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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sarclisa

International non-proprietary name: Isatuximab

Procedure No. EMEA/H/C/004977/II/0035

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ADA:	anti-drug antibody
ADCC:	antibody dependent cell mediated cytotoxicity
ADCP:	antibody dependent cellular phagocytosis
ADO:	adenosine
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
ASCT:	autologous stem cell transplant
AUC:	area under the curve
B/R:	benefit/risk
BCMA:	B-cell maturation antigen
BMI:	body mass index
BOR:	best overall response
CAR-T:	chimeric antigen receptor - T
CD:	cluster of differentiation
CDC:	complement dependent cytotoxicity
CHMP:	Committee for Medicinal Products for Human Use
CI:	confidence interval
CL/CLinf:	clearance/clearance at steady state
C _{max} :	maximum serum concentration
C _{trough} :	trough concentration
COVID-19:	coronavirus disease-19
(s)CR:	(stringent) complete response
CrCl:	creatinine clearance
CSR:	clinical study report
CT:	computed tomography
CT4W:	C _{trough} values at the end of 4 weeks
CV:	coefficient of variation
CYP3A4:	cytochrome P450 3A4
D:	day
d:	low dose dexamethasone
Dara:	daratumumab
DL:	dose level
DLT:	dose limiting toxicity
DMC:	Data Monitoring Committee
DOR:	Duration of response
DRd:	daratumumab, lenalidomide and dexamethasone

EC:	European Commission
ECG:	Electrocardiogram
ECOG PS:	Eastern Cooperative Oncology Group performance status
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
ELISA:	enzyme-linked immunosorbent assay
EMA:	European Medicines Agency
EORTC:	European Organisation for Research and Treatment of Cancer
ESMO:	European Society for Medical Oncology
Fc:	fragment crystallizable
FCGR3A:	Fc Gamma Receptor IIIa
FDA:	Food and Drug Administration
FISH:	fluorescence in situ hybridization
g:	gram
GCP:	good clinical practice
G-CSF:	granulocyte colony-stimulating factor
GM-CSF:	granulocyte-macrophage colony-stimulating factor
HDT:	high dose chemotherapy
HDT1:	first high dose chemotherapy
HDT2:	second high dose chemotherapy
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high-level term
HR:	hazard ratio
HRQoL:	health-related quality of life
I:	isatuximab
ICF:	informed consent form
IEC:	Independent Ethics Committee
IF:	information fraction
IFE:	immunofixation electrophoresis
Ig:	immunoglobulin
IMiD:	immunomodulatory drugs
IMWG:	International Myeloma Working Group
IPd:	isatuximab, pomalidomide and dexamethasone
IPW:	inverse probability weighting
IR:	infusion reaction
IRB:	Institutional Review Board
IRC:	Independent Response Committee
IRd:	isatuximab, lenalidomide, and dexamethasone combination

IRT:	interactive response technology
ISS:	international staging system
ITT:	intention to treat
IV:	intravenous
IVRd:	isatuximab, bortezomib, lenalidomide, and dexamethasone combination
K ₂ /K ₃ EDTA:	potassium ethylenediaminetetraacetic acid
kg:	kilogram
L:	liter
LDH:	lactate dehydrogenase
LDWB:	low dose whole-body
LLoQ:	lower limit of quantification
LLT:	low-level term
mAb:	monoclonal antibody
MAD:	maximum administered dose
MAH:	marketing authorization holder
mg:	milligram
MM:	multiple myeloma
mPFS:	median PFS
MRD:	minimal residual disease
MRI:	magnetic resonance imaging
MSD:	MesoScale Discovery
MTD:	maximum tolerated dose
Nab:	neutralizing antibody
NC:	not Calculated
NCA:	non-compartmental analysis
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
ND:	newly diagnosed
NGF:	next generation flow cytometry
NGS:	next generation sequencing
NK:	natural killer
OR:	odds ratio
ORR:	overall response rate
OS:	overall survival
PBRER:	Periodic benefit-risk evaluation report
PD:	disease progression OR pharmacodynamics
PET:	positron emission tomography
PFS:	progression-free survival
PI:	proteasome inhibitors
PIP:	paediatric investigation plan

PK:	pharmacokinetic
PO:	orally
PR:	partial response
PSUR:	Periodic safety update report
PT:	preferred term
Q2W:	once every 2 weeks
Q4W:	once every 4 weeks
QW:	once a week
QoL:	quality of life
R:	lenalidomide
RD:	recommended dose
Rd:	lenalidomide and dexamethasone combination
R-ISS:	revised international staging system
RMP:	risk management plan
RR:	relapsed/refractory
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SD:	standard deviation
sFLC:	serum free light chain
SmPC:	summary of product characteristics
SMQs:	standardised MedDRA queries
SOC:	system organ class <i>or</i> standard of care
SPM:	Secondary primary malignancies
TEAE:	treatment-emergent adverse event
Ti:	transplant ineligible
TLS:	tumour lysis syndrome
TTBR:	time to best response
V:	bortezomib
VGPR:	very good partial response
VRd:	bortezomib, lenalidomide, and dexamethasone combination

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 26 November 2024 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include, in combination with bortezomib, lenalidomide and dexamethasone, the induction treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT) for Sarclisa, based on the results from study IIT15403 (GMMG-HD7); this is a randomized phase III study designed to assess the efficacy and safety of Sarclisa for the induction and maintenance treatment of NDMM. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial and formatting changes to the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0144/2023) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0144/2023) was completed.

The PDCO issued an opinion on compliance for the PIP (P/0144/2023).

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received scientific advice from the CHMP on 13 October 2022 (EMA/SA/0000099699). The scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Timetable	Actual dates
Submission date	26 November 2024
Start of procedure:	28 December 2024
CHMP Rapporteur Assessment Report	21 February 2025
CHMP Co-Rapporteur Assessment	5 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 March 2025
Request for supplementary information (RSI)	27 March 2025
CHMP Rapporteur Assessment Report	26 May 2025
CHMP members comments	10 June 2025
Updated CHMP Rapporteur Assessment Report	12 June 2025
CHMP opinion:	19 June 2025
The CHMP adopted a report on similarity of Sarclisa with Darzalex, Farydak, Kyprolis, Ninlaro, Carvykti, Talvey and Abecma on date	19 June 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The indication sought by the MAH is:

"Sarclisa in combination with bortezomib, lenalidomide and dexamethasone is indicated for the induction treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT)."

The application is based on part 1 of the pivotal study ITT5403 (GMMG-HD7).

Epidemiology

Multiple myeloma (MM) is the second most-common adult blood cancer, with an estimated incidence in Europe of 4.5-6.0/100, 000/year. More than 175,000 cases were reported in 2020, and incidence appears to be highest in countries with a higher human development index. Median age at diagnosis ranges from 65 to 74 years. MM is slightly more frequent in males than in females (approximately 1.4:1), and incidence seems to vary by ethnicity; the incidence in African Americans and black

populations is two to three times that in White populations, as shown in studies from the United States and United Kingdom. The reason for this variance is not known.

Aetiology and pathogenesis

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

Clinical presentation, diagnosis and prognosis

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

Diagnosis is based on serum protein electrophoresis and immunofixation electrophoresis to detect IgG/IgA monoclonal gammopathy. A plasma cell staining in a bone marrow aspirate and imaging (MRI/PET-CT) are used to confirm the MM diagnosis. The international scoring system (ISS) for MM stratifies patients into three stages based on serum β 2-microglobulin level (I < 3.5 mg/L; 3.5 mg/L $\leq$ II < 5.5 mg/L; III $\geq$ 5.5 mg/L), with higher levels being unfavourable. High-risk patients are identified through cytogenetic analysis of the malignant plasma cells and Serum Lactate Dehydrogenase (LDH). The presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16) and high LDH levels are associated with a worse prognosis. The revised ISS (R-ISS) combines ISS stratification with cytogenetics and serum LDH.

Management

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

The last two decades have seen the approval of three generations of immunomodulatory drugs (IMiDs; thalidomide, lenalidomide, and pomalidomide), two generations of proteasome inhibitors (PIs; bortezomib, then carfilzomib and ixazomib) and most recently, first generation monoclonal antibodies (mAbs), two of which target CD38 (isatuximab and daratumumab) and another targeting SLAMF7 (elotuzumab). Furthermore, daratumumab also has a formulation that allows for s.c. injection, which is less burdensome than i.v. administration.

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

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

Transplant ineligible patients

According to the 2017 ESMO Clinical Practice Guidelines, in transplant ineligible, older/frail patients, a typical first-line treatment strategy would consist of bortezomib-lenalidomide-dexamethasone (VRd). With the 2021 update of the ESMO guidelines, daratumumab-lenalidomide-dexamethasone (DRd) and daratumumab-bortezomib-melphalan-prednisone (DaraVMP) are now also recommended as first option for transplant ineligible patients.

Transplant eligible patients

ASCT-eligible patients with NDMM generally receive an induction therapy, high-dose chemotherapy+ASCT, sometimes followed by consolidation treatment and commonly followed by lenalidomide maintenance therapy. VRd, along with quadruplet regimen DaraVTd (daratumumab-bortezomib-thalidomide-dexamethasone), is one of the preferred frontline regimens recommended by NCCN and ESMO treatment guidelines for the primary therapy of patients with NDMM who are transplant candidates (Kumar 2023, Dimopoulos 2021).

In the largest trial using VRd triplet therapy (DETERMINATION), 722 patients received three cycles of induction with bortezomib, lenalidomide, and dexamethasone (VRd) followed by stem cell collection and were randomly assigned to either receive an additional five cycles of VRd consolidation or high-dose melphalan plus ASCT plus two cycles of VRd consolidation. Subsequently, each group was put on lenalidomide maintenance until progression or unacceptable toxicity.

