be ≥200 mg/24 h). • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL). • Appearance of new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis. **Two consecutive assessments are needed for serum and or urine. If radiological progression is documented, no need to repeat the assessment.**

Abbreviations: CR = complete response; FLC = free light chain; IMWG = International Myeloma Working Group; M = monoclonal; MRD = minimal residual disease; NGF = next-generation flow; NGS = next-generation sequencing; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD =, sum of the products of the maximal perpendicular diameters of measured lesions; SUV = maximum standardized uptake value; VGPR = very good partial response.

A plasmacytoma that has been radiated is not suitable for response assessment; however, it must be monitored to assess for progressive disease.

For participants achieving VGPR by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the products of the maximal perpendicular diameters of measured lesions (SPD) compared with baseline.

For IgA and IgD myeloma, quantitative immunoglobulin measurements are preferred for assessments, the same percentage changes apply for serum M-spike (see table above).

Definite increase in the size of existing bone lesions or soft tissue plasmacytomas is defined as below:

- ≥50% increase in the size of at least one bidimensionally measurable lesion (in comparison with the measurements at Nadir) or appearance of a new lesion.
- Pathological fracture or collapse of bone are not necessarily evidence of disease progression.

Reminder: definitions of Response and Progression are based on IMWG Uniform Reporting Criteria:

- Any response category (sCR, CR, VGPR, PR, and MR) or progression needs to be confirmed by two consecutive disease assessments according to the Study Flow Chart. A disease assessment at one time point not matched by the same disease assessment at the next time point will be considered unconfirmed (except for progression by imaging, bone marrow PC counts, where one time point is adequate for confirmed response or progression).
- Urine M-protein is not needed to document PR or minor response if baseline urine M-protein was not measurable; however, it is still required for CR and VGPR.
- Documentation of response requires two consecutive readings of the applicable disease parameter (serum M-protein, urine M-protein or serum FLC), performed at any time (no minimum interval is required, it can be done the same day); however, to confirm response or progressive disease, two discrete samples are required; testing cannot be based upon the splitting of a single sample.
- Participants will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; participants cannot move to a lower response category.
- Percent decreases for response calculations are from baseline values (Cycle 1, Day 1).
- Percent increases for progression calculations are from lowest response values or baseline values, whichever is the smaller number. The lowest value does not need to be confirmed.
- The lowest confirmed value before suspected progression will be used as baseline for calculation of progression; if a serum and/or urine spike is considered too low to quantitate, this value can be assigned as zero as a baseline for documentation of subsequent progressive disease. Participants will be considered to have progressive disease

if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for participants who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.

Radiographic and BM assessments do not need to be confirmed.

Participants with measurable serum and/or urine M-protein and/or sFLC during screening, but below level of eligibility on efficacy laboratory performed on Cycle 1 Day 1
(eg, participants with M-protein value >0 [or IF positive] and <0.5 g/dL):

- These participants can have only 3 possible overall responses: **CR, non-PD, or PD**.
- Participants with previous measurable M-protein (urine and/or serum) but at Cycle 1 Day 1 below the level of measurability and no measurable sFLC can have CR, non-PD, or PD responses only according to the increase or decrease of M-protein or extra/para medullary soft tissue plasmacytoma if applicable, following the IMWG criteria.
- If measurable sFLC at Cycle 1 Day 1, the participant will be followed on this value, based on IMWG criteria.
- If during screening only serum M-protein was measurable, but at Cycle 1 Day 1 only urine M-protein becomes measurable, the participant will be followed on this last parameter during the treatment, regardless of sFLC level.
- Inversely, if during screening only urine M-protein was measurable, but at Cycle 1 Day 1 only serum M-protein becomes measurable, the participant will be followed on this last parameter during the treatment, regardless of sFLC level.

10.12 APPENDIX 12: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

Performance status	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead.

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.

10.13 APPENDIX 13: NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Refer to NCI CTCAE v5.0 in the Study Reference Manual, or online at the following NCI website: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

10.14 APPENDIX 14: CD38 BLOOD TEST INTERFERENCE GUIDELINES

When they exist, local guidelines shall be applicable. Otherwise, the following guidelines should be followed.

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

Date: January 15, 2016
To: AABB Members
From: [redacted]

Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary

A new class of therapeutic agents for multiple myeloma, CD38 monoclonal antibodies, can result in interference with blood bank serologic tests and thereby cause delays in issuing Red Blood Cell (RBC) units to patients receiving these agents. To minimize these delays, hospitals should set up procedures to inform the transfusion service when patients start receiving these agents. Considerations for the transfusion service, both before and after initiation of anti-CD38 therapy, are detailed below.

The AABB Clinical Transfusion Medicine Committee has developed this bulletin to provide background information and guidance to members regarding anti-CD38 interference with serologic testing. The bulletin includes recommendations for its prevention and treatment.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations. No new standards are proposed.

Background

CD38 monoclonal antibodies are a new treatment for multiple myeloma

CD38, an integral membrane protein that is highly expressed on myeloma cells, has been identified as an effective target antigen for monoclonal antibody therapies. In November 2015, the first therapeutic CD38 monoclonal antibody [daratumumab (Darzalex, Janssen Biotech, Horsham, PA)] was approved by the Food and Drug Administration.[1] Other CD38 monoclonal antibodies are under development.

CD38 monoclonal antibodies interfere with blood bank serologic tests

CD38 is weakly expressed on red cells. Anti-CD38 binds to CD38 on reagent RBCs, causing panreactivity in vitro.[2,3] Plasma samples from anti-CD38-treated patients consistently cause positive reactions in indirect antiglobulin tests (IATs), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches. Agglutination due to anti-CD38 may occur in all media (eg, saline, low ionic strength saline, polyethylene glycol),

and with all IAT methods (eg, gel, tube, solid phase). Agglutination reactions caused by anti-CD38 are usually weak (1+), but stronger reactions (up to 4+) may be seen in solid-phase testing. However, anti-CD38 does NOT interfere with ABO/RhD typing or with immediate-spin crossmatches.

Other notes on anti-CD38 serologic interference:

- Adsorptions using either untreated or ZZAP-treated cells fail to eliminate the interference.
- Anti-CD38 variably interferes with direct antiglobulin tests (DATs) and antibody identification panel autocontrols.
- Some rare Lu(a–b–) cells are not reactive in the presence of anti-CD38, potentially giving the false impression that the patient has a Lutheran-related antibody.[4,5]
- Positive IATs can be observed for up to six months after anti-CD38 is discontinued.[1,3]
- Anti-CD38 may cause a small decrease in hemoglobin in vivo (~1 g/dL), but severe hemolysis has not been observed among treated patients.[3,6]

Anti-CD38 interference can cause delays in issuing RBCs
If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient's sample is tested:

1. ABO/RhD typing: no issues.
2. Antibody detection (screening) test: all cells positive.
3. Antibody identification panel: all cells positive (autocontrol may be negative).
4. DAT: positive or negative.
5. AHG crossmatches: positive with all RBC units tested.
6. Adsorptions: panreactivity cannot be eliminated.

This leads to delays in issuing RBCs to the patient. In some cases, the anti-CD38 interference could mask the presence of a clinically significant alloantibody.

Recommendations
To avoid problems with transfusion, hospitals should set up procedures to inform the transfusion service whenever any patient is scheduled to begin taking anti-CD38.

BEFORE a patient begins taking anti-CD38:

- A baseline type and screen should be performed.
- In addition, a baseline phenotype or genotype is recommended.

AFTER a patient begins taking anti-CD38:

- ABO/RhD typing can be performed normally.
- For antibody detection (screening) and identification, dithiothreitol (DTT)-treated cells can be used to eliminate the interference.[2,7]
    - Because DTT treatment destroys Kell antigens, K-negative units should be provided unless the patient is known to be K-positive.
    - Antibodies against other DTT-sensitive blood group antigens (anti-k, anti-Yt^a, anti-Do^a/Do^b, etc) will not be detectable when the antibody screen with DTT-

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treated cells is performed; such antibodies are encountered infrequently, however.

Crossmatch

- For patients with a negative antibody screen using DTT-treated cells, an electronic or immediate-spin crossmatch with ABO/RhD-compatible, K-matched units may be performed.
- For patients with known alloantibodies, phenotypically or genotypically matched RBC units may be provided.[6,8]
    - As some typing antisera require the use of AHG, phenotyping should be performed before the patient receives anti-CD38.
    - Genotyping can be performed either before or after the patient receives anti-CD38.
    - AHG crossmatches with phenotypically or genotypically matched units will still be incompatible.
    - Some clinically significant antibodies may be missed with the use of uncrossmatched phenotypically or genotypically matched units, although this will occur infrequently.
- Alternatively, an AHG crossmatch may be performed using DTT-treated donor cells.
- If an emergency transfusion is required, uncrossmatched ABO/RhD-compatible RBCs may be given per local blood bank practices.

Future/alternative approaches to mitigating the anti-CD38 interference

It is possible to neutralize anti-CD38 in plasma and eliminate the interference using either recombinant soluble human CD38 or daratumumab idiotype antibody.[2,3] Neither reagent is widely available at this time, and additional validation would be needed. In principle, soluble CD38 could be used to neutralize any anti-CD38, while different idiotype antibodies would be needed to neutralize different CD38 therapeutic antibodies. Finally, antigen-typed cord cells have been used for the antibody screen as an alternative to DTT-treated cells.[9]

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10.15 APPENDIX 15 : GLOBAL POMALIDOMIDE PREGNANCY PREVENTION PLAN

1. POMALIDOMIDE PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving pomalidomide within a clinical trial. The following PPP documents are included:

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving pomalidomide in the study
   - Pregnancy testing requirements for subjects receiving pomalidomide who are FCBP
2. The Pomalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of pomalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Pomalidomide Information Sheet (Section 5) will be given to each subject receiving pomalidomide. The subject must read this document prior to starting pomalidomide and each time the subject receives a new supply of pomalidomide.

2. POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated with Pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. Females of Childbearing Potential

For a FCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence pomalidomide as soon as it is dispensed following a negative pregnancy test

- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2. Females Not of Childbearing Potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

2.2.3. Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

2.3. Contraception

2.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) while taking pomalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

[Please note, the above highlighted text is applicable for protocols with dexamethasone-containing pomalidomide regimens.]

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

2.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

2.5. Pregnancy Precautions for Pomalidomide Use

2.5.1. Before Starting Pomalidomide

2.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

2.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.5.2. During and After Study Participation

2.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

2.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking pomalidomide, the Investigator must be notified immediately.

2.5.3. Additional Precautions

- Subjects should be instructed to never give pomalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- No more than a 28-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

3. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

3.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide).

     One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     - Examples of highly effective methods:
       - Intrauterine device (IUD)
       - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])

- Tubal ligation
- Partner's vasectomy

– Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of pomalidomide and at the last dose of pomalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days, and a second within 24 hours of the start of pomalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking pomalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking pomalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of pomalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of pomalidomide.

☐ The subject confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will never share pomalidomide with anyone else.

☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.

☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

2. I have provided the Pomalidomide Information Sheet to the subject.

3.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

5. POMALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rats and rabbits.

   If you are a female who is able to become pregnant:

   - **Do not take pomalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting pomalidomide
     - while taking pomalidomide
     - during breaks (dose interruptions) of pomalidomide
     - for at least 28 days after the last dose of pomalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of pomalidomide
     - 24 hours prior to the first dose of pomalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking pomalidomide if you become pregnant while taking pomalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.

- **Do not breastfeed while taking pomalidomide and for at least 28 days after the last dose of pomalidomide**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During breaks (dose interruptions) of pomalidomide
  - For at least 28 days after the last dose of pomalidomide
- **Male subjects should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share pomalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **Do not break, chew, or open pomalidomide capsules at any point.**
- You will get no more than a 28-day supply of pomalidomide at one time.
- Return unused pomalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

10.16 APPENDIX 16: PATIENT REPORTED OUTCOMES

10.16.1 European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋
Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

10.16.2 European Organization for Research and Treatment of Cancer quality of life myeloma module (EORTC QLQ-MY20)

ENGLISH

EORTC QLQ – MY20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

10.16.3 European Quality of Life Group measure with 5 dimensions and 5 levels per dimension (EQ-5D-5L)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

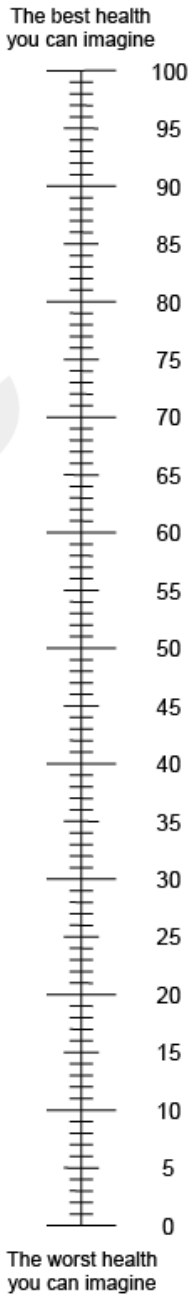
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

10.16.4 Health Resource Utilization and Productivity Questionnaire (HRUPQ)

Health Resource Utilization & Productivity Questionnaire

Please answer the following questions and statements. Answer as honestly as you can without assistance from anyone else. Remember, there are no right or wrong answers; the answers should be based on your own personal experience.

Section 1. Baseline Health Care Utilization

[To be completed at Cycle 1 Day 1 before treatment]

Instructions: The following questions ask you about your health care use in the past 6 months. If you do not know the exact answer to a question, please give your best estimate. Answer as honestly as you can without assistance from anyone else.

I. During the **past 6 months**, how many times have you...

1. received care in a clinic or hospital emergency room to receive urgent care for any health issue (including Multiple Myeloma)? (*Include emergency room visits that resulted in a hospital admission.* (Enter '0' for None)	_____ times
2. received care at a clinic or hospital emergency room due to Multiple Myeloma? (Enter '0' for None)	_____ times
3. received at-home care from a nurse or other health professional for any health issue (including Multiple Myeloma)? (Enter '0' for None)	_____ times
4. # times you have received at-home care from a nurse or other health professional due to Multiple Myeloma? (Enter '0' for None)	_____ times

II. During the **past 6 months**, how many nights have you

5. stayed in hospital for any health issue (including Multiple Myeloma) ? (Enter '0' for None)	_____ nights
6. stayed in hospital (from Q5) due to Multiple Myeloma? (Enter '0' for None)	_____ nights
7. # stayed in the intensive care unit (ICU)? (Enter '0' for None)	_____ nights
8. stayed in the ICU (from Q7) due to multiple myeloma? (Enter '0' for None)	_____ nights

III. During the **past 6 months**, how many times have you seen or talked to following health care professionals?

August 26, 2022

1

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US English V2.3

9. A general doctor or primary care clinician who treats a variety of illnesses, such as a doctor or nurse practitioner in general practice, family medicine, or internal medicine for any health issue (including Multiple Myeloma) *(other than an urgent care center clinician.* Enter '0' for None)	_____ times
10. A general doctor or primary care clinician who treats a variety of illnesses, such as a doctor or nurse practitioner in general practice, family medicine, or internal medicine for a health issue related to multiple myeloma *(other than an urgent care center clinician.* Enter '0' for None)	_____ times
11. A physical or occupational therapist for any health issue (including Multiple Myeloma) (Enter '0' for None)	_____ times
12. A physical or occupational therapist for a health issue related to multiple myeloma (Enter '0' for None)	_____ times
13. A mental health professional, such as a psychiatrist, psychologist, psychiatric nurse, or clinical social worker for any health issue (including Multiple Myeloma) (Enter '0' for None)	_____ times
14. A mental health professional, such as a psychiatrist, psychologist, psychiatric nurse, or clinical social worker for a health issue related to multiple myeloma (Enter '0' for None)	_____ times
15. A medical doctor or clinician who specializes in a particular medical disease or issue for any health issue (including Multiple Myeloma) (other than a mental health professional, physical therapist, occupational therapist, or urgent care center clinician) (Enter '0' for None)	_____ times
16. A medical doctor or specialist clinician for a health issue related to multiple myeloma (other than a mental health professional, physical therapist, occupational therapist, or urgent care center clinician) (Enter '0' for None)	_____ times

Section 2. During Isatuximab administration visit and End of Trial (EoT) visits: Health Care Resource Utilization

Regarding the last Isatuximab administration:

17. How long was your hospital visit (from arrival to departure)?	...minutes
18. How long were you monitored for, after the administration of the treatment?	...minutes

19. Since the last Isatuximab administration, have you had a visit with a healthcare professional not required by the clinical trial?

August 26, 2022

□ Yes

□ No

[SKIP LOGIC: If Item 19 ="no", skip to Section 3; else Item 20]

If yes, how many times have you:

20. received care in a clinic or hospital emergency room to receive urgent care for any health issue (including Multiple Myeloma)? (*Include emergency room visits that resulted in a hospital admission. Do not include visits to urgent care centers*. Enter '0' for None)	_____ times
21. received care at a clinic or hospital emergency room to receive urgent care due to Multiple Myeloma? (Enter '0' for None)	_____ times
22. received at-home care from a nurse or other health professional for any health issue (including Multiple Myeloma)? (Enter '0' for None)	_____ times
23. received at-home care from a nurse or other health professional due to Multiple Myeloma? (Enter '0' for None)	_____ times

24. Did any of these visits take place within 24 to 48 hours after last Isatuximab administration?

□ Yes
□ No

[SKIP LOGIC: If Items 20 and 21 = 0, skip to Item 29; else Item 25]

If you have been hospitalized overnight, how many nights have you

25. stayed in hospital for any health issue (including Multiple Myeloma)? (Enter '0' for None)	_____ nights
26. stayed in hospital (from Q24) due to Multiple Myeloma? (Enter '0' for None)	_____ nights
27. stayed in the intensive care unit (ICU)? (Enter '0' for None)	_____ nights
28. stayed in the ICU (from Q26) due to multiple myeloma? (Enter '0' for None)	_____ nights

Excluding visits related to your Isatuximab treatment and the clinical trial, since the last Isatuximab administration, how many times have you seen:

29. A general doctor or primary care clinician who treats a variety of illnesses, such as a doctor or nurse practitioner in general practice, family medicine, or internal medicine (other than an urgent care center clinician. Enter '0' for None)	_____ times
30. A physical or occupational therapist (Enter '0' for None)	_____ times
31. A mental health professional, such as a psychiatrist, psychologist, psychiatric nurse, or clinical social worker (Enter '0' for None)	_____ times
32. A medical doctor or specialist clinician or issue (other than a mental health professional, physical therapist, occupational therapist, or urgent care center clinician) (Enter '0' for None)	_____ times

33. **Since the last Isatuximab administration**, have you had any health tests or procedures not mandated by the clinical trial (blood test, imagery, diagnostic tests etc.)?

□ Yes

□ No

[SKIP LOGIC: If Item 33 = "No", skip to Section 3; else Item 34]

34. Add the number of times you have done different Blood, Imagery and Diagnostic tests or procedures not mandated by the clinical trial. If you do not know the exact answer to a question, please answer as best as you can. (Enter '0' for None since last Isatuximab administration)

How many <u>blood tests</u> have you had? (Enter '0' for None)	_____number of times
How many <u>imagery exams</u> have you done? (e.g. MRI scan, CT scan, echography, PET scan, etc.) (Enter '0' for None)	_____number of times
Other tests not already listed (e.g. Diagnostic tests): please specify which test(s) and the number of times it was done	

Section 3. During Isatuximab administration visit and End of Trial (EoT) visits: Employment

Instructions: The following questions ask about your employment. If you do not know the exact answer to a question, please answer as best as you can.

35. Are you retired?

□ Yes

□ No

[SKIP LOGIC: If Item 35= "yes", administer Item 36 and do not repeat in future visits; else skip to Item 37]

36. Did you retire earlier than you would have liked due to multiple myeloma?

☐Yes
☐No

[SKIP LOGIC: If Item 35 =" yes", end and do not repeat Section 3 in future visits; else Item 37]

37. **Since the last Isatuximab administration**, did you work for pay at a job or business?

☐ Yes

☐ No

[SKIP LOGIC: If Item 37 = "yes", administer Item 38-44; else skip to Item 45]

38. **Since the last Isatuximab administration**, how many hours per week did you work?

_____ number of hours per week

39. **Since the last Isatuximab administration**, did you reduce your weekly work hours because of any issue related to your multiple myeloma?

☐ Yes
☐ No

40. **Since the last Isatuximab administration**, how many hours per week did you reduce your work because of any issue related to your multiple myeloma?

_____ number of hours per week reduced

41. **Since the last Isatuximab administration**, did you change the type of work you do because of any issue related to your multiple myeloma?

☐ Yes
☐ No

[SKIP LOGIC: If Item 40 = "yes", administer Item 42; else skip to Item 43]

42. **Since the last Isatuximab administration**, was your income reduced as a result of changing the type of work you do?

☐ Yes
☐ No

43. **Since the last Isatuximab administration**, how many days did you miss from work because of any issue related to your multiple myeloma? *(Do not include any days you missed from work to participate in this study.)*

_____ number of days missed from work

44. **Since the last Isatuximab administration**, how many days were you at work but less productive than you would like because of any issue related to your multiple myeloma?