After a median follow-up of 76 months, incorporation of ASCT improved PFS (median PFS 68 versus 46 months; hazard ratio [HR] 1.53, 95% CI 1.23-1.91), but did not improve OS (estimated five-year OS 81 versus 79 percent; HR 1.10, 95% CI 0.73-1.65). A similar PFS benefit and lack of OS benefit from ASCT was reported in another large, randomised trial that used the VRd induction regimen and lenalidomide maintenance therapy (IFM 2009 Study).

In September 2024, the CHMP issued a positive opinion for another quadruplet regimen in transplant eligible patients. Addition of daratumumab to VRd during induction treatment before ASCT, to consolidation treatment after ASCT and subsequently to R during maintenance treatment was approved in transplant eligible patients with newly diagnosed MM. The pivotal study for this approval was PERSEUS (MMY3014). With a median followup of 47.5 months, the primary analysis of PFS demonstrated an improvement in PFS in the DVRd arm as compared to the VRd arm (HR=0.42; 95% CI: 0.30, 0.59; $p<0.0001$). OS data were immature.

Unmet medical need

As survival has greatly improved over the last decades, and the disease mostly manifests at a later age, the highest unmet medical need may lie in refinement of current treatment strategies. Many drugs seem to be effective and have made it to the first line of treatment, where they are combined. Another unmet medical need concerns 'real world patients' with significant co-morbidities (e.g. diabetes, prostate cancer), but these patients are not represented in clinical trials. Lastly, MM remains incurable, and even though survival is quite good in the standard-risk patients, there is still room for improvement (e.g. prolonged disease control) particularly in the high-risk patients.

2.1.2. About the product

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

On 26 March 2020, the CHMP issued a positive opinion for isatuximab in combination with pomalidomide and dexamethasone (IPd), for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy. The EC decision was granted on 30 May 2020.

On 25 February 2021 an extension of indication was granted by the CHMP for isatuximab in combination with carfilzomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. The EC decision was granted on 15/04/2021.

On 14 November 2024 an extension of indication was granted by the CHMP for isatuximab in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. The EC decision was granted on 20/01/2025.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received scientific advice from the CHMP on 13 October 2022. The main points discussed were:

- Late updates to the analysis plan that were proposed by the MAH. As all patients had already been recruited and top-line results were available for the first part of the trial and the open-label setting, the CHMP could not exclude that these decisions were data-driven.
- The MAH proposed MRD-negativity as primary endpoint supplemented by PFS as key secondary endpoint. CHMP advised that an application for the induction treatment based on a positive MRD result alone would be insufficient and a positive PFS result would be required as well as OS results showing no detrimental effect.
- Two additional statistical analysis plans Sanofi-EU and Sanofi-US were added to the initial statistical analysis plan, to reflect the different choices of primary endpoint for different regulatory authorities. Each SAP has its own testing strategy. This led to a multiplicity issue which had not been sufficiently addressed by the MAH at the time.
- The study is divided into two parts, namely induction treatment with VRd or IVRd (part 1), followed by ASCT, re-randomisation and then maintenance treatment with lenalidomide or isatuximab + lenalidomide (part 2). The MAH's intention to control the type I error in each study part as if they were completely independent experiments was not agreed by the CHMP. It was advised that a study-wise control of the type I error should be implemented instead (e.g. implementing hierarchical testing the treatment effect for the induction treatment before

testing the treatment effect in maintenance). At a minimum stratification for patients with respect to prior treatment is needed for the assessment of PFS after second randomisation.

- Interpretation of PFS/OS analyses from first randomisation, regardless of the second randomisation, was anticipated to be challenging, and to raise concerns over bias at the time of regulatory assessment, since differences between treatment groups are expected if there is interaction of maintenance treatment with induction treatment. The MAH proposed a weighted log-rank test based on the inverse probability weighting (IPW) framework which was agreed as an approach to reduce bias in treatment effect estimates.
- The PFS censoring rules do not follow the EMA guideline (EMA/CHMP/27994/2008/Rev.1). The MAH was advised not to censor patients before the initiation of further anti-myeloma treatment for the primary analysis.

2.2. *Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. *Ecotoxicity/environmental risk assessment*

A claim of exclusion from submission of environmental risk assessment studies was made and agreed in accordance to Section 4 of the 2024 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (1) because isatuximab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the ERA Guideline, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

2.3. *Clinical aspects*

2.3.1. *Introduction*

GCP

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

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

- Tabular overview of clinical studies

Study Number	Study Design and Indication	Treatment regimen and sample size
Pivotal Study ITT5403 (GMMG-HD7) (Ongoing; interim CSR cut-off date of 31 January 2024 corresponding to Part 1 of the study)	A prospective, multicenter, randomised, parallel group, open-label, Phase 3 clinical trial to compare the efficacy of lenalidomide, bortezomib, dexamethasone (VRd) induction therapy with or without isatuximab in Part 1 (induction phase pre-HDT and ASCT), and to compare the maintenance therapy of lenalidomide with or without isatuximab in Part 2 (maintenance phase post-ASCT; outside the scope of this application).	Induction: Isatuximab 10 mg/kg IV in combination with Velcade, lenalidomide and dexamethasone (IVRd) or control administered for 3 x 42-day cycles Q1W x 5, then Q2W Experimental group: IVRd (N=331) Control group: VRd (N=331) Intensification: High dose therapy + autologous stem cell transplantation Patients were re-randomised to one of the two maintenance regimens after intensification Maintenance: Isatuximab 10 mg/kg IV in combination with lenalidomide and dexamethasone (IRd) or control administered in 28-day cycles Q1W/Q2W/Q4W Cycle 1: Days 1, 8, 15, and 22 Cycles 2 and 3: Days 1 and 15 Cycle 4 onward: Day 1

2.3.2. Pharmacokinetics

PK data for the IVRd combination are from the pivotal Phase 3 study IIT15403 conducted in patients with NDMM who were eligible for ASCT. Additional data are included from the phase 3 study EFC12522 conducted in patients with NDMM who were not eligible for ASCT and supportive Phase 1b study TCD13983 Parts A and B, also conducted in patients with NDMM who were not eligible for transplantation or with no immediate intent for transplantation (Part B). The pharmacokinetic data from studies EFC12522 and TCD13983 have been discussed in procedure EMEA/H/C/004977/II/0030.

In the current submission, an integrated analysis (POH1230) was conducted by pooling the data from EFC12522, IIT15403, and TCD13983 to build a population PK model in the newly diagnosed multiple myeloma (NDMM) population when isatuximab is given in combination with VRd. This approach was used to characterize the PK of isatuximab in combination with VRd in NDMM patients eligible or not eligible for transplantation and to assess the impact of covariates including ADA in the NDMM population.

PopPK analysis (POH1230)

The objectives of this analysis were to develop a population PK model for isatuximab in NDMM patients when isatuximab is given in combination with VRd in order to 1) characterize its nonlinear (target-specific clearance) and linear (target-nonspecific clearance) PK and its time dependency, and 2) to perform an evaluation of the impact of the covariates including ADA effect on isatuximab PK.

Data from 386 NDMM patients (6232 plasma concentrations), eligible or not for ASCT, treated in the combination with VRd studies were used. The 386 patients with NDMM were as follows:

- Phase 3 EFC12522 (N=281 transplant non-eligible patients),

- **Phase 3 IIT15403 (N=33 transplant eligible patients),**
- Phase 1b/2 TCD13983 Part A (N=26 transplant non eligible patients), and
- Phase 1b/2 TCD13983 Part B (N=33 transplant non eligible patients and N=13 patients with no intent for immediate transplantation).

The same dose and same schedule of administration was used in all studies: 10 mg/kg QW/Q2W by IV infusion.

A base model (ie, structural model) was initially developed to describe the PK of isatuximab without consideration of any covariate effect. Then, considering the impact of immunogenicity on isatuximab PK, an anti-drug antibody (ADA) model was developed. Finally, a full covariates model was developed by incorporating selected covariates identified during the screening univariate analysis. In the final step, the final population PK model was developed by retaining covariates that improved goodness-of-fit statistic using backward elimination procedure.

The following baseline demographic and patho-physiological covariates (ie, age, sex, race, body weight, body mass index (BMI), obesity status, serum albumin (ALB), lymphocytes, lactate dehydrogenase, alanine amino transferase, aspartate amino transferase, total bilirubin, beta-2 microglobulin, bone marrow plasma cells, serum M-protein, Ig Multiple Myeloma Type [Ig MM-type; ie, IgG vs non IgG], performance status by Eastern Cooperative Oncology Group [ECOG], International staging system [ISS], renal and hepatic impairment and ASCT status) on PK parameters were evaluated.

Qualification of the population PK model was performed using GOF and visual predictive check (VPC). The analyses were performed using nonlinear mixed effects modeling methodology as implemented in Monolix R1 2023 with the SAEM algorithm. Pre- and post-processing of data from each modeling step was conducted using R software or SAS/JMP software.

Consistent with the earlier population PK analysis in RRMM (POH0503), the PK of isatuximab was best described by a 2-compartment model with parallel linear and Michaelis-Menten eliminations from the central compartment (approximation of target mediated - drug disposition model) with a combined error model. The inclusion of a function describing a time-varying change in linear clearance significantly improved the model. As in POH0503, the time-varying change was implemented in the model with a sigmoidal function (Equation 1, below).

Since the ADA incidence is higher in NDMM and as most patients who had ADA positive status presented transient ADA response with early onset within the first cycle of treatment, ADA effect was included as a time-varying covariate (beta2: ADA effect) on top of the time-dependent linear clearance model (CLlin) (Equation 2, below).

Equations of time-dependent effect with time-varying ADA covariate effect are as follows:

- Equation 1: $CL_{lin} = CL_{inf} * \exp [CL_m * (1 - t / (KCL + t))]$

with CL_m being the maximum change from baseline clearance to steady-state clearance (CL_{inf}), KCL being the time estimated to achieve 50% change in linear clearance, and γ being the sigmoidal coefficient.

- Equation 2: $CL_{linwithADA} = CL_{lin} * (1 + \beta_2 * ADA_Period)$

with ADA Period defining the occasion time where the patient had ADA positive status.