_____ number of days

45. **Since the last Isatuximab administration**, did you not work for pay because of any issue related to your multiple myeloma?
    - ☐ Yes
    - ☐ No

46. What is the main reason you did not work **last month**? (Select one)
    - ☐ Unemployed
    - ☐ On temporary leave from work
    - ☐ Permanently disabled
    - ☐ Working at job or business but not for pay
    - ☐ Work seasonally and off-season
    - ☐ Other, please describe: _____

Please note if you are having any severe symptoms, side effects, health issues or other concerns, please be sure to discuss with your doctor or nurse. Answers to the questions/questionnaires completed on this device are not reviewed by your doctor or nurse (data to be analyzed by study statisticians at future prespecified time points).

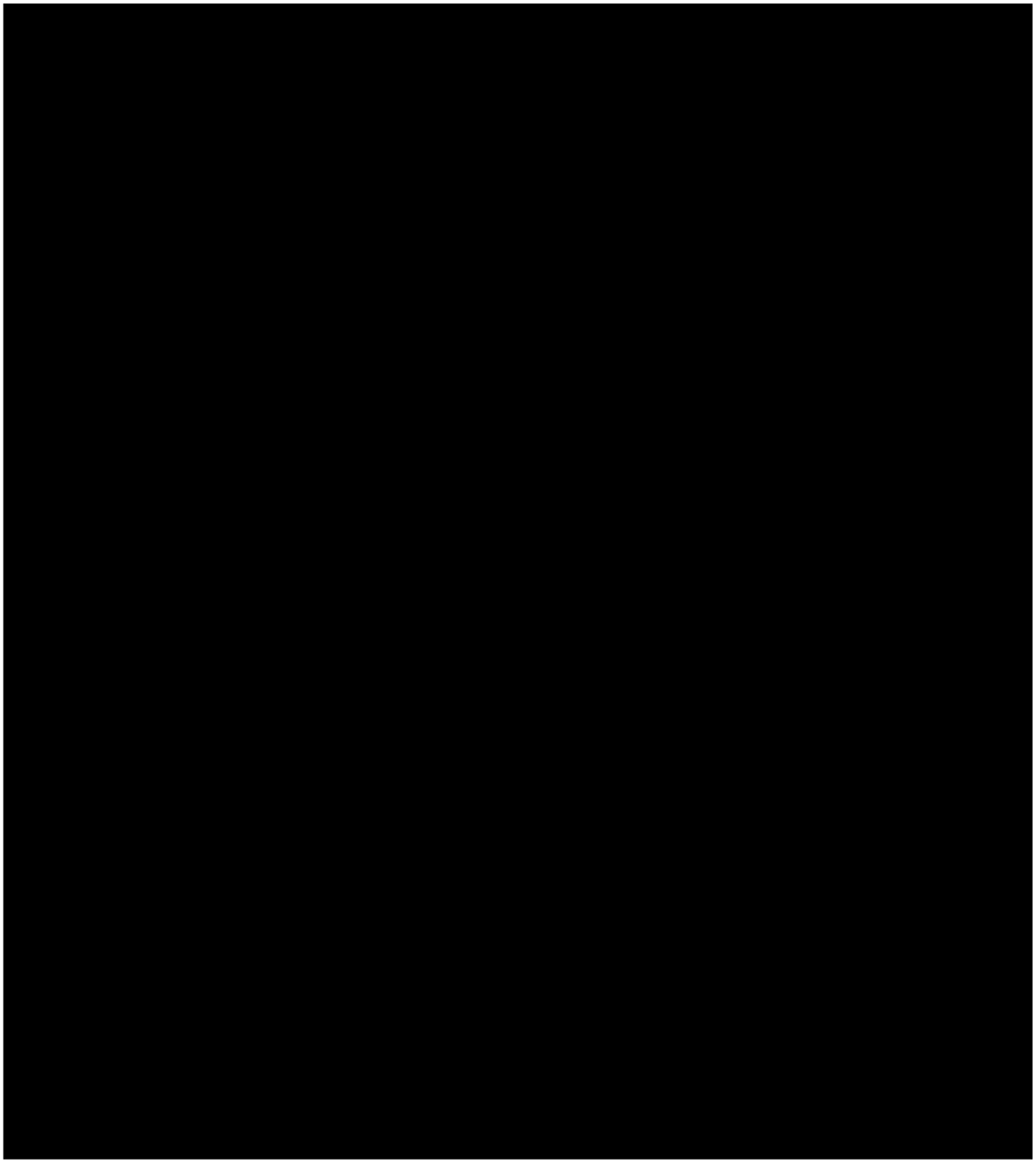
10.16.5 Patient Expectations Questionnaire at Baseline (PEQ-BL)

[redacted]

[redacted]

PEQ-BL_ English-USv4_Sept.-7-2021

10.16.6 Patient experience and satisfaction follow-up questionnaire (PESQ-FU)

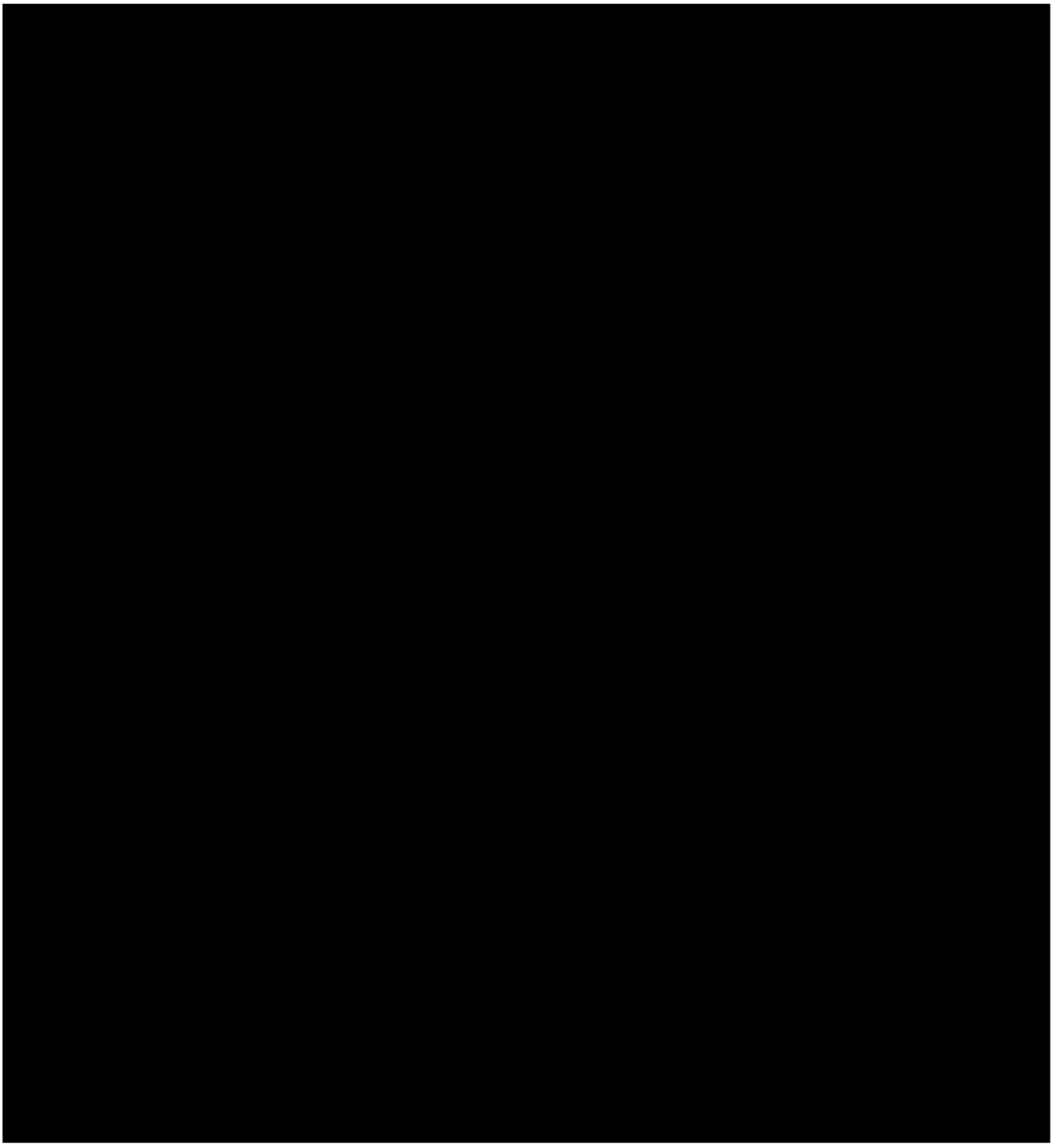


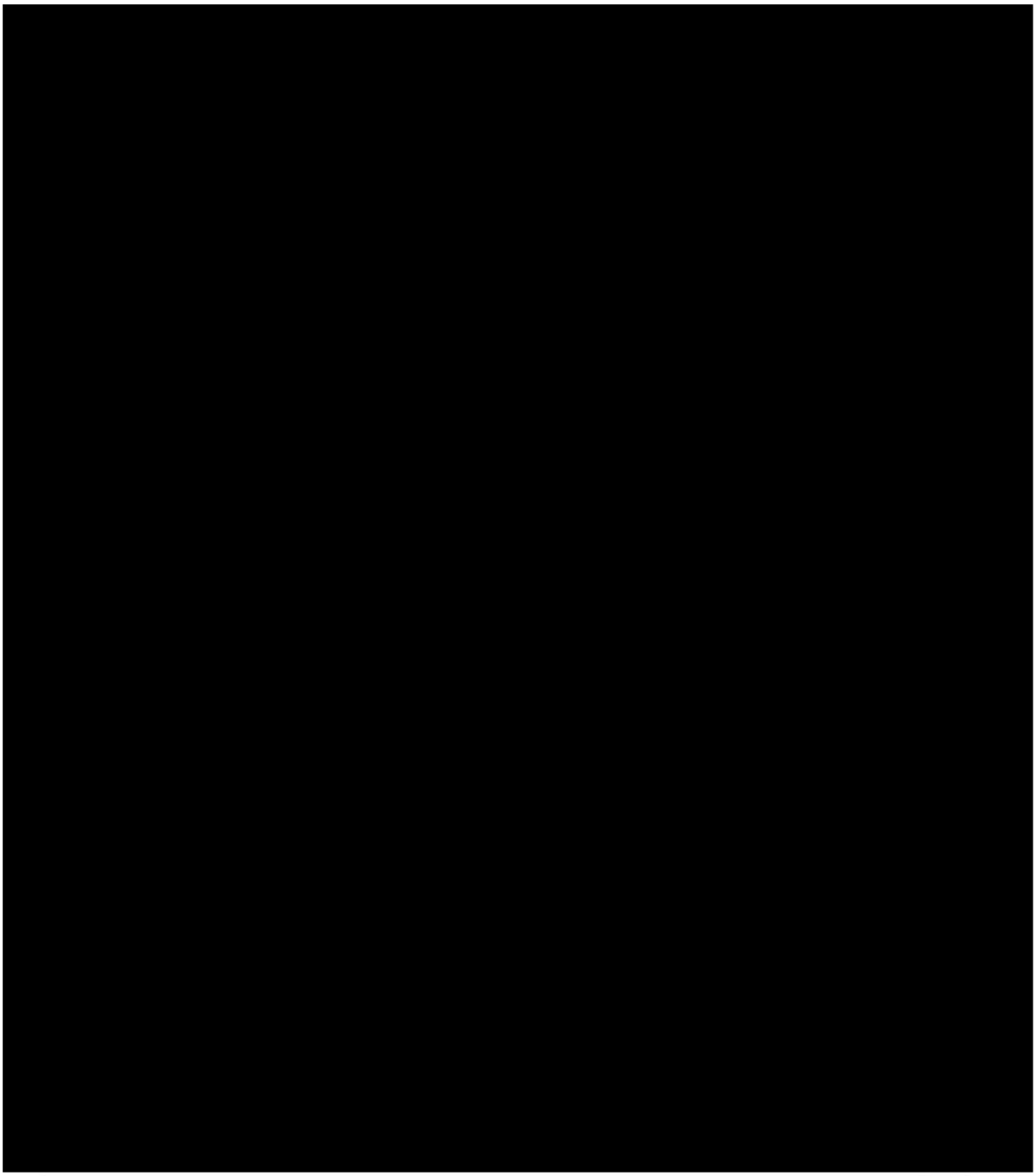
PESQ-FU_English-US-v6_Sept.-7-2021

[redacted]

PESQ-FU_English-US-v6_Sept.-7-2021

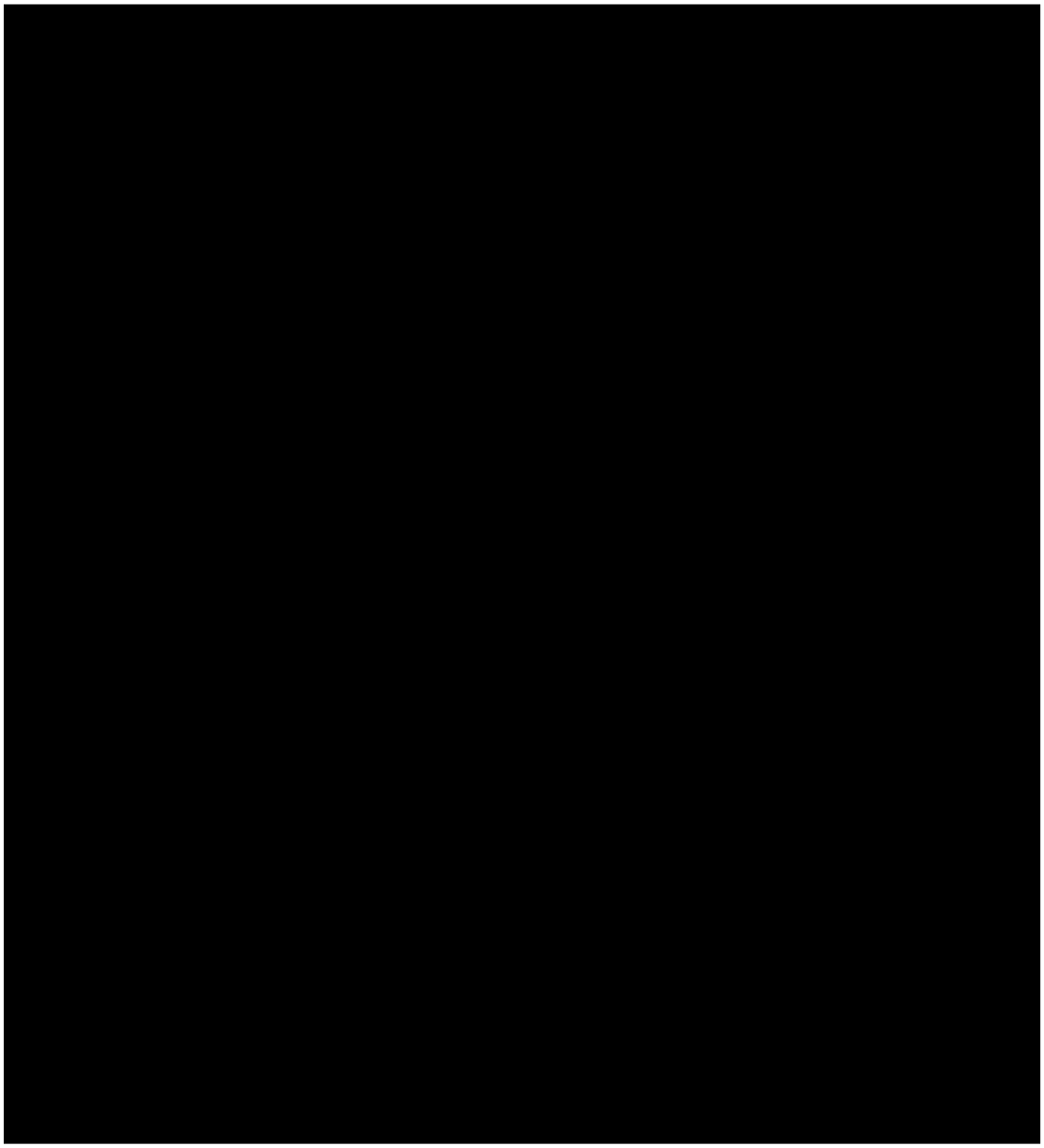
10.16.7 Patient experience and satisfaction end-of-treatment questionnaire (PESQ-EOT)





PESQ-EOT_ English-US-v4_Sept.-14-2021

13. What are the main reasons that make you prefer this **Injection method**?

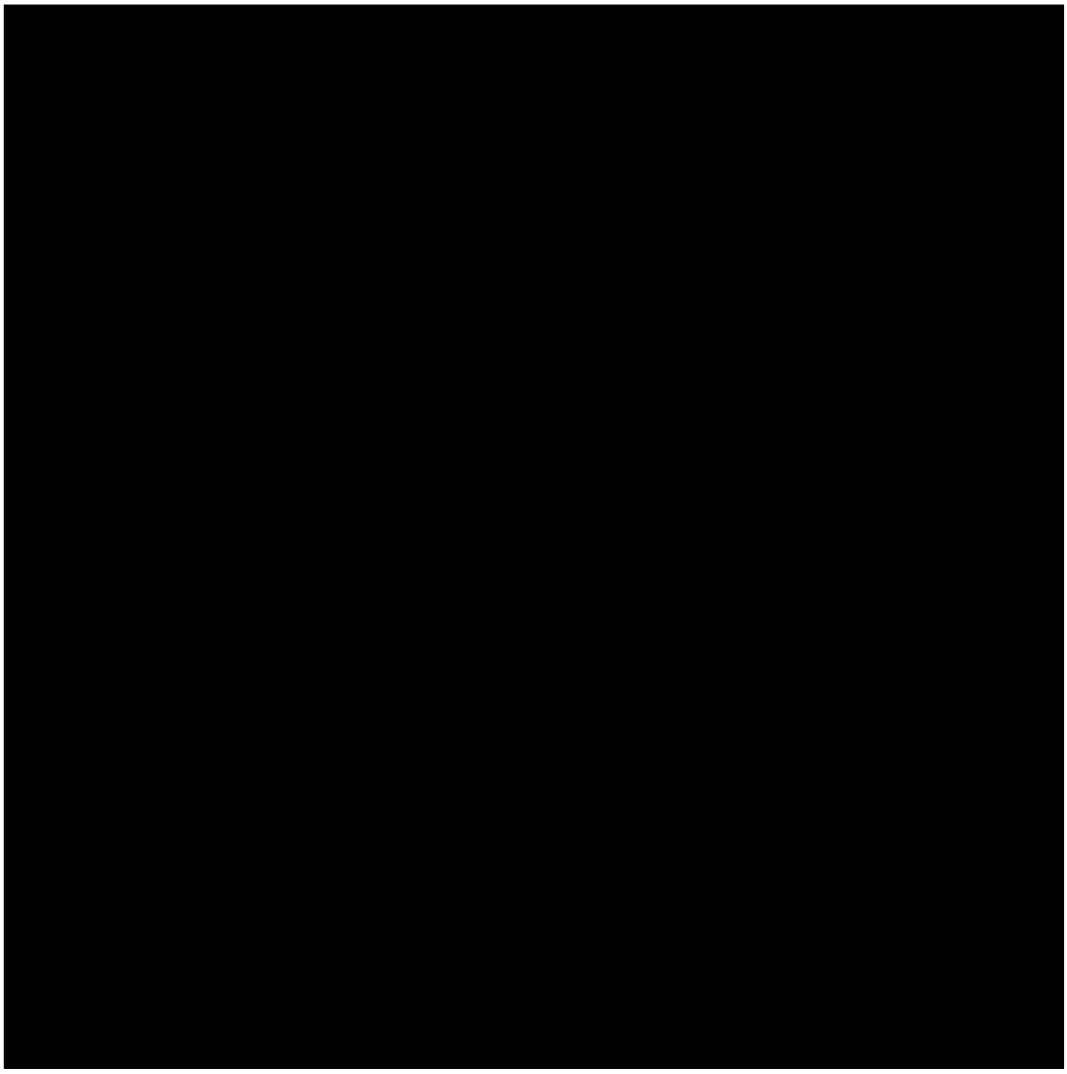


PESQ-EOT_ English-US-v4_Sept.-14-2021

PESQ-EOT_ English-US-v4_Sept.-14-2021

10.16.8 Patient's Assessment of Treatment questionnaire (PAT)

Patient's Assessment of Treatment Questionnaire (PAT)



PAT Sanofi, 2021 Page [redacted]

Patients' assessment of treatment questionnaire (PAT)_ 9 Sept 2021

10.16.9 Local Tolerability at Injection Site After Isatuximab Administration - Patient Assessment Using Diary

Patient Local Tolerability Questionnaire (PLTQ): At-home symptom diary: one page per date and per Event (symptom experienced)

Please note if you are having any severe symptoms, side effect, health issues or other concerns, please be sure to discuss these with your doctor or nurse as this questionnaire is not reviewed by your health care team.