This time-varying covariate was entered in the structural model as a regressor variable. The inclusion of time-varying ADA effect showed an improvement in model fit.

Population parameters from the final model are presented in **Table 1**.

Table 1. Population parameters from final model in NDMM patients with IVRd (POH1230)

Parameter	Estimate	RSE (%)	Wald p-value
CLINF (L/h)	0.00355	2.53	
beta_WGHT	1.03	8.08	<2.2e-16
CLm	1.47	3.64	
beta_ALB	-0.813	22.9	1.26e-05
beta_BMI	-1.01	21.3	2.68e-06
beta_IgG_Type=Not_IgG	-0.388	19	1.42e-07
KCL (h)	1300	5.22	
gamma	2.55	9.77	
V1 (L)	3.49	2.68	
beta_ALB	-0.489	20.1	6.85e-07
beta_WGHT	0.559	16.8	2.79e-09
beta_SEX=Female	-0.159	24.8	5.43e-05
Q (L/h)	0.0313	16	
V2 (L)	3.73	6.06	
beta_SEX=Female	-0.357	20.7	1.36e-06
Vm (mg/L.h)	0.0716	10.6	
Km (mg/L)	0.046		
beta2*	0.887	5.15	
ω CLINF (%)	22.9	6.98	
ω CLm (%)	49.7	6.45	
ω KCL (%)	54.7	7.8	
ω gamma (%)	96	8.68	
ω V1 (%)	26.2	5.58	
ω Q (%)	143	8.78	
ω V2 (%)	27	22.6	
ω Vm (%)	45.5	17.5	
ω Km (%)	-	-	
ω beta2 (%)	-	-	
σ_{add} (mg/L)	14.2	5.73	
σ_{prop} (%)	23	1.37	

*: ADA effect.

The goodness of fit plots showed good agreement between observed and predicted concentrations and no pattern in residuals/NPDE plots (**Figure 1**). The corrected predicted VPC demonstrated a good description of the observed data by the model (**Figure 2**).

Figure 1. Population/ Individual WRES or NPDE vs time/isatuximab concentrations from the final popPK model

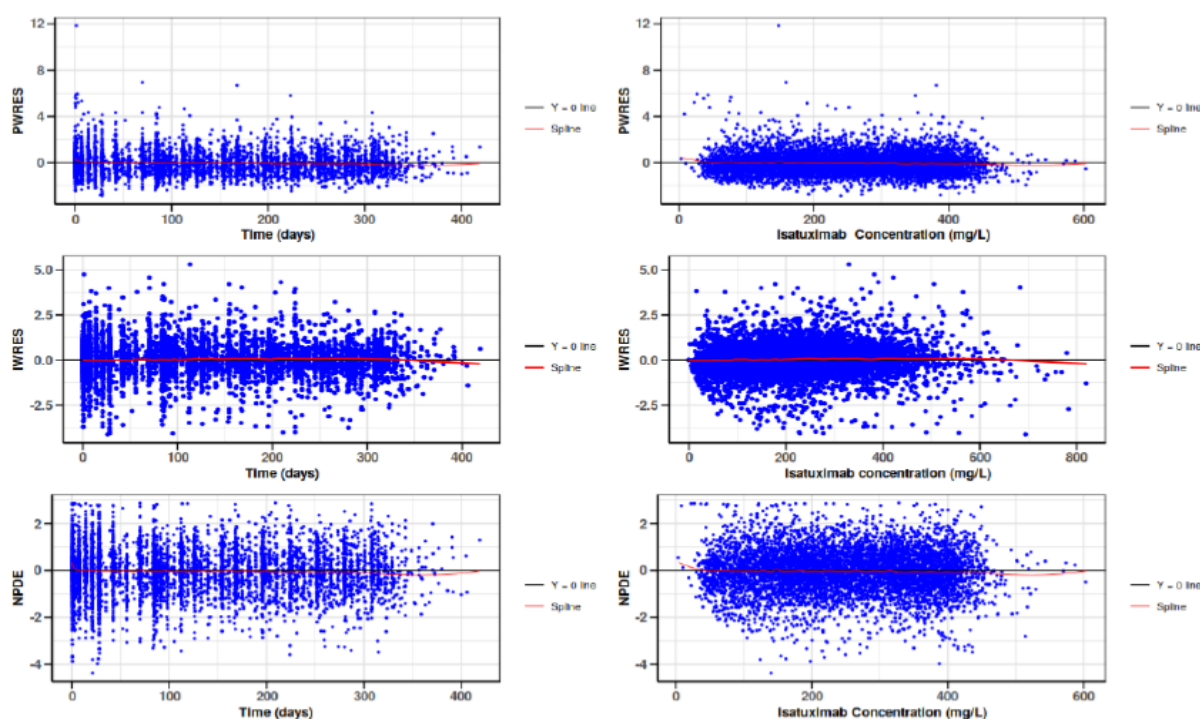
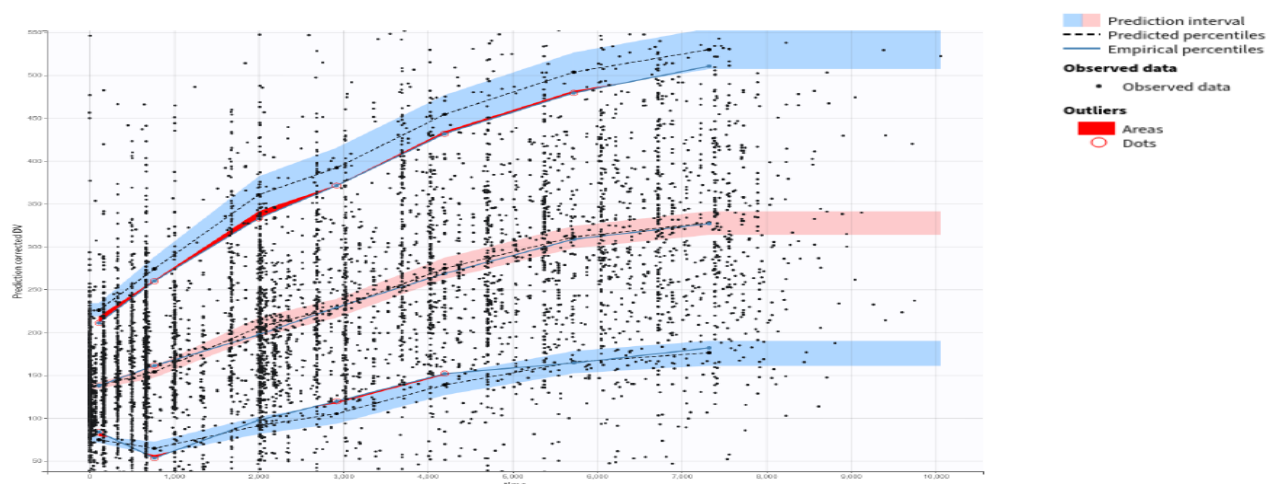


Figure 2. Corrected predicted visual prediction check from final model



Pharmacokinetic results popPK analysis

The population PK analysis was based on the combined datasets from three clinical studies (EFC12522, IIT15403 and TCD13983 parts A and B). Patient characteristics in this popPK model are summarised in **Table 2**.

Table 2. Characteristics of patients included in popPK model POH1230

All				All			
		Nb.	Percent			Nb.	Percent
AGE_GRP (years)	65[	47	12.2	CHINESE	No	356	92.2
	[65-75[	257	66.6		Yes	30	7.8
	[75	82	21.2	RENAL_FUNCTION	Normal	107	27.7
SEX	Female	180	46.6		Mild	190	49.2
	Male	206	53.4		Moderate	84	21.8
WGHT_GRP (kg)	50[	22	5.7		Severe	5	1.3
	[50-100[	346	89.6	HEPATIC_FUNCTION	Normal	352	91.2
	[100	18	4.7		Mild	34	8.8
BMI_GRP (kg/m²)	18.5[	6	1.6	ALB_GRP (g/L)	35[	137	35.5
	[18.5-25[	165	42.8		[35	249	64.5
	[25-30[	149	38.6	B2M_GRP (mg/L)	3.5[	183	47.4
	[30	66	17.1		[3.5-5.5[	110	28.5
OBESE	No	320	82.9		[5.5-7.5[	55	14.3
	Yes	66	17.1		[7.5	38	9.8
RACE	Asian	54	14.0	BMPC_GRP (%)	5[	12	3.1
	Black	3	0.8		[5-20[	124	32.1
	Caucasian	266	68.9		[20-50[	155	40.2
	Other	63	16.3		[50	95	24.6
JAPANESE	No	369	95.6	ISS	1	136	35.2
	Yes	17	4.4		2	157	40.7
					3	93	24.1

All			
		Nb.	Percent
ECOG	0	192	49.7
	1	157	40.7
	2	36	9.3
	3	1	0.3
Serum_M_Prot	No	60	15.5
	Yes	326	84.5
IgG_Type	No	144	37.3
	Yes	242	62.7
ADA_Patient	No	342	88.6
	Yes	44	11.4
ASCT	No	340	88.1
	Yes	46	11.9

Exposure parameters estimated in NDMM patients eligible for ASCT (IIT15403) are consistent with those estimated in NDMM non-eligible for ASCT (studies EFC12522 and TCD13983) when isatuximab is administered in combination with VRd (**Table 3**).

Table 3. Simulated mean (%CV) post-hoc isatuximab exposure by study at Cycle 1 and at steady state by study a 10 mg/kg QW/Q2W in NDMM patients (POH1230)

Combination with bortezomib/lenalidomide/dexamethasone (IVRd) - NDMM (overall, transplant eligible and not eligible)								
Study (N)	Cycle 1					Steady-state		
	C _{max} (µg/mL)	AUC _{1week} (µg•h/mL)	CT _{1W} (µg/mL)	AUC _{4W} (µg•h/mL)	CT _{4W} (µg/mL)	C _{max} (µg/mL)	AUC _{2week} (µg•h/mL)	C _{trough} (µg/mL)
IIT15403 (N=33)	211 (20.1)	18 400 (25.3)	66.6 (35.5)	122 000 (30.3)	183 (44.6)	617 (17.8)	160 000 (18.1)	405 (20.1)
EFC12522 (N=281)	220 (22.6)	19 200 (29.6)	68.2 (39.1.)	125 000 (31.7)	186 (43.3)	616 (20.9)	158 000 (23.8)	394 (27.8)
TCD13983 Part A and Part B (N=72)	196 (42.7)	16 300 (39.2)	56.8 (39.7)	103 000 (35.5)	148 (48.4)	550 (25.7)	141 000 (25.3)	352 (28.5)
Overall IVRd (N=386)	215 (26.8)	18 600 (31.4)	66.0 (39.4)	121 000 (32.9)	179 (44.9)	604 (21.9)	155 000 (23.9)	387 (27.6)

A large inter-individual variability was associated with the time-dependent linear clearance, not the CL at steady state itself (22.9%), but more on magnitude of the time dependency (CL_m [49.7%] and KCL [54.7%]). In a typical patient, the linear clearance decreased 74% from the treatment initiation to Cycle 4 (week 21), and 77% to the steady state (ie, 42 weeks), whereas the time needed to reach 50% decrease in linear clearance was about 8 weeks.

Linear CL at steady state was significantly related to body weight while the magnitude of the time dependency of CL, as CL_m, was significantly related to serum albumin, BMI, and Ig MM type. The impact of covariates was limited on drug exposure at both Cycle 1 and at steady state in a typical patient with a maximum effect of up to $\pm 21\%$ for all covariates except for Ig MM type, which showed a 30% higher C_{trough} at Cycle 1 in non-IgG MM patients compared to IgG MM patients.

The impact of body weight on drug exposure was limited (less than $\pm 15\%$) since dose adjustment based on body weight takes into account the variation of CL_{inf} upon body weight.

There was no effect of age, liver or renal impairment at baseline, or ASCT on isatuximab PK parameters.

Immunogenicity

Thirty-seven patients who received isatuximab in study IIT15403 (cohorts IB) were evaluable for ADA assessment. Eight of 37 evaluable patients had treatment-induced ADA response, resulting in an ADA incidence of 21.6% (**Table 4**). Among the 8 patients with treatment-induced ADA, 6 (75%) were considered to have a transient ADA response and 2 (25%) were considered to have an indeterminate ADA response. Corresponding titers were low () with the exception of 3 patients (. In addition, among those with treatment-induced ADA, 4 had a neutralizing response resulting in an NAb incidence of 10.8% (3 transient and 1 indeterminate NAb responses).

Table 4. ADA data - Summary of ADA to isatuximab - IVRd treated NDMM - ADA population

	EFC12522 IVRd ^a (N=275)	IIT15403 IVRd (N=37)	TCD13983 IVRd (N=71)
ADA-positive patient at baseline (pre-existing ADA)	0	3 (8.1)	0
Patients with treatment boosted ADA	0	0	0
Post-baseline peak titer			
Number	0	1	0
Median	NC	400.0	NC
Min ; Max	NC ; NC	400 ; 400	NC ; NC
Q1 ; Q3	NC ; NC	400.0 ; 400.0	NC ; NC
ADA-negative patient at baseline	272 (98.9)	32 (86.5)	68 (95.8)
Patients with treatment induced ADA	25 (9.1)	8 (21.6)	12 (16.9)
Post-baseline peak titer			
Number	25	8	12
Median	10.0	150.0	10.0
Min ; Max	10 ; 1280	50 ; 819200	10 ; 80
Q1 ; Q3	10.0 ; 20.0	100.0 ; 2000.0	10.0 ; 20.0
Patients with transient ADA response	24 (8.7)	6 (16.2)	11 (15.5)
Patients with persistent ADA response	0	0	1 (1.4)
Patients with indeterminate ADA response	1 (0.4)	2 (5.4)	0
ADA negative patients	250 (90.9)	29 (78.4)	59 (83.1)
ADA prevalence	25 (9.1)	11 (29.7)	12 (16.9)
ADA incidence	25 (9.1)	8 (21.6)	12 (16.9)

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone.

EFC12522 IVRd ^a (N=275)	IIT15403 IVRd (N=37)	TCD13983 IVRd (N=71)
--	----------------------------	----------------------------

^a Include IVRd treated NDMM patients from EFC12522 (global portion and China expansion).

Note: ADA prevalence is the proportion of ADA positive patients including pre-existing ADA positive, ADA incidence is the proportion of ADA positive patients excluding pre-existing ADA positive.

NC: not calculable.

For most ADA positive patients, the transient increase in clearance due to ADA effect is predicted to have a limited impact on drug exposure overall. For very few patients, the ADA response was persistent (or indeterminate); for those patients, a worst case-scenario with ADA positive occurrence lasting from Cycle 1 Day 15 up to Cycle 4 Day 1 predicted a maximum of 24% to 40% decrease in early drug exposure (Cycle 1) and a maximum of 30% to 41% decrease in drug exposure at Cycle 4 (**Table 5**).

Table 5. Simulated mean (%CV) post-hoc isatuximab exposure at Cycle 1 and at steady-state by ADA status at 10 mg/kg QW/Q2W (POH1230)

ADA status (N)	Cycle 1							Steady State ^c		
	1 st administration ^a			4 th administration ^a		5 th administration ^b		C _{max} (µg/mL)	C _{trough} (µg/mL)	AUC _{2weeks} (µg.h/mL)
	C _{max} (µg/mL)	C _{trough} (µg/mL)	AUC _{1week} (µg.h/mL)	CT4W (µg/mL)	AUC4W (µg.h/mL)	CT6W (µg/mL)	AUC6W (µg.h/mL)			
Negative (342)	217 (25.7)	67.6 (38.5)	18900 (30.9)	187 (41.2)	124000 (31.5)	165 (50.2)	204000 (33)	610 (21.2)	391 (27.2)	157000 (23.6)
Positive (44)	198 (34.9)	53.2 (42.1)	16300 (32.8)	114 (65.9)	95200 (36.9)	85.9 (96.0)	144000 (42.8)	557 (26)	357 (29.9)	144000 (25.9)

Source: 5.3.3.5 POH1230 Tables 59, 60, 61, 63, 64, 67, 68, 69, 70, 72

AUC_{1week} and AUC_{2weeks} = area under the plasma concentration time curve over the dosing interval of 1 or 2 weeks, respectively; AUC4W = Cumulative area under the plasma concentration-time curve over 4 weeks; C_{max} = maximum concentration; C_{trough} = predose concentration during repeated dosing; CT4W = C_{trough} at 4 weeks; N = number of patients

^a Represents the 1st and 4th administration (QW loading regimen) in Cycle 1.

^b Represents the 1st Q2W administration in Cycle 1.

^c Represents Cycle 9 (Q2W maintenance regimen, predose [Week 42] C_{max} and AUC_{2weeks} after the first dose of the cycle)

2.3.3. Discussion on clinical pharmacology

The clinical pharmacology of isatuximab for treatment of patients with newly diagnosed multiple myeloma (NDMM) who are eligible for ASCT is primarily based on an active-controlled Phase 3 study IIT15403 and supported by pharmacokinetic data in patients with NDMM who are not eligible for transplantation (studies EFC12522 and TCD13983).

Pharmacokinetics of isatuximab in subjects with NDMM eligible for ASCT was evaluated by popPK analysis (POH1230) by pooling the data from EFC12522, IIT15403, and TCD13983 to build a population PK model in the NDMM population when isatuximab is given in combination with VRd.

The objectives of the popPK analysis were to characterize the PK of isatuximab in combination with VRd in NDMM patients eligible or not eligible for transplantation and to assess the impact of covariates including ADA in the NDMM population.

Development and evaluation of the popPK model was sufficiently reported. The popPK model describes the data adequately and is considered fit for purpose.

The pharmacokinetics of isatuximab is characterized by a linear, time-dependent and a nonlinear Michaelis-Menten (concentration-dependent) elimination pathways. Isatuximab CL decreases over time. This is consistent with the pharmacokinetics of isatuximab in patients with RRMM in the previous submissions (POH0503), and it is thought that the decrease in CL is due to the status improvement on the PK of isatuximab by mechanisms such as reduction in inflammation and IgG MM protein, leading to

a greater proportion of isatuximab going through salvage pathways and subsequently resulting in lower clearance.

Pharmacokinetics of isatuximab was similar in subjects with NDMM eligible or not for transplantation. The incidence of treatment emergent ADAs in study IIT15403 was 21.6%. This is similar or somewhat higher than the incidence in NDMM patients in the other two studies (9.1% and 16.9%) and considerably higher compared to RRMM patients (<2%). This might be attributed to a more immunocompetent status in NDMM patients compared to RRMM patients. The majority of patients who developed treatment-induced ADA (in the data pooled across VRd combination studies), had a transient response. Lower isatuximab exposures were observed in subjects with ADA positivity especially in subjects with high ADA titers. However, as ADA kinetics was transient with an onset time primarily at the beginning of isatuximab treatment (i.e. during the first month of isatuximab treatment), the mean linear CL at steady state between ADA-positive and ADA-negative patients remained comparable. This is adequately reported in section 5.2 of the SmPC.

No PK/PD analyses have been performed for isatuximab in patients with NDMM who are eligible for transplant. The mechanism of action of isatuximab is known and given the low number of subjects in study IIT15403, absence of exposure-response analysis is considered acceptable.

2.3.4. Conclusions on clinical pharmacology

The clinical pharmacology of isatuximab in subjects with NDMM eligible for transplantation has been sufficiently characterised and relevant information has been included in the SmPC.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies for the combination of isatuximab with VRd or Rd were submitted.