Complete checklist on next page if any of pain, swelling, redness, itching, bruising, hardening, burning, cold sensation(s) or other symptoms at injection site experienced; use the scoring for severity and interference scales provided below:

Bring all pages of at-home symptom diary (Patient Local Tolerability Questionnaire) to next study visit

Use Scales below to complete Severity and Interference columns on next page

Severity (at its worst)	Interference (at its worst) with your usual or daily activities
0=None	0=Not at all
1= Mild	1= A little bit
2=Moderate	2=Somewhat
3=Severe	3=Quite a bit
4=Very severe	4=Very much

If none of the symptoms experienced (on form next page) please check box below:

☐ **No** pain, swelling, redness, itching, bruising, hardening, burning, cold sensation(s), tenderness or other symptoms at injection site experienced**.**

Page 1
PLTQ _ English-US –v4.nov-2-2020

Patient Local Tolerability Questionnaire (PLTQ): At-home symptom diary: one page per date and per Event (symptom experienced)

Complete below if any 1. Pain, 2. Swelling, 3. Redness, 4. Itching, 5. Bruising, 6. Hardening, 7. Burning, 8. Cold sensation(s) or 9. Warm sensation(s), 10. Tenderness or Other symptoms at injection site experienced; **SEEK APPROPRIATE MEDICAL CARE/CONTACT YOUR NURSE/DOCTOR IMMEDIATELY IF ANY SEVERE SYMPTOMS OR CONCERNS**

Symptom (at its worst):	**Start date** Time started (eg 8:23 AM or 0823) DD-MMM-YEAR (eg 25-MAY-2021)	**Stop Date** Time stopped (eg 8:25 AM or 0823) DD-MMM-YEAR (eg 25-MAY-2021)	**Start Time** HH-mm	**Stop Time** HH-mm	**Severity (at worst):** **0=Not at all 1=Mild 2=Moderate 3=Severe 4=Very severe**	**Interference (at worst)** **0=Not at all 1=A little 2=Somewhat 3=Quite a bit 4=Very much**
1. Pain at injection site						
2. Swelling at injection site						
3. Redness at injection site						
4. Itching at injection site						
5. Bruising at injection site						
6. Hardening at injection site						
7. Burning at injection site						
8. Cold sensation(s) at injection site						
9. Warm sensation(s) at injection site						
10. Tenderness at injection site						
11. Other injection site symptom, specify_____						
12. Other injection site symptom, specify_____						

10.17 APPENDIX 17: IADL AND ADL QUESTIONNAIRES

INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (IADL)

M.P. Lawton & E.M. Brody

A. Ability to use telephone	
1. Operates telephone on own initiative; looks up and dials numbers, etc.	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone at all.	0
B. Shopping	
1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip.	0
4. Completely unable to shop.	0
C. Food Preparation	
1. Plans, prepares and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats, serves and prepares meals or prepares meals but does not maintain adequate diet.	0
4. Needs to have meals prepared and served.	0
D. Housekeeping	
1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1
2. Performs light daily tasks such as dish-washing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness.	1
4. Needs help with all home maintenance tasks.	1
5. Does not participate in any housekeeping tasks.	0
E. Laundry	
1. Does personal laundry completely	1
2. Launders small items; rinses stockings, etc.	1
3. All laundry must be done by others.	0
F. Mode of Transportation	
1. Travels independently on public transportation or drives own car.	1
2. Arranges own travel via taxi, but does not otherwise use public transportation.	1
3. Travels on public transportation when accompanied by another.	1
4. Travel limited to taxi or automobile with assistance of another.	0
5. Does not travel at all.	0
G. Responsibility for own medications	
1. Is responsible for taking medication in correct dosages at correct time.	1
2. Takes responsibility if medication is prepared in advance in separate dosage.	0
3. Is not capable of dispensing own medication.	0
H. Ability to Handle Finances	
1. Manages financial matters independently (budgets, writes checks, pays rent, bills goes to bank), collects and keeps track of income.	1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Incapable if handling money.	0

Source: Lawton, M.P., and Brody, E.M. "Assessment of older people: Self-maintaining and instrumental activities of daily living." Gerontologist 9:179-186, (1969).

Katz Index of Independence in Activities of Daily Living

ACTIVITIES POINTS (1 OR 0)	INDEPENDENCE: (1 POINT) **NO** supervision, direction or personal assistance	DEPENDENCE: (0 POINTS) **WITH** supervision, direction, personal assistance or total care
BATHING POINTS:_____	(1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	(0 POINTS) Needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING POINTS:_____	(1 POINT) Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	(0 POINTS) Needs help with dressing self or needs to be completely dressed.
TOILETING POINTS:_____	(1 POINT) Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	(0 POINTS) Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING POINTS:_____	(1 POINT) Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	(0 POINTS) Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE POINTS:_____	(1 POINT) Exercises complete self control over urination and defecation.	(0 POINTS) Is partially or totally incontinent of bowel or bladder.
FEEDING POINTS:_____	(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.	(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.

TOTAL POINTS = _____ *6 = High (patient independent) 0 = Low (patient very dependent)*

Slightly adapted from Katz, S., Down, T.D., Cash, H.R., & Grotz, R.C. (1970) Progress in the development of the index of ADL. *The Gerontologist,* 10(1), 20-30.

The Hartford Institute for Geriatric Nursing recognizes Mary Shelkey, PhD, ARNP and Meredith Wallace Kazer, PhD, APRN, A/GNP-BC as the original authors of this issue.

10.18 APPENDIX 18: ABBREVIATIONS AND DEFINITIONS

ADA: anti-drug antibodies
ADE: adverse device effect
ADL: index of independence in activities of daily living
AE: adverse event
AESI: adverse event of special interest
ALT: alanine aminotransferase
ANC: absolute neutrophil count
anti-HBc: antibody to hepatitis B core antigen
anti-HBs: antibody to hepatitis B surface antigen
AST: aspartate aminotransferase
AUC: area under the curve
AUC_{1week}: area under the plasma concentration time curve over the first week
AUC_{2weeks}: area under the plasma concentration time curve over two weeks
AxMP: auxiliary medicinal product
BM: bone marrow
CI: confidence interval
CID: clinically important difference
C_{max}: maximum concentration
CR: complete response
C_{trough}: observed concentration before dosing
CV: coefficient of variation
CYP1A2: cytochrome P450 family 1 subfamily A member 2
DLT: dose limiting toxicity
DMC: Data Monitoring Committee
DOR: duration of response
EC: ethics committee
ECG: electrocardiogram
eCRF: electronic case report form
eGFR: estimated glomerular filtration rate
EMA: European Medicines Agency
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-MY20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Myeloma Module 20
EOT: end of treatment
ePRO: electronic patient-reported outcome
EQ-5D-5L: the European Quality of Life Group Questionnaire with 5 Dimensions and 5 Levels
EU: European Union
FCBP: female of childbearing potential
FDA: Food and Drug Administration
FISH: fluorescent in situ hybridization
FLC: free light chain

G-CSF:	granulocyte-colony stimulating factor
GLP:	good laboratory practice
GvHD:	graft versus host disease
HA:	health authority
HBC:	hepatitis C virus
HBV:	hepatitis B virus
HCP:	health care professional
HIV:	human immunodeficiency virus
HR:	hazard ratio
HRUPQ:	health resource utilization and productivity questionnaire
IADL:	instrumental activities of daily living
IB:	Investigator's brochure
ICF:	informed consent form
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IMWG:	international myeloma working group
IR:	infusion reaction
IRB:	Institutional Review Boards
IRC:	Independent Review Committee
IRT:	interactive response technology
IsaPd:	isatuximab in combination with pomalidomide and dexamethasone
ISRs:	injection site reactions
ITT:	intent-to-treat
IV:	intravenous
LPI:	last patient in
MDRD:	modification of diet in renal disease
MM:	multiple myeloma
MR:	minimal response
MRD:	minimal residual disease
MRI:	magnetic resonance imaging
MTD:	maximal tolerated dose
NCI CTCAE:	National Cancer Institute, Common Terminology Criteria for Adverse Events
NK:	natural killer
NMPA:	National Medical Products Administration
OBDS:	on body delivery system
ORR:	overall response rate
OS:	overall survival
PAT:	patient's assessment of treatment
PCSA:	potentially clinically significant abnormality
Pd:	pomalidomide and dexamethasone
PD:	progressive disease
PDy:	pharmacodynamic
PEQ:	patient expectation questionnaire
PEQ-BL:	patient expectations questionnaire at baseline
PESQ:	patient experience and satisfaction questionnaire
PESQ-EOT:	patient experience and satisfaction end of treatment questionnaire

PESQ-FU:	patient experience and satisfaction follow-up questionnaire
PET-CT:	positron emission tomography- Computed tomography
PFS:	progression free survival
PI:	proteasome inhibitor
PK:	pharmacokinetic
PML:	progressive multifocal leukoencephalopathy
PO:	per os
PP-PK:	per protocol PK
PR:	partial response
PRO:	patient-reported outcome
Q2W:	every 2 weeks
QTL:	quality tolerance limit
QWx4:	every week for 4 weeks
RP2D:	recommended Phase 2 dose
RRMM:	relapsed/refractory multiple myeloma
SADE:	serious adverse device effect
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SC-IP:	subcutaneous route using an infusion pump
SC-OBDS:	subcutaneous on body delivery system
sCR:	stringent complete response
SmPC:	summary of product characteristics
SoA:	schedule of activities
SPD:	sum of the products of the maximal perpendicular diameters of measured lesions
SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment emergent adverse event
TT1R:	time to first response
TTBR:	time to best response
TTR:	time-to-response
ULN:	upper limit of normal
USADE:	unanticipated serious adverse device effect
VAS:	visual analogue scale
VGPR:	very good partial response

10.19 APPENDIX 19: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

10.19.1 Amended protocol 01 (11-October-2022)

This amended protocol is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amended protocol is to incorporate feedback received from health authorities (HA) and ethics committees (EC), to ensure consistency across sections and across program documents, and to provide clarifications in several sections.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 6.1.2 Non investigational medicinal products	Under heading Non-Investigational Medicinal Products (Premedication): Montelukast 10 mg orally (C1 only) changed to Montelukast 10 mg orally (Cycle 1 only). Added “except montelukast that should be administered only on Cycle 1” in the statement where it is mentioned that premedication reconsidered at the Investigator’s discretion. Section 6.1.2: Text updated to include that Montelukast is to be administered on Cycle 1 only.	Clarification and readability improvement.
1.2 Schema	Add additional details on key secondary endpoints: • C_{trough} at 4 weeks (CT4W corresponding to C2D1 predose). • Patient satisfaction: PESQ.	Consistency between sections.
1.3 Schedule of Activities (SoA)	• Hepatitis viral assessment changed to Hepatitis B and C. • Footnote “g” also updated with same change.	Consistency between sections.
1.3 Schedule of Activities (SoA)	• Updated the assessment name: Patient experience and satisfaction questionnaire (PESQ) and Patient's assessment of treatment (PAT) Questionnaire. • Corresponding footnotes also updated.	Consistency between sections.
1.3 Schedule of Activities (SoA) 8.4 Patients Reported Outcomes	• Patient experience and satisfaction Questionnaire (PESQ) and Patient's assessment of treatment (PAT) Questionnaire - assessment removed from follow-up visit, and updated corresponding footnote ‘k’ to remove “90 ±7 days after last study treatment administration”. • Section 8.4 in timing of assessments, removed “and at 90 ±7 days after last study treatment administration”.	Correction in assessment timepoint.
2.2.3.2 Isatuximab SC in combination with pomalidomide and dexamethasone	TCD15484 study results updated as per cutoff date of 16 May 2022.	New data.
2.3.1 Risk assessment	Updates in Table 5 – Risk assessment • Identified risk neutropenia: Following text added in mitigation strategy. Exclusion of patients with ANC <1000 µL (1×10^9/L). The use of G-CSF is not allowed to reach this level. • Potential risk second primary malignancies: Following text deleted from mitigation strategy. International Myeloma Working Group (IMWG) guidelines: specific routine screening for SPMs not recommended in MM.	Consistency across program documents.