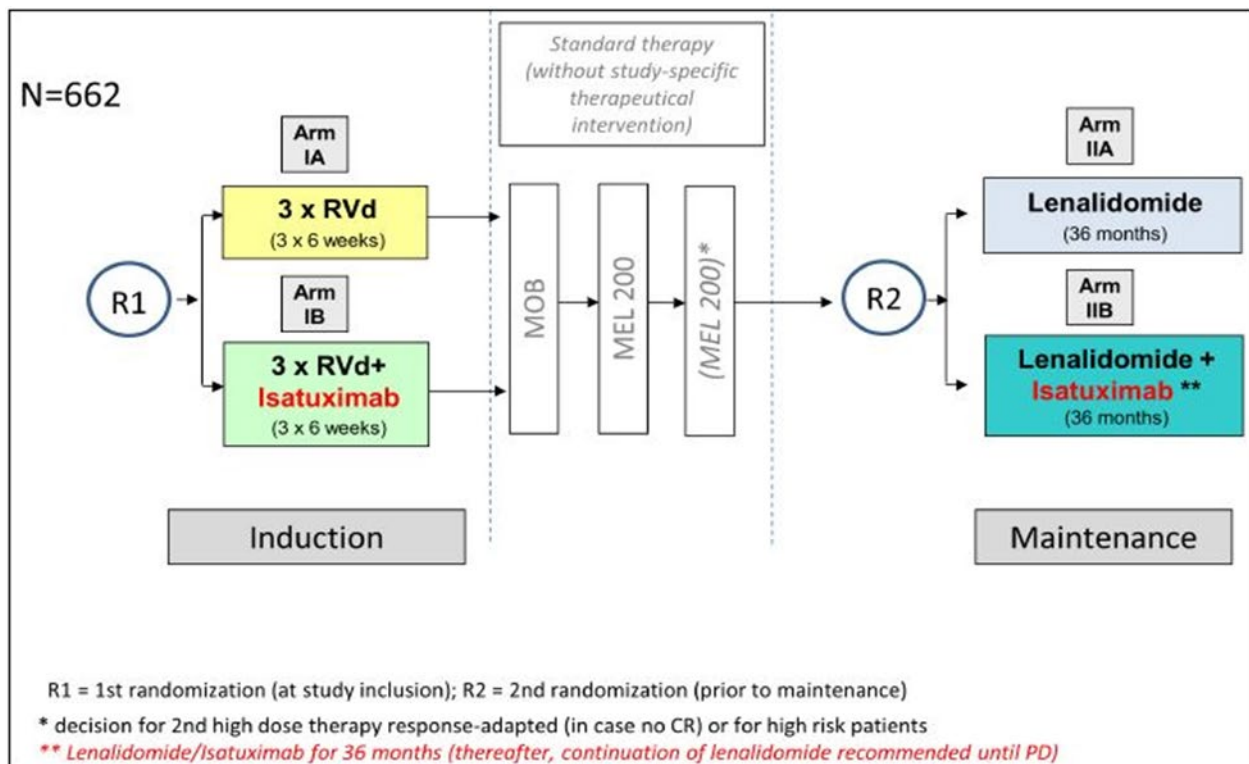
2.4.2. Main study

IIT15403 (GMMG-HD7): A randomized phase III trial assessing the benefit of the addition of isatuximab to lenalidomide / bortezomib / dexamethasone (RVd) induction and lenalidomide maintenance in patients with newly diagnosed multiple myeloma.

Methods

A diagrammatic representation of the study design is presented in **Figure 3**.

Figure 3. GMMG-HD7 study design



The study consists of two parts. Part 1 includes the induction and the intensification phase, and Part 2 includes the maintenance phase. This application concerns only part 1, but both parts are briefly described here.

Induction period (Part 1):

Induction therapy consisted of three 42-day treatment cycles, in which consenting symptomatic myeloma participants were randomly assigned to 1 of 2 treatment groups: Groups IA or IB.

Intensification period (Part 1):

All eligible participants were given an intensified therapy regimen according to GMMG standard protocols. For all participants, stem cells were mobilized by GMMG Standard protocols (CAD: cyclophosphamide, doxorubicin, dexamethasone) and granulocyte-colony stimulating factor (G-CSF). Target stem cell collection yield was at least 7.5×10^6 CD34+ cells/kg body weight. High dose chemotherapy (HDT) (melphalan 200 mg/m²) followed by ASCT was started 4 to 6 weeks after CAD. For participants not in CR after first high dose chemotherapy (HDT1) and for all cytogenetic high risk participants at baseline, a second HDT (HDT2) was to be performed within 3 months.

Maintenance (Part 2):

Prior to maintenance therapy, a second randomisation was done between Groups IIA and IIB for all eligible participants. Eligibility criteria were similar to inclusion/exclusion criteria for first randomisation. The second randomisation was stratified by R-ISS at study entry (R-ISS I/II versus III versus not classified) and MRD negativity (no/yes) after HDT. Maintenance therapy was started approximately 3 months after the intensification phase and was given until confirmed progression, for 3 years, or until unacceptable toxicity, whichever occurred first. For participants still in remission after 36 months of maintenance therapy, it was recommended to continue lenalidomide maintenance therapy until disease progression outside of the study protocol. Each maintenance cycle was defined as

a period of 28 days. Within the trial, a maintenance period of 36 months was scheduled, i.e., 39 cycles.

Follow-up period:

After individual EoT, the participant entered the follow-up period of the trial. The time span of the follow-up period varies for the individual participants. The clinical end of the trial is defined as the timepoint at completion of study treatment for the last participant, after which there will be a follow-up period without study specific intervention. The duration of the follow-up period will depend on the number of PFS events. The overall end of the trial will be the "Last Participant Last Visit" during the follow-up period.

Study participants

Key inclusion criteria:

1. Confirmed diagnosis of untreated multiple myeloma requiring systemic therapy (IMWG updated criteria 2014).
2. Patient is eligible for high dose therapy and autologous stem cell transplantation.
3. Measurable disease, defined as any quantifiable monoclonal protein value, defined by at least one of the following three measurements:
 - Serum M-protein $\geq 10\text{g/l}$ (for IgA $\geq 5\text{g/l}$)
 - Urine light-chain (M-protein) of $\geq 200\text{ mg/24 hours}$
 - Serum FLC assay: involved sFLC level $\geq 10\text{ mg/dl}$ and abnormal sFLC ratio
4. Age 18 - 70 years inclusive
5. WHO performance status 0-2
6. Negative pregnancy test at inclusion (females of childbearing potential)
7. All patients must agree to preventive measures regarding pregnancy, blood donation and safe use of the study treatment.
8. All patients must be able to understand the consequences of the clinical trial participation and must have provided written informed consent before enrolment in the trial.

Key exclusion criteria:

1. Systemic AL amyloidosis (except for AL amyloidosis of the skin or the bone marrow)
2. Plasma cell leukaemia
3. Previous chemotherapy or radiotherapy during the past 5 years, except local radiotherapy in case of local myeloma progression or benign diseases, such as non-malignant thyroid diseases. (Note: patients may have received a cumulative dose of up to 160 mg of dexamethasone or equivalent as emergency therapy.)
4. Severe cardiac dysfunction (NYHA classification III-IV), ejection fraction $< 40\%$.
5. Significant hepatic dysfunction (ASAT and/or ALAT ≥ 3 times normal level and/or serum bilirubin ≥ 1.5 times normal level if not due to hereditary abnormalities as Gilbert's disease), unless related to myeloma.

6. Patients with active, uncontrolled infections
7. Patients with severe renal insufficiency (Creatinine Clearance < 30ml/min)
8. Patients with peripheral neuropathy or neuropathic pain, CTC grade 2 or higher (as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0)
9. Patients with a history of active malignancy during the past 5 years with the exception of the following malignancies after curative therapy: basal cell carcinoma of the skin, squamous cell skin carcinoma, stage 0 cervical carcinoma or any in situ malignancy (A history of an early stage malignancy during the past 5 years may be acceptable. In this case the GMMG study office has to be consulted prior to study inclusion.)
10. Patients with acute diffuse infiltrative pulmonary and/or pericardial disease
11. Autoimmune haemolytic anaemia with positive Coombs test or immune thrombocytopenia
12. Platelet count < 75 x 10⁹/l (Platelet transfusions are not permitted to improve platelet count prior to study inclusion.)
13. Haemoglobin ≤ 8.0 g/dl, unless related to myeloma
14. Absolute neutrophil count (ANC) < 1.0 x 10⁹/l (the use of colony stimulating factors within 14 days before the test is not allowed)
15. Corrected serum calcium > 14 mg/dl (> 3.5 mmol/l)
16. Pregnancy and lactation

Criteria for second randomisation:

The following conditions must be met prior to the 2nd randomisation:

1. No withdrawal from study between 1st and 2nd randomisation for any reason (e.g. PD after high dose chemotherapy)
2. Haemoglobin > 8.0 g/dl
3. Absolute Neutrophile Count (ANC) ≥ 1.0 x 10⁹/l
4. Platelets ≥ 75 x 10⁹/l
5. For females of childbearing potential: negative pregnancy test
6. no severe cardiac dysfunction (NYHA classification III-IV), ejection fraction ≥ 40%
7. no significant hepatic dysfunction (ASAT and/or ALAT ≥ 3 times normal level and/or serum bilirubin ≥ 1.5 times normal level if not due to hereditary abnormalities as Gilbert's disease), unless related to myeloma
8. no active or history of hepatitis B or C (Prior hepatitis B may be acceptable if an adequate prophylaxis is being implemented during the course of the study.)
9. no HIV positivity
10. no severe renal insufficiency (Creatinine Clearance > 30ml/min, determined by using the MDRD formula (required parameter: serum creatinine, age, sex, ethnicity)
11. WHO performance status 0-2

Criteria for permanent treatment discontinuation:

A patient will be withdrawn from the trial treatment for the following reasons:

- Withdrawal at the patient's request
- Withdrawal based on the Investigator's opinion based on:
 - Disease progression after intensification (HDT + ASCT) or during maintenance (in case of a confirmed PD early during induction therapy the patient may be withdrawn from the trial treatment at the discretion of the investigator if a more suitable therapy is available)
 - Unacceptable AE
 - Poor compliance to study protocol
- for women, if it becomes known that the patient is pregnant
- major protocol violations
- intercurrent illness
- non-eligibility for maintenance treatment

Cytogenetics at study entry:

Characterization of cytogenetic risk of the myeloma cells was performed by central laboratory FISH testing. For all participants, iFISH analyses from bone marrow samples were performed. The bone marrow samples had to be sent prior to the treatment start. The iFISH was performed on CD138-purified myeloma cells using a comprehensive panel of probes (current standard: IgH break apart, t(11;14), t(4;14), t(14;16), 1q21/13q14, 11q22.3/17p13, 5p15/5q35, 9q34/15q22, 8p21/19q13, MYC break apart. In case IgH break apart was positive and t(11;14), t(4;14), t(14;16) were negative, then also t(6;14) was tested). For gains, deletions and break apart abnormalities, a threshold of 10% was applied and for translocations, thresholds of 10% in case of 2 fusion signals and 20% for 1 fusion signal were applied. High-risk cytogenetic status was defined as the presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).

Treatments

Participants received isatuximab, bortezomib, lenalidomide and dexamethasone (IVRd) or bortezomib, lenalidomide and dexamethasone (VRd) for an induction period of 18 weeks (three 42-day cycles) followed by HDT + ASCT intensification (Part 1). After transplant, patients were re-randomised to receive maintenance therapy with isatuximab, lenalidomide and dexamethasone (IRd) or Rd alone (Part 2). Treatment continued until disease progression, unacceptable AE, or participant's decision to discontinue. An overview of the induction treatment schedule for both study arms is provided in **Figure 4**.

Figure 4. Induction treatment schedule per study arm

	Induction Cycle 1				Induction Cycle 2 & 3			
	IsaVRd				IsaVRd			
	VRd				VRd			
Cycle Day	Bortezomib	Lenalidomide *	Dexamethasone **	Isatuximab	Bortezomib	Lenalidomide *	Dexamethasone **	Isatuximab
D1	SC 1.3 mg/m ²	PO 25 mg	IV or PO 20 mg	IV 10 mg/kg	SC 1.3 mg/m ²	PO 25 mg	IV or PO 20 mg	IV 10 mg/kg
D2								
D3								
D4	SC 1.3 mg/m ²		PO 20 mg		SC 1.3 mg/m ²		PO 20 mg	
D5								
D6								
D7								
D8	SC 1.3 mg/m ²	PO 25 mg	IV or PO 20 mg	IV 10 mg/kg	SC 1.3 mg/m ²	PO 25 mg	PO 20 mg	
D9								
D10								
D11	SC 1.3 mg/m ²		PO 20 mg		SC 1.3 mg/m ²		PO 20 mg	
D12								
D13								
D14								
D15			IV or PO 20 mg	IV 10 mg/kg			IV or PO 20 mg	IV 10 mg/kg
D16 - D21	STOP				STOP			
D22	SC 1.3 mg/m ²	PO 25 mg	IV or PO 20 mg	IV 10 mg/kg	SC 1.3 mg/m ²	PO 25 mg	PO 20 mg	
D23								
D24								
D25	SC 1.3 mg/m ²		PO 20 mg		SC 1.3 mg/m ²		PO 20 mg	
D26								
D27								
D28								
D29	SC 1.3 mg/m ²	PO 25 mg	IV or PO 20 mg	IV 10 mg/kg	SC 1.3 mg/m ²	PO 25 mg	IV or PO 20 mg	IV 10 mg/kg
D30								
D31								
D32	SC 1.3 mg/m ²		PO 20 mg		SC 1.3 mg/m ²		PO 20 mg	
D33								
D34								
D35								
D36 - D42	STOP				STOP			

* Lenalidomide dose reduction in case of impaired renal function:

- moderate renal impairment ($30 \leq \text{CLcr} < 50$ ml/min): 10 mg
- severe renal impairment ($\text{CLcr} < 30$ ml/min, not requiring dialysis): 15mg every other day

** On days of isatuximab infusion, dexamethasone will be administered intravenously as part of the premedication. If an isatuximab dose is skipped or discontinued dexamethasone should be administered orally.

Treatment periods

Treatment administration consisted of an induction period, an intensification period without addition of the investigational medicinal product (IMP), and a maintenance treatment period for which patients were re-randomised. Dose reduction, omission, delay, or treatment discontinuation were planned in case of associated drug reactions. Infusion reactions (IRs) were monitored for patients receiving isatuximab.

Screening period

The screening phase was up to 21 days until enrolment/randomisation and up to 28 days until start of study treatment. The median time from initial diagnosis to randomisation was similar in both treatment arms: 0.85 month in VRd arm and 0.82 month in IVRd arm. More than one third of the patients received emergency treatment during the screening period with a cumulative dose of up to 160 mg of dexamethasone or equivalent in relation with existing myeloma symptoms, such as pain. This emergency treatment was balanced between the arms.

Induction period

The total duration of the induction period was 18 weeks (3 cycles). The duration of each cycle in the induction period was 42 days (6 weeks) and a total of 3 cycles were planned. Induction therapy was stopped in case of disease progression (at the discretion of the investigator), unacceptable AE,

patient's decision to discontinue, or completion of the induction period, whichever occurred first. The following medications were used during the induction period:

- Isatuximab (IVRd arm only) was given intravenously (IV) at the dose of 10 mg/kg on Days 1, 8, 15, 22, 29 in Cycle 1; from Cycle 2 onwards, it was given on Days 1, 15, 29 of each cycle.
- Bortezomib was given subcutaneously (SC) at a dose of 1.3 mg/m² on Days 1, 4, 8, 11, 22, 25, 29, and 32 of each cycle.
- Lenalidomide was given per o.s. (PO) at a dose of 25 mg/day (10 mg/day for patients with creatinine clearance [CrCl] ≥ 30 to < 50 mL/min; 15 mg every other day for patients with CrCl < 30 mL/min not requiring dialysis) from Day 1 to Day 14 and from Day 22 to Day 35 of each cycle.
- Dexamethasone IV was given at a dose of 20 mg/day on the days of isatuximab administration (for patients in the IVRd arm) and PO otherwise on Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 (IVRd and VRd arms)

Because of the COVID-19 pandemic, clinical trial sites were advised to postpone HDT-ASCT and it was decided to allow up to two bridging cycles with (I)VRd at the Investigator's discretion to make postponement possible.

Intensification period

All eligible patients were given an intensified therapy regime according to GMMG standard protocols. The commonly used regimen for intensified therapy and GMMG standard is CAD (Cyclophosphamide/Adriamycin/Dexamethasone) followed by high dose melphalan (200mg/m²) and autologous stem cell rescue. This is a background treatment given for all patients with no study-specific therapeutical intervention.

Subsequent to the induction therapy, the next treatment cycle should start between d43 and d57 after start of the third VRd (+/- isatuximab) cycle

Eligibility was assessed according to local standards. Recommended criteria were

- WHO performance 0-2
- Absence of severe pulmonary, neurologic, or psychiatric disease
- Bilirubin and transaminases of less than 2.5 times the upper limit of normal values

Patients who were not eligible for intensification treatment anymore, were recommended to continue with second randomisation and maintenance treatment according to the randomisation arm. In this case the MRD negativity status after induction treatment (instead of after last HDT) was used as a stratification factor.

Maintenance period

Maintenance therapy should have started approximately 3 months after the high dose therapy and was given until confirmed progression, for 3 years or until unacceptable toxicity, whichever occurs first.

For patients still in remission after 36 months of maintenance therapy, it was recommended to continue lenalidomide maintenance therapy until disease progression outside of the study protocol.

The lenalidomide maintenance therapy was given continuously. A maintenance cycle was defined as a period of 28 days. "Day 29" is equivalent to day 1 of the subsequent cycle. Within the trial a maintenance period of 36 months was scheduled, i.e. 39 cycles.

The following medications were used during this period:

- Isatuximab IV (IR arm only) was given at a dose of 10 mg/kg Q1W during the first cycle and Q2W in cycles 2 and 3. Starting with Cycle 4 of maintenance treatment, the schedule was switched to a Q4W administration.
- Lenalidomide PO was given continuously at a dose of 10 mg/day (5 mg/day for patients with CrCl $\geq$ 30 to $<$ 50 mL/min; 5 mg every other day for patients with CrCl $<$ 30 mL/min), with recommendation for dose modification to 15 mg/day after 3 cycles based on tolerability.
- Dexamethasone IV was given at a dose of 20 mg/day on the days of isatuximab administration (for patients in IR arm only), or PO otherwise on Days 1, 8, 15, and 22. Following the fourth administration of isatuximab in maintenance treatment, corticosteroid premedication was switched from dexamethasone to methylprednisolone 100 mg iv (or equivalent at the investigator's discretion)

Premedication to prevent infusion reactions (IRs)

On the day of isatuximab infusion, a total of 20 mg of dexamethasone was to be administered as premedication and as part of the backbone treatment before isatuximab. The list of isatuximab premedications is provided below and was to be administered in the following order:

- Acetaminophen 650 mg to 1000 mg orally (PO)
- Ranitidine 50 mg IV (or equivalent)*
- Diphenhydramine 25 mg to 50 mg IV (or equivalent)
- Dexamethasone 20 mg IV

In case of dexamethasone being prematurely stopped and other study treatment being continued, steroid premedication could be considered with methylprednisolone 100 mg IV, if infusion reaction premedication was still needed for isatuximab according to Investigator judgment.

Montelukast 10 mg oral administration (PO) (30-60 minutes prior to isatuximab infusion) was highly recommended as additional premedication on Days 1, 8, and 15 of the first cycle (optional during the following infusions/cycles).