Section # and Name	Description of Change	Brief Rationale
	• Potential risk Viral reactivation: added "herpes zoster" reactivation and added text for antiviral prophylaxis. • Injection site reaction: Updated text to mention that no Grade >1 ISRs were reported in the Phase 1 trial with SC isatuximab.	
4.9 Study committees, 6.3.1 Blinding rules and 8.1 Efficacy assessments	Added information that an IRC is blinded to treatment assignment.	Updated as per feedback from HA.
5.1 Inclusion criteria	Updated text in Inclusion criterion 6 (I 06), from "before study entry" to "before signing the informed consent form (ICF)".	Further clarification on text.
5.1 Inclusion criteria	Added Inclusion criterion 9 (I 09), other inclusion criteria included for country specific requirement applicable for Norwegian clinical sites.	Updated as per feedback from HA.
5.2 Exclusion criteria	Updated exclusion criterion 18 (E18) text from previous wording: *Hypersensitivity to dexamethasone, sucrose histidine (as base and hydrochloride salt) and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents.* to *Known intolerance or hypersensitivity to dexamethasone, to any of isatuximab subcutaneous formulation excipients (L-histidine; L-histidine hydrochloride monohydrate, L-arginine monohydrochloride, sucrose, polysorbate 80, and poloxamer 188), or to any of the components study therapy that are not amenable to premedication with steroids, or H2 blockers, that would prohibit further treatment with these agents.*	Updated as per feedback from HA.
5.2 Exclusion criteria	Additional sub-criteria added for exclusion criterion E19; E 19 b): Participants with contraindication to pomalidomide and E 19 c): with ≥Grade 2 peripheral neuropathy.	Updated as per feedback from HA.
5.2 Exclusion criteria	Updated text in exclusion criterion 22 (E 22) to include details of participants with hepatitis B and hepatitis C: *Known acquired immunodeficiency syndrome (AIDS)-related illness or known human immunodeficiency virus (HIV) disease requiring antiviral treatment, known active hepatitis A infection (defined as positive hepatitis A antigen or positive IgM), and current active or chronic hepatitis B (HBV) or hepatitis C (HCV) infection. Participants with chronic HBV or HCV disease that is controlled under antiviral therapy are allowed. HIV serology will be tested at screening for participants of countries where required as per local regulations. Hepatitis B and C serology will be tested at screening for all participants.*	Updated as per feedback from HA.
6.1.1.2 Dexamethasone	Details added for requirement of particular care when treating patients with glaucoma and ocular herpes simplex.	Updated as per feedback from HA.
6.1.1.3 Pomalidomide	Details on monitoring and management of worsening neurologic, cognitive or behavioral signs and symptoms, including progressive multifocal leukoencephalopathy (PML) suspicion.	Updated as per feedback from HA.

Section # and Name	Description of Change	Brief Rationale
6.1.1.4 Study arms (Table 10)	Timepoints of administration of intervention (isatuximab SC/IV) added: on Day 1, 8, 15, and 22 in the first Cycle and on Day 1 and Day 15 for subsequent cycles. Timepoints of administration of dexamethasone added: Day 1, 8, 15, and 22 of every 28 days cycle.	Clarification following comments from HA.
6.3.1 Blinding rules	Added statement regarding use of an IRT centralized randomization. Additional steps which reduce potential bias are described: • Despite the open-label administration of treatments, assessment of efficacy outcomes will be based on objectively collected data, which are radiological assessments for tumor response and central laboratory assessment that will be reviewed by an IRC blinded to study intervention arms. • During the course of the study, an external independent statistician will perform unblinded safety and efficacy analyses for the data review of DMC. Access to these data and analyses will be restricted to the DMC members.	Updated as per feedback from HA.
6.4.1 Subcutaneous isatuximab at-home administration	Mention clear instructions for participants on ISRs at injection site in participants diary and timing for same.	Consistency across program documents.
6.5.5 Management of infusion reactions and injection site reactions and 8.5.6 Adverse event of special interest	Table 15: Deleted “Report AESI if the reaction lasts >24 hours” as only ISR ≥Grade 2 to be considered as an AESI and not ISR Grade 1 lasting more than 24 hours. Section 8.5.6: Deleted “Grade 1 lasting >24 hours” from ISRs AESI criteria.	Consistency across program documents.
6.5.5 Management of infusion reactions and injection site reactions	Table 15: Changed “SC isatuximab administration” to “isatuximab administration” for ISRs and following additional details added for Grade 3 and Grade 4 IRs: *In case of Grade 3, isatuximab administration may be resumed at the next planned administration at Investigator’s discretion.* *If a Grade 3 IR occurs for a 3rd time, treatment with isatuximab will be definitively discontinued for that participant.* *In case of Grade 4, isatuximab will be permanently discontinued.*	Consistency with the IB.
6.8.4 Prohibited concomitant therapy	Added time frame: Live vaccines should be avoided up to 90 days after last dosing of study IMP. Added word “non-live vaccines” for routine vaccinations.	Updated as per feedback from HA.

Section # and Name	Description of Change	Brief Rationale
7.1.1 Permanent discontinuation	Details added on the management of permanent treatment discontinuation and follow up period changed from 90 days to 3 months (following text added). *If one of the study treatments is prematurely permanently discontinued, then other drug(s) can be continued until disease progression or unacceptable toxicity or patient's wish to discontinue further study treatment. During this period the participant will remain in the study and continue being assessed per SoA. If all study treatments are permanently discontinued, the visit will be treated as the last dosing day with the IMPs, with subsequent relevant assessments per SoA.* *In case of permanent treatment discontinuation due to disease progression, follow up will be every 3 months for further antimyeloma therapy, second primary malignancies, PFS2, and survival until death, or final OS analysis cut-off date, whichever occurs first.*	Updated as per feedback from HA and correction.
7.1.1.1 List of criteria for permanent discontinuation	Pregnancy in a female participant added as criteria for permanent treatment discontinuation.	Updated as per feedback from HA.
8.3 Safety assessments	*"Participants will stay at the site after each administration for at least 4 hours in Cycle 1"* re-worded to. *"Participants will stay at the site between 1 and 4 hours after each administration in Cycle 1".*	Reworded for clarification and consistency among sections.
8.3.7 Assessment of local tolerability	Table 19 summarizing the assessment of local tolerability added for better visualization.	Clarification and readability improvement.
8.4 Patients reported outcomes	Updated text to mention that patient's own device can also be used and added text on dedicated website. *All PROs are in electronic form (electronic patient reported outcomes [ePRO]) and will be completed by the patient (study participant) using either the study mobile phone provided or the patient's own device.* *Alternatively, a dedicated website could be proposed to collect PROs as a backup solution in case of unavailability of handheld devices.*	Updated as per feedback from HA.
8.5 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting	Included words ADE, SADE, and their definitions as these are also reportable events as per MDR Article 80 at applicable places (Sections 8.5, 8.5.3, and 8.5.7.1.1).	Updated as per feedback from HA.
8.5.6 Adverse events of special interest	Clarified and updated timing of collection of follow up information on a participant pregnancy or female partner of a male participant up to 1 year after delivery of a newborn from previously 6 to 8 weeks.	Aligned with protocol program template.
8.6 Genetics	Clarified further that "No congenital genetic testing is planned in this study; however, tumoral genetic and genomics analyses will be performed on bone marrow samples."	Comment from IRB.

Section # and Name	Description of Change	Brief Rationale
10.1.3 Informed consent process	Removed word “their legally authorized representative “.	Consistency with Exclusion criteria. Following comments from EC.
10.1.6 Dissemination of clinical study data	Replace clinicalstudydatarequest.com in this protocol with https://vivli.org.	Update as per template change.
10.4.2.2 Contraception guidance for female subjects	Table Contraceptives allowed during the study include: … Highly effective methods (b) that are user dependent… Oral contraceptive method removed and added footnote “c” for “combined (estrogen- and progestogen-containing) hormonal contraception” for clarification. *A patient can use ‘oral’ combination if they have discontinued pomalidomide.* *As per pomalidomide/Imnovid Summary of Product Characteristics (SmPC), combined oral contraceptive pills are not recommended because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone.*	Updated as per feedback from HA.
10.4.4.2 Male participants	Clarified and updated timing of follow up of partner pregnancy to 1 year as previously captured 6 to 8 weeks after estimated delivery date.	Aligned with protocol program template.
10.8 Country-specific requirements	Included country specific requirement applicable for Norwegian clinical sites (inclusion criteria) and France (regarding home-based administration).	Updated as per feedback from HA.
10.13 Appendix 13: CD38 Blood test interference guidelines	Added following text: *When they exist, local guidelines shall be applicable. Otherwise, the following guidelines should be followed.*	Clarification and readability improvement.
10.15.4 Health Resource Utilization and Productivity Questionnaire (HRUPQ)	Specify more details on Question 34: New/updated Health Resource Utilization and Productivity Questionnaire (HRUPQ) provided.	Clarification to avoid open text questions; Data management requirement.
Throughout	Minor editorial, typographical error corrections and document formatting revisions.	Minor, therefore, have not been summarized.