For participants who did not experience an infusion related reaction upon 4 consecutive administrations of isatuximab, the need for subsequent premedication was allowed to be reconsidered at the Investigator's discretion.

* = Note, an H2 blocker, such as ranitidine 50 mg IV or equivalent, was no longer considered for use as premedication for isatuximab trials, but the change was implemented in Protocol 1.3 dated 15 December 2022. As a consequence, all participants received ranitidine during induction.

Prohibited concomitant medication

Concomitant chemotherapy or myeloma-specific therapy other than trial treatment (incl. standard intensification) was not permitted. Co-administration of strong CYP3A4 inhibitors/inducers was to be avoided, when possible, as these agents may have impact on the bortezomib exposure.

Localized myeloma-related radiation therapy was allowed.

Dose modifications and treatment discontinuation

The following rules were upheld regarding dose delays:

- Isatuximab should be administered in the weekly schedule +/- 1 day, in the biweekly schedule +/- 3 days and in the monthly schedule +/- 1 week.
- Bortezomib doses could be administered at a deviation of +/- 2 days, but there had to be a minimum of 72 h between two doses.

The following instructions were given for dose modification:

- For bortezomib and/or lenalidomide related $\geq$ grade 3 non-hematologic or grade 4 haematological toxicities (except lymphopenia), the next dose was held until toxicity improved to grade 2 or better, and then the treatment was restarted at a dose reduced one level from dose received previously. The minimal dose for bortezomib was 0.7mg/m² and for lenalidomide 5 mg daily (if started with 25mg/d) or 5 mg/2 days (if started with 10mg/d), respectively.
- No dose modifications were allowed for isatuximab. Dose modifications of the other drugs due to toxicities were performed in predefined dose levels:
 - Lenalidomide could be reduced in five 5 mg steps, starting from 15 mg PO daily as the first step (i.e. 15 mg – 10 mg – 5 mg – 5 mg every 2 days). Lenalidomide could be restarted at full dose despite a previous toxicity grade $\geq$ 3 at the investigator's discretion.
 - In general, dose reduction of dexamethasone were to be avoided. Dexamethasone could be reduced from the starting dose of 20 mg PO or IV to 12 mg, 8 mg or 4 mg. One or several doses could be omitted, and administrations could be decreased to once every week or every 2 weeks. After resolution of the toxicity, therapy could be continued at the initial dose or a reduced dose of dexamethasone.
 - Bortezomib could be reduced from 1.3. mg/m² SC starting dose to 1.0 mg/m² or 0.7 mg/m². Administrations could be decreased to once every week. Bortezomib could be restarted at full dose despite a previous toxicity grade $\geq$ 3 at the investigator's discretion.
- If a patient experienced multiple toxicities and there were conflicting recommendations, dose modifications were based on the toxicity requiring the highest dose reduction (i.e. lowest dose given).
- Doses missed for reasons other than toxicity were made up if possible and appropriate.
- If toxicities persisted longer than the remainder of the (half) cycle, the start of the following (half) cycle was delayed until the patient was fit to continue study treatment.

The following instructions were given for treatment discontinuation:

- If one of the study treatments was permanently discontinued, then other drug(s) were continued until regular end of study, disease progression, unacceptable toxicity or the patient wishes to discontinue further study treatment.
- Patients with a grade 4 or reoccurring grade 3 isatuximab infusion reaction(s) had isatuximab permanently discontinued. These patients continued to receive bortezomib, lenalidomide and dexamethasone as per protocol.

Objectives

The primary objective purpose of the first part of this open-label study was to compare induction therapy without isatuximab (group IA) versus induction therapy with isatuximab (group IB) regarding the MRD negativity after induction (assessed by flow cytometry).

The key secondary objectives of part 1 of this study were:

- To compare the induction treatment groups (overall group IA versus group IB) regardless of second randomisation regarding the progression-free survival (PFS) from first randomisation.
- To assess and compare the induction treatment policy (group IA-IIA versus group IB IIA) in absence of isatuximab maintenance treatment regarding the PFS from first randomisation.
- To assess and compare the induction treatment policy (group IA-IIA versus group IB IIA) in absence of isatuximab maintenance treatment regarding the overall survival (OS) from first randomisation.
- To assess and compare the induction treatment groups (overall group IA versus group IB) regardless of second randomisation regarding the OS from first randomisation.

Outcomes/endpoints

The primary endpoint was:

Minimal residual disease (MRD) negativity after induction (assessed by flow cytometry [NGF]; sensitivity at least 10^{-5}), defined as proportion of participants with negative MRD after induction.

The key secondary endpoints were:

- PFS from first randomisation regardless of second randomisation (overall group IA versus IB comparison), defined as time from first randomisation to progression or death from any cause whichever occurs first
- PFS from first randomisation by induction treatment policy (group IA-IIA versus group IB IIA)
- OS, defined as the time from first randomisation to time of death from any cause, by induction treatment policy (group IA-IIA versus group IB IIA)
- OS, defined as the time from first randomisation regardless of second randomisation to time of death from any cause (overall group IA versus IB comparison)

Other secondary endpoints included:

- PFS from first randomisation by induction treatment policy (group IA-IIB versus group IB IIB)
- MRD negativity rate at the end of induction phase by NGS, defined as the proportion of participants with negative MRD at the end of induction phase assessed by NGS with sensitivity at least 10^{-5}
- MRD negativity rate at the end of intensification phase by NGF, defined as the proportion of participants with negative MRD at the end of intensification phase assessed by NGF with sensitivity at least 10^{-5}
- MRD negativity rate at the end of intensification phase by NGS, defined as the proportion of participants with negative MRD at the end of intensification phase assessed by NGS with sensitivity at least 10^{-5}

- MRD[-] CR rate at the end of induction phase, defined as the proportion of participants with negative MRD and CR at the end of induction phase assessed by NGF method with sensitivity at least 10⁻⁵
- MRD[-] CR rate at the end of induction phase, defined as the proportion of participants with negative MRD and CR at the end of induction phase assessed by NGS method with sensitivity at least 10⁻⁵
- MRD[-] CR rate at the end of intensification phase, defined as the proportion of participants with negative MRD and CR at the end of intensification phase assessed by NGF method with sensitivity at least 10⁻⁵
- MRD[-] CR rate at the end of intensification phase, defined as the proportion of participants with negative MRD and CR at the end of intensification phase assessed by NGS method with sensitivity at least 10⁻⁵
- Complete response rate, defined as the proportion of participants achieving CR or better as best overall response according to the IMWG response criteria from the start of induction treatment until end of induction phase
- Complete response rate, defined as the proportion of participants achieving CR or better as best overall response according to the IMWG response criteria from the start of induction treatment until end of intensification phase
- Time to first CR, defined as the time from first randomisation to the date of first CR during the induction and intensification treatment periods, according to the IMWG response criteria
- Response (ie, complete renal response, partial response, minor response, and durable renal response), determined as per improvement in eGFR from baseline to at least 1 assessment during the induction and intensification treatment periods
- Toxicity during induction and intensification with respect to adverse events of CTC Grade >3 (and specific adverse events of CTC Grade >2 (as defined in protocol Section 11.3) and serious adverse events
- Health-related quality of life (HRQL) will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer specific module with 30 items (EORTC QLQ-C30) and the EORTC QLQ myeloma-specific module with 20 items (MY20). Health status and health utility will be assessed using the EuroQol measure with 5-dimensions and 5-levels per dimension EQ 5D 5L

Sample size

According to the SAP, the study sample size was primarily determined based on the primary endpoint for Part 2, PFS from 2nd randomisation. This endpoint is not part of the current application, but information is nevertheless reported here, since it drove the sample size requirements.

Study ITT5403 was designed based on the IFM2009 trial, which randomly assigned 700 patients with multiple myeloma to receive induction therapy with 3 cycles of VRD and then consolidation therapy with either five additional cycles of VRd (350 patients) or high-dose melphalan plus stem-cell transplantation followed by 2 additional cycles of RVD (350 patients). Patients in both groups received maintenance therapy with lenalidomide for 1 year. The primary endpoint was progression-free survival. PFS from second randomisation assumption was based on these VRd data: Median PFS was 50 months

in the transplantation group and 36 months in the VRD-alone group (adjusted hazard ratio for disease progression or death, 0.65; 95% confidence interval [CI], 0.53 to 0.80; $P < 0.001$).

A group-sequential design was implemented for PFS from second randomisation (arm IIA vs IIB), allowing for early stopping for efficacy using O'Brien and Fleming's boundary. 2.5 years of recruitment was assumed, i.e., of patients' entering the second randomisation and maintenance phase, 3 years of follow-up after end of recruitment, equal group sizes, and an interim analysis after 70% of the required events. A sample size of 514 patients was thought to be adequate to achieve approximately 211 PFS events required to allow for rejecting the null hypothesis of no treatment difference in the final analysis with 87% power at 1-side 2.5% alpha level assuming an increase in 3-year PFS rate from 60% (arm IIA) to 71.75% (arm IIB), which corresponds to a hazard ratio of 0.65. The statistical power was calculated to be 80% when testing at 1-sided 0.83% alpha level. An efficacy interim analysis with approximately 158 PFS events (75% of the required PFS event from second randomisation at final analysis) was planned. Assuming 3% of patients being lost to follow-up during maintenance and 80% entering the maintenance phase, the study needed to recruit $n=662$ patients before first randomisation.

The primary objective of part 1 regarding MRD negativity is to compare the induction arms (arm IA vs IB). Based on presented data on MRD negativity after VRd treatment before and after high dose therapy and on MRD negativity after Lenalidomide/Dexamethasone + Daratumumab therapy, respectively it was hypothesized that MRD negativity rates would be 25% and 40% (of patients tested for MRD negativity, i.e., patients with an evaluable bone marrow sample) in the two induction arms without and with isatuximab, IA and IB, respectively.

Assuming approximately 90% of patients being on study until end of induction therapy with bone marrow samples available from 80% of these patients, MRD data were estimated to be available for approximately 476 of 662 patients.