10.19.2 Amended protocol 02 (15-March-2023)

This amended protocol is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amended protocol is 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. Secondary purposes are to remove reference to bone plasmocytoma and to clarify definition and follow-up of extramedullary disease (EMD) and paramedullary disease; to allow switching of patients to long-term follow-up study after the final OS analysis cut-off; to clarify guidelines for Urine 24-hour M-protein (UPEP); to definie overdose for non-IMPs; to clarify overdose for IMPs following an internal audit finding; and to apply minor corrections (inconsistencies) following internal audit findings.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Adding “switching to a long-term safety study”.	Specifying additional possibility of study treatment access after final analysis.
1.1 Synopsis	“Montelukast 10 mg orally (Cycle 1 only)” has been changed by “Montelukast 10 mg orally (or equivalent, Cycle 1 only)”.	Adding the possibility to use a Montelukast equivalent.
1.3 Schedule of Activities (SOA), Table 1, Footnote d	Removing redundant sentence: “After confirmation of disease progression or the start of further antimyeloma therapy, participants will be followed up every 3◦months (12 weeks) for information on antimyeloma therapy, second primary malignancies, PFS2 and survival, until death or final study cut-off date, whichever occurs first.”	Editorial.
1.3 Schedule of Activities (SOA), Table 1, Footnote y	Chaging the footnote by “Soft tissue plasmacytoma assessment (extramedullary disease OR paramedullary disease with a soft tissue lesion of diameter >= 2cm): • If known soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline, repeated every 12 weeks (±1 week) until progressive disease (PD) (even for participants who would initiate further anti-myeloma therapy without PD), and if clinically indicated. PET-CT should be the preferred option whenever possible. From two years post-randomization, the radiological assessment frequency will be done every 6 months (±1 month), • If suspected soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline and if plasmacytoma confirmed on the exam to be repeated every 12 weeks (±1 week) until PD (even for participants who would initiate further anti-myeloma therapy without PD) and if clinically indicated. PET-CT should be the preferred option whenever possible, • To be done in case of suspicion of progression or if clinically indicated in a participant with no previous positive image for soft tissue plasmacytoma, • The bone component of paramedullary disease with a soft tissue lesion of diameter >= 2cm will not be used for disease response assessment as per IMWG,	Guidelines clarification and definition.

Section # and Name	Description of Change	Brief Rationale
	• Paramedullary (paraskeletal) plasmacytoma (bone plasmacytoma extending beyond the bone cortex into the surrounding tissues) with soft tissue lesions of diameter <2cms will be collected but will not be used for disease response assessment as per IMWG. No follow-up with repeated imaging is needed, except if clinically indicated Note: For bone lesion assessment and soft tissue plasmacytoma, the same modality (low-dose whole body CT scan; CT scan, PET-CT scan, or MRI) should be used throughout the study for each individual participant when radiological follow-up is needed. All imaging will be sent for central review. Intravenous contrast is recommended if not medically contra-indicated. Participants who have contra-indication to CT scan with IV contrast may have MRI exams performed instead".	
1.3 Schedule of Activities (SOA), Table 1, Footnote z	Adding "lytic". Adding "MRI". Adding "(±1 month)".	To align with current clinical practice in some countries/sites.
1.3 Schedule of Activities (SOA), Table 1, Footnote bb	Removed "Urine M-protein (24-hour urine) immunoelectrophoresis (UPEP) and immunofixation: UPEP to be performed at screening, C1D1 (predose), prior to each cycle thereafter and at end of treatment (if last tests were >4 weeks or if disease progression was not confirmed on the last test). If urine M-protein is negative (UPEP and IF) at baseline, UPEP assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc), and to confirm CR and Very good partial response (VGPR) on blood laboratory parameters. After baseline, immunofixation to be done if UPEP shows no measurable monoclonal protein in participants whose disease is evaluable in urine." Added "Urine M-protein (24-hour urine) immunoelectrophoresis (UPEP) and immunofixation: UPEP to be performed at screening, C1D1 (predose), prior to each cycle thereafter and at end of treatment (if last tests were >4 weeks or if disease progression was not confirmed on the last test). If urine M-protein is negative (UPEP and IF) at baseline, UPEP assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc), and to confirm CR and Very good partial response (VGPR) on blood laboratory parameters. After baseline, immunofixation to be done if UPEP shows no measurable monoclonal protein in participants whose disease is evaluable in urine. Urine M-Protein (24-hour urine), immunoelectrophoresis (UPEP) and IF: to be performed at screening and Cycle 1 Day 1. If urine M-protein is measurable or detectable or IF is positive at Cycle 1 Day 1, urine M-protein assessment should be done prior to study treatment administration in all subsequent cycles and at EOT (if last tests were >4 weeks or if disease progression was not confirmed on the last test). If urine M-protein is negative (UPEP and IF) at screening and Cycle 1 Day 1, this assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc), and to confirm CR and VGPR on blood laboratory parameters. After Cycle 1 Day 1, urine immunofixation is to be done only if urine M-protein is not detected in UPEP."	Guidelines clarification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SOA), Table 1, Footnote bb	Removing "(maximum of 1 year)".	To align with follow-up.
2.3.1 Risk assessment, Table 5	Removing ", and in consultation with the Sponsor to avoid unnecessary sedation." Adding ", except for montelukast which should be administered only on Cycle 1".	To be consistent throughout the protocol.
5.2 Exclusion criteria, E27	Adding "(R2)".	Updating version according to German Medicinal Products Act (AMG), the GCP Ordinance (GCP-V) and the Guideline for Good Clinical Practice (ICH-GCP E6 (R2)) apply in Germany.
6.1.1.1.1 Isatuximab IV formulation	Replacing "in experimental" by "active comparator".	Correction following audit finding.
6.1.2 Non investigational medicinal products	Adding "or equivalent".	Adding the possibility to use a Montelukast equivalent.
6.5.4 Dose adjustments according to adverse events, Table 14, Renal dysfunction	Replacing "CrCl" by "eGFR". Replacing "CrCl" by "eGFR".	Consistency across the protocol, the study is considering eGFR instead of CrCl.
6.7 Treatment of overdose	Replacing "For this study, any administration of an IMP at least twice the intented administered dose at each cycle will be considered as an overdose. Of note, dexamethasone dose will be evaluated on a whole cycle. For intravenous product, increase of at least 30% of the infusion rate will be considered as an overdose. Non investigational medicinal product overdose is defined as at least twice the intented dose within the intended therapeutic interval." by "For the study, IMP overdose is defined as any of the following conditions: - any administration of isatuximab IV or isatuximab SC at least 30% above the intended dose at each administration. - any administration of an oral IMP (pomalidomide and dexamethasone) at least twice the intended dose within the intended therapeutic interval. Of note, dexamethasone dose will be evaluated on a whole cycle. Non-investigational medicinal product overdose is defined as at least twice the intended dose within the intended therapeutic interval."	Consistency between sections, following audit finding.
6.7 Treatment of overdose	Replace "study treatment" by "IMP/NIMP".	Consistency across protocol.

Section # and Name	Description of Change	Brief Rationale
8.5.6 Adverse event of special interest	Adding “or injctable adminstration” and “NIMP”. Removing “injectable administration: at least twice the dose during the planned intervals”.	Consistency across protocol.
10.2 Appendix 2: Clinical Laboratory Tests, Table 21	Replacing “surface antigen [HBsAg]” by “(HBsAg, anti-HBs, anti-HBc total and IgM) and hepatitis C”.	Consistency across protocol (following an audit finding).
10.10 Appendix 10: IMWG Response Criteria	Removing “Two consecutive assessments are needed.”	To be aligned with IMWG response criteria.
Throughout	Minor editorial, typographical error corrections and document formatting revisions.	Minor, therefore, have not been summarized.

10.19.3 Amended protocol 03 (03-October-2023)

This amended protocol is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to provide simplification and clarifications on different sections as well as to align with the isatuximab program, including the updated IB Edition 14 date 30 May 2023.

Inclusion criterion I04 and exclusion criterion E03 have been reworded for simplification purposes. A 14-day timeframe was introduced following granulocyte-colony stimulating factor (G-CSF) use in exclusion criterion E11 following request from Ethics Committee. Recommendations regarding antithrombotic prophylaxis were modified to allow for oral anticoagulants in patients with at least one risk factor for thromboembolism, so to align with general recommendations in pomalidomide SmPC, while still making the difference between patients with standard risk versus patients with at least one risk factor. Semi-quantitative urinalysis is allowed at baseline as several countries faced operational issues performing quantitative analysis.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SOA)	From timelines of vital signs/ECOG/weight/physical examination in the SoA, the indication "≤7 days before randomization" is removed. The same change has been made in Footnotes l and m.	Allowing more flexibility on the timing to perform physical examination, vital signs assessments, weight measurement and ECOG assessment for operational and patient comfort reasons.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SOA), Table 1, Footnote l	Added "(a flexibility of a maximum of 24 hours before IMP administration is allowed)" to give flexibility for performance of physical examination on Day 1 of each cycle.	Flexibility given for performance of physical examination on Day 1 of each cycle.
1.3 Schedule of Activities (SOA), Table 1, Footnote q	Footnote q updated as "Quantitative or alternatively semi-quantitative urinalysis at baseline (including red blood cells, protein, glucose, pH, ketones, bilirubin, and leukocytes), and qualitative urinalysis (dipstick) after start of study treatment (including blood, protein, glucose, pH, ketones, bilirubin, and leukocytes)".	Clarification, to align with clinical sites not performing a full quantitative urinalysis assessment.
1.3 Schedule of Activities (SOA), Table 1, Footnote y	First and second sub-pointers in foontnote y updated as follows: • "If known soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline, repeated every 12 weeks (±1 week) until progressive disease (PD) from C1D1 (even for participants who would initiate further anti-myeloma therapy without PD), and if clinically indicated. From two years after randomization, the radiological assessment will be done every 6 months (±1 month). Assessment to be done until PD, or initiation of further anti-myeloma therapy, or final cut-off date, whichever occurs first. • If suspected soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline and if plasmacytoma confirmed on the exam to be repeated as indicated above." After sub pointer 5, the following subpointer is added: • "PET-CT should be the preferred option whenever possible."	For clarification, to align with isatuximab program.
1.3 Schedule of Activities (SOA), Table 1, Footnote z	Footnote z updated as follows: "Bone disease (lytic or focal depending on the method): Whole-body low-dose CT scan, PET-CT scan or MRI at baseline (within 28 days prior to randomization), once a year (±1 month), and anytime during the study if clinically indicated, until PD, initiation of further anti-myeloma therapy, or final cut-off date, whichever occurs first. PET-CT should be the preferred imaging modality whenever possible."	To align with isatuximab program.
1.3 Schedule of Activities (SOA), Table 1, Footnote bb	For Serum M-protein immunoelectrophoresis (SPEP) and immunofixation, "C1D1 (predose)" changed to "C1D1 (predose, baseline for response assessment)," Similar change is also done for Urine M-protein (24-hour urine) immunoelectrophoresis (UPEP) and immunofixation.	For clarification and alignment with rest of isatuximab program.
4.8 Study Committees	Removed "on PFS" from the text.	For clarification.
5.1 Inclusion criteria, I 04	Removed "at least 2 consecutive cycles of" from inclusion criteria I 04.	Criterion simplification as to align to intended future product label.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria, I 05	Inclusion criteria I 05 modified as "Participants must have documented evidence of progressive disease on or after the last regimen."	For clarification.
5.2 Exclusion criteria, E 03	Modified criteria E 03 from "Participants with prior anti-CD38 treatment are excluded if: a) Progression on or within 60 days after end of anti-CD38 mAb treatment or failure to achieve at least MR to treatment (ie, refractory to anti-CD38) with a washout period inferior to 9 months before randomization or, b) Intolerant to the anti-CD38 previously received." To "Participants with prior anti-CD38 treatment: a) administered less than 9 months before randomization or, b) Intolerant to the anti-CD38 previously received."	Clarification.
5.2 Exclusion criteria, E 11	Added the timeframe "within 14 days from the screening hematological test" for granulocyte-colony stimulating factor (G-CSF).	Following Ethics Committee request.
6.1.1.3 Pomalidomide	The guidance for treatment with pomalidomide in cases of suspected or confirmed progressive multifocal leukoencephalopathy is amended as follows. "If progressive multifocal leukoencephalopathy (PML) is suspected, study treatments should be put on hold immediately until a diagnosis of PML has been definitively excluded. If suspected, the Investigator should refer participant to a specialist and appropriate diagnosis testing should be initiated [Serial Magnetic resonance imaging (MRI) with contrast and cerebrospinal fluid analysis for John Cunningham Virus] [Please refer to PML diagnostic criteria by American Association of Neurology (AAN)]. If PML is confirmed, pomalidomide should be discontinued and isatuximab and dexamethasone should be put on hold. [Please refer to PML diagnostic criteria by AAN]. Isatuximab and dexamethasone could be resumed after recovery of PML based on Investigator's judgement and after discussion with the Sponsor."	Clarification on guidance on detecting and managing PML as per diagnostic criteria by AAN.
6.5 Dose Modification	Removed the first line of paragraph 2 which is "Cycle delay (ie, delay of all study treatments at Day 1) are permitted in case of toxicity." In the next line, "by the day" is removed and "within 3 days after the planned day" is added there. The line "Within a cycle, the treatment window is ±1 day for each of QW IMP administrations and ±3 days for each of Q2W IMP administrations." Is moved to the paragraph above. First sentence of next paragraph is replaced from "Between cycles, the treatment window is ±3 days if 4-week cycle" to "Cycle delays are permitted in case of toxicity (see Section 6.5.7). Cycle is considered delayed if Day 1 is performed more than 3 days after the planned Day 1 of this cycle."	For consistency through the protocol and through the isatuximab program. The top paragraph is about delay WITHIN a cycle, while the following paragraph is about delay BETWEEN cycles.
6.5.1 Isatuximab	Removed the portion "starting from Cycle 2" for the second sentence and removed the last sentence "No more than 2 isatuximab consecutive administrations omitted per patient are permitted (study stopping rule)."	Correction and consistency throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
6.5.4 Dose adjustments according to adverse events, Table 13, footnote c	Modified the footnote c as – "A dose delay of up to 14 days between cycles is permitted in order to recover to the participant´s baseline status. Beyond 14 days, the participant should be discontinued from study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment (see Section 6.5.7)." and removed the portion "must be permanently discontinued from the study (Section 7.1.1)."	For consistency throughout the protocol.
6.5.4 Dose adjustments according to adverse events, Table 14, footnote a	Modified the footnote a as – "A dose delay of up to 14 days between cycles is permitted in order to recover to the participant´s baseline status. Beyond 14 days, the participant should be discontinued from study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment (see Section 6.5.7)." and removed the portion "the participant must be permanently discontinued from the study Section 6.5.7)."	For consistency throughout the protocol.
6.5.4 Dose adjustments according to adverse events, Table 14	Added an additional row to Table 14 providing guidance for treatment with IMPs in cases of suspected or confirmed PML. Additionally footnote d added as – "See Section 6.1.1.3 for monitoring of PML and dose modification of study IMPs."	Clarification on guidance on detecting and managing PML as per diagnostic criteria by AAN.
6.5.5 Management of infusion reactions and injection site reactions, Table 15	Recommendation for Grade 2 and Grade 3/4 ISRs occurring post-administration modified from "Report AE/AESI" to "Report AE and AESI"; and "premedication" changed to "medication." In recommendation for Grade 2 IRs, "definitive stop of current" removed and statement amended as "If during administration, interrupt isatuximab administration without possibility to restart the current injection. For subsequent cycles, give additional medication with IV diphenhydramine 25 mg IV (or oral equivalent) and/ or IV methylprednisolone 100 mg (or oralequivalent) and/or other supportive care as needed. Report AE."	Update according to IB Edition 14 date 30 May 2023.
6.5.5 Management of infusion reactions and injection site reactions, Table 16	In infusion reaction grading (NCI-CTCAE) V5.0 criteria, specification added to Grade 2 as "moderate reaction" and Grade 3/4 as "severe or life-threatening reaction." Grade 2 recommendation is amended as "Stop isatuximab infusion. Give additional medication with IV diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed only after participant recovery, at half the infusion rate before the interruption, and with close monitoring, and may be increased subsequently, at the Investigator's discretion." In Grad 3/4 recommendation "definitive treatment discontinuation" is removed and recommendation is amended as "Stop the isatuximab infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed until the resolution of the AE or until the AE improves to Grade 1. Only then, if previous Grade 3, the infusion may be restarted at the Investigator's discretion; if so, the infusion rate should be half of the initial infusion rate and it may be increased subsequently, at the Investigator's discretion. If the severity	Update according to IB Edition 14 date 30 May 2023.

Section # and Name	Description of Change	Brief Rationale
	of an infusion-related AE returns to Grade 3 after the restart of the infusion, the same procedure described above may be repeated at the Investigator's discretion. If a Grade 3 infusion-related AE occurs for a 3rd time, treatment with isatuximab will be definitely discontinued for that patient. In case of Grade 4, isatuximab will be permanently discontinued."	
6.8.1 Antithrombic therapy	This section is amended as "Pomalidomide increases the risk of venous thromboembolism. Anticoagulation prophylaxis is required after an assessment of each participant's underlying risk factors. Unless there is an excess risk of bleeding (those participants are to be excluded from the study; see exclusion criterion E2) all participants should receive prophylactic antithrombotic treatment. Patients with known risk factors for thromboembolism – including prior thrombosis - should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (eg, smoking, hypertension, and hyperlipidemia). Aspirin prophylaxis is recommended for participants with standard risk. If aspirin is contraindicated, participants will receive another form of antithrombotic therapy according to hospital guidelines or physician preference. Participants with at least 1 risk factor (ie, history of prior venous thromboembolism, immobilization, and concomitant use of an erythropoiesis-stimulating agent) should use low-molecular weight heparin or alternatively a direct oral anticoagulant (factor Xa inhibitors, direct oral factor IIa inhibitors) or a vitamin K antagonist."	To align with general recommendations in pomalidomide SmPC, while still making the difference between patients with standard risk versus patients with at least 1 risk factor.
8.1 Efficacy assessments	The Bone imaging point is amended as "Whole-body low-dose (WBLD) computed tomography (CT) scan, Positron emission tomography-Computed tomography (PET-CT) scan or MRI at baseline (within 28 days prior to randomization), once a year (±1 month) from C1D1, and anytime during the study if clinically indicated, until PD, initiation of further anti-myeloma therapy, or final cut-off date, whichever occurs first. PET-CT should be the preferred imaging modality whenever possible." Additional point added to section as • "Soft tissue plasmacytoma assessment (extramedullary disease OR paramedullary disease with a soft tissue lesion of diameter ≥2 cm): - If known soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline, repeated every 12 weeks (±1 week) until progressive disease (PD) from C1D1 (even for participants who would initiate further anti-myeloma therapy without PD), and if clinically indicated. From two years after randomization, the radiological assessment will be done every 6 months (±1 month). Assessment to be done until PD, or initiation of further anti-myeloma therapy, or final cut-off date, whichever occurs first. - If suspected soft tissue plasmacytoma at baseline, CT scan, PET-CT scan or MRI is to be done at baseline and if plasmacytoma confirmed on the exam to be repeated as indicated above.	To align with isatuximab program.

Section # and Name	Description of Change	Brief Rationale
	- To be done in case of suspicion of progression or if clinically indicated in a participant with no previous positive image for soft tissue plasmacytoma. - The bone component of paramedullary disease with a soft tissue lesion of diameter ≥2 cm will not be used for disease response assessment as per IMWG. - Paramedullary (paraskeletal) plasmacytoma (bone plasmacytoma extending beyond the bone cortex into the surrounding tissues) with soft tissue lesions of diameter <2cm will be collected but will not be used for disease response assessment as per IMWG. No follow-up with repeated imaging is needed, except if clinically indicated. - PET-CT should be the preferred option whenever possible. Note: For bone lesion assessment and soft tissue plasmacytoma, the same modality (whole-body low-dose CT scan; CT scan, PET-CT scan, or MRI) should be used throughout the study for each individual participant when radiological follow-up is needed. Intravenous contrast is recommended if not medically contra-indicated."	
10.2 Appendix 2: Clinical Laboratory tests, table 21	Parameter "Prothrombin time (PT)/international normalized ratio (INR) Partial thromboplastin time (PTT)" shifted from Hematology test and added under "coagulation" test.	Based on request from GER EC to separate hematology from coagulation tests.
10.2 Appendix 2: Clinical Laboratory tests, table 21	Removed from routine urinalysis • "Microscopic examination (if blood or protein is abnormal)".	For simplification following acceptance of semi-quantitaitve urinalysis at baseline.
10.2.1 Modification of diet in renal disease (MDRD) equation	Added the word "Estimated" to glomerular filtration rate.	Clarification.
10.4.2.2 Contraception guidance for female subjects	Under sub-heading c, the portion "pomalidomide/Imnovid Summary of Product Characteristics (SmPC)," changed to "pomalidomide Summary of Product Characteristics (SmPC),"	Clarification.
10.7.2 Definition of medical device SAE, SADE and USADE	The definition of a medical device SAE reworded as "A medical device SAE is any adverse event that".	Correction to align with EU MDR.
10.10 APPENDIX 10: IMWG RESPONSE CRITERIA, Table 22	Under Standard IMWG criteria, the last point on IMWG criteria for CR amended as "A normal FLC ratio of 0.26-1.65 is required for FLC disease only."	For alignment with IMWG criteria.
Throughout	Minor editorial, typographical error corrections and document formatting revisions.	Minor, therefore, have not been summarized.

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