Based on the conservative assumption that missingness of MRD data was going to be equally distributed between the two induction arms, MRD negativity rates of 18% and 29% were hypothesized in the induction arms IA and IB, respectively. A total of 662 patients would then allow for rejecting the null hypothesis of no difference between the two induction arms at a one-sided significance alpha level of 2.5% with a power of 90.5%. The power becomes 87.2% under one-sided alpha level of 1.67%.

Additional information was added to the SAP for a secondary endpoint that was considered in the SAP – but not in the protocol – as the key secondary endpoint of Part 1. For PFS from first randomisation regardless of second randomisation (overall arm IA vs arm IB comparison), a total of 159 PFS events from first randomisation would provide 90% power at 1-sided 1.67% alpha level to detect a target hazard ratio of 0.58 (a 42% risk reduction in hazard rate in comparison to arm IA). The assumed target hazard ratio of 0.58 was consistent with the PFS hazard ratio reported in trials assessing the combination of anti-CD38 agent (daratumumab) and other backbone regimens; PFS hazard ratio ranged from 0.37 to 0.63 across different studies in NDMM and RRMM.

Randomisation

At time of study inclusion, a first randomisation was performed (into arm IA or IB). The first randomisation was stratified by the classification according to the R-ISS at study entry (R-ISS I/II versus III versus not classified). Not classified is defined as inconclusive or missing iFISH results unless if stage can be determined on lactate dehydrogenase (LDH), albumin and beta-2 microglobulin only).

A second randomisation was done prior to start of maintenance treatment, approximately 3 months after last HDT. Maintenance treatment should have started within 2 weeks after second randomisation. The second randomisation was stratified by R-ISS at study entry (R-ISS I/II versus III versus not classified) and MRD negativity (no vs yes vs unknown) after last HDT.

Stratification factors were used in the first and second randomisation in order to achieve a balance of treatment groups with respect to these prognostic covariates.

The probability for assignment to each of the two treatment arms was 50% for each randomisation, the randomisation ratio is 1:1.

Blinding (masking)

This is an open label study.

Statistical methods

Primary endpoint: MRD negativity

The primary efficacy analysis of MRD negativity compared induction groups VRd versus IVRd in the intent-to-treat population using logistic regression, including stratification factors used at the first randomisation (i.e., R-ISS: I/II versus III versus not classified) in the model. The null hypothesis of no difference between induction groups in MRD negativity rate after induction was tested at the planned one-sided 0.1667 level. Confidence intervals were computed using the Clopper-Pearson method.

Participants without MRD assessment at the end of the induction period were considered as non-responders, i.e., MRD positive.

A number of additional analyses were planned to assess the impact of missing data in the analysis of MRD negativity rate. First, a complete case analysis with missing values being ignored. Second, a tipping point analysis considering all combinations of missing MRD values in both IVRd and VRd arms, being imputed as negative or positive MRD. Third, MRD negativity was analysed using multiple imputation for missing values. In the tipping point and multiple imputation analyses, participants who had PD or death during the induction period or who had MRD not evaluable (<LOD) were considered as MRD positive; the rest of missing data were imputed.

Secondary endpoint: PFS from first randomisation

An inverse probability approach was used for the comparison of induction treatment policy IA-IIA vs arm IB-IIA, with an inverse probability weighted (IPW) analytical framework, where:

- Weight is equal to 2 for patients randomised to receive treatment IIA during the maintenance period;
- Weight is equal to 1 for patients who did not have the second randomisation or who have an event before the second randomisation (regardless the maintenance arm);
- Weight is equal to 0 for patients randomised to receive treatment IIB during the maintenance period.

All events from arm IIA regardless of first randomisation during the maintenance period were included, so were all events during the induction and intensification period from arm IA and IB regardless of second randomisation, and all events during the follow-up period from patients who were not randomised a second time.

The p-value from the inverse probability weighted log-rank test stratified by the stratification factor for first randomisation, i.e. R-ISS stage (I/II vs III vs Not classified) at baseline will be reported.

A total of nine sensitivity analyses were conducted:

- Progression regardless of further anti-cancer treatment;
- Progression considering initiation of further anti-myeloma treatment as an event;
- Progression, without censoring of progression or death occurring more than 7 months after the last valid disease assessment;
- Sensitivity to stratification;
- Sensitivity to randomisation strata;
- Progression based disease assessment in the population without trial impact (disruption) due to Covid-19;
- Progression based disease assessment and censoring death event due to Covid-19 infections;
- Censoring patients randomised to receive isatuximab during maintenance (i.e. arm IIB) at second randomisation;
- Censoring patients randomised to receive isatuximab during maintenance (i.e. arm IIB) at second randomisation and without censoring late events.

Secondary endpoint: OS from first randomisation

According to the SAP, OS from first randomisation was analysed in the same way as PFS from first randomisation. The following sensitivity analyses were conducted:

- Sensitivity to stratification;
- Progression based disease assessment in the population without trial impact (disruption) due to Covid-19;
- Progression based disease assessment and censoring death event due to Covid-19 infections.

Estimand for the primary endpoint from the protocol

Treatment: VRd induction (arm IA) vs IVRd induction (arm IB); variable: minimal residual disease (MRD) negativity after induction, defined as proportion of patients with negative MRD after induction; no information on estimand strategies.

Estimand for the key secondary endpoint from the protocol

Treatment: VRd induction + R maintenance (arm IA-IIA) vs VRd induction + IR maintenance (arm IA-IIB) vs IVRd induction + R maintenance (arm IB-IIA) vs IVRd induction + IR maintenance (arm IB-IIB);

variables:

* PFS, defined as time from first randomisation (at study inclusion) to progression or death from any cause whichever occurs first; estimand strategies defined in the PFS censoring rules.

* OS, defined as time from first randomisation to time of death from any cause; strategies: participants still being alive at the time of the analysis censored at the date last known to be alive.

Estimand for further secondary endpoints from the protocol

variable: PFS from first randomisation;

- Treatment: VRd vs IVRd (independent of the second randomisation); no information on estimand strategies (or censoring rules).
- Treatment: VRd+Rd vs IVRd+Rd (induction treatment followed by lenalidomide maintenance); no information on estimand strategies (or censoring rules).

variable: OS defined as time from first randomisation to time of death from any cause;

- Treatment: VRd+R (arm IA-IIA) vs VRd+IR (arm IA-IIB) vs IVRd+R (arm IB-IIA) vs IVRd+IR (arm IB-IIB); strategies: participants still being alive at the time of the analysis censored at the date last known to be alive.
- Treatment: VRd vs IVRd (independent of the second randomisation); strategies: participants still being alive at the time of the analysis censored at the date last known to be alive.

variable: CR

- Treatment: VRd+R (arm IA-IIA) vs VRd+IR (arm IA-IIB) vs IVRd+R (arm IB-IIA) vs IVRd+IR (arm IB-IIB); variable: complete response (CR) rate, defined as the proportion of patients achieving complete response (CR) to treatment adjusted after removal of isatuximab interference in the immunofixation test in the relevant patient subpopulations.
- Treatment: VRd vs IVRd (independent of the second randomisation); variable: complete response (CR) rate, defined as the proportion of patients achieving complete response (CR) to treatment adjusted after removal of isatuximab interference in the immunofixation test in the relevant patient subpopulations.

Best response to treatment during the trial (adjusted after removal of isatuximab interference in the immunofixation test in the relevant patient subpopulations).

Quality of life questionnaires EORTC-QLQC30, EORTC-QLQMY20, and EQ-5D-5L questionnaires).

The **(EU-)SAP** provided additional information about estimands for the primary and secondary endpoints.

Intercurrent event handling strategy for the primary endpoint from the SAP:

- Interruption/discontinuation of study intervention: MRD negativity was assessed based on assessments irrespective of study intervention interruption/discontinuation (treatment policy strategy)
- Start of new anti-myeloma therapy: MRD negativity was assessed based on assessments up to time of new anti-myeloma therapy (while not initiating anti-myeloma strategy)

These two strategies come in addition to what was stated in the protocol.

The following censoring rules were applied for PFS:

- Patients without any valid post-baseline disease assessments were censored at the date of first randomisation.
- Patients without disease progression or death before the analysis cut-off date were censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a new antimyeloma treatment (if any) or performed prior to the analysis cut-off date, whichever came first.
- Patients with progression or death after initiation of a new antimyeloma treatment were censored at the date of last valid disease assessment without evidence of progression before

the start of further antimyeloma treatment or performed prior to the cutoff date, whichever came first.

- Patients with progression or death occurring more than 7 months (213 days) during the treatment period (until end of study) or during follow-up period after the last valid disease assessment (i.e., after ≥ 2 consecutive missed scheduled disease assessments) were censored at the date of the last valid disease assessment without evidence of progression before the start of further antimyeloma treatment (if any) or performed prior to the cutoff date, whichever came first.

Selection of outcomes for the investigation of subgroups, as defined in the EU SAP

The following variables were considered for the evaluation of consistency of results for important endpoints: age, gender ECOG PS, ISS staging at study entry, R-ISS staging at study entry, cytogenetic risk, MM type, diagnostic criteria, baseline creatinine criteria, serum involved/uninvolved FLC ratio, baseline haemoglobin levels, baseline serum calcium, chromosomal abnormality 1q21+, chromosomal abnormality (gain 1q21), chromosomal abnormality (amplification 1q21), chromosomal abnormality del(17p), chromosomal abnormality t(4;14), chromosomal abnormality t(14;16), chromosomal abnormality (1q21+ and t(4;14)), chromosomal abnormality (1q21+ and t(14;16)), chromosomal abnormality (1q21+ and (t(4;14) or t(14;16))), chromosomal abnormality (del(17p), t(A;14), t(14;16)), 1q21+, lytic lesions and soft tissue plasmacytoma.

Results

Participant flow

Figure 5. Participant flow in study GMMG-HD7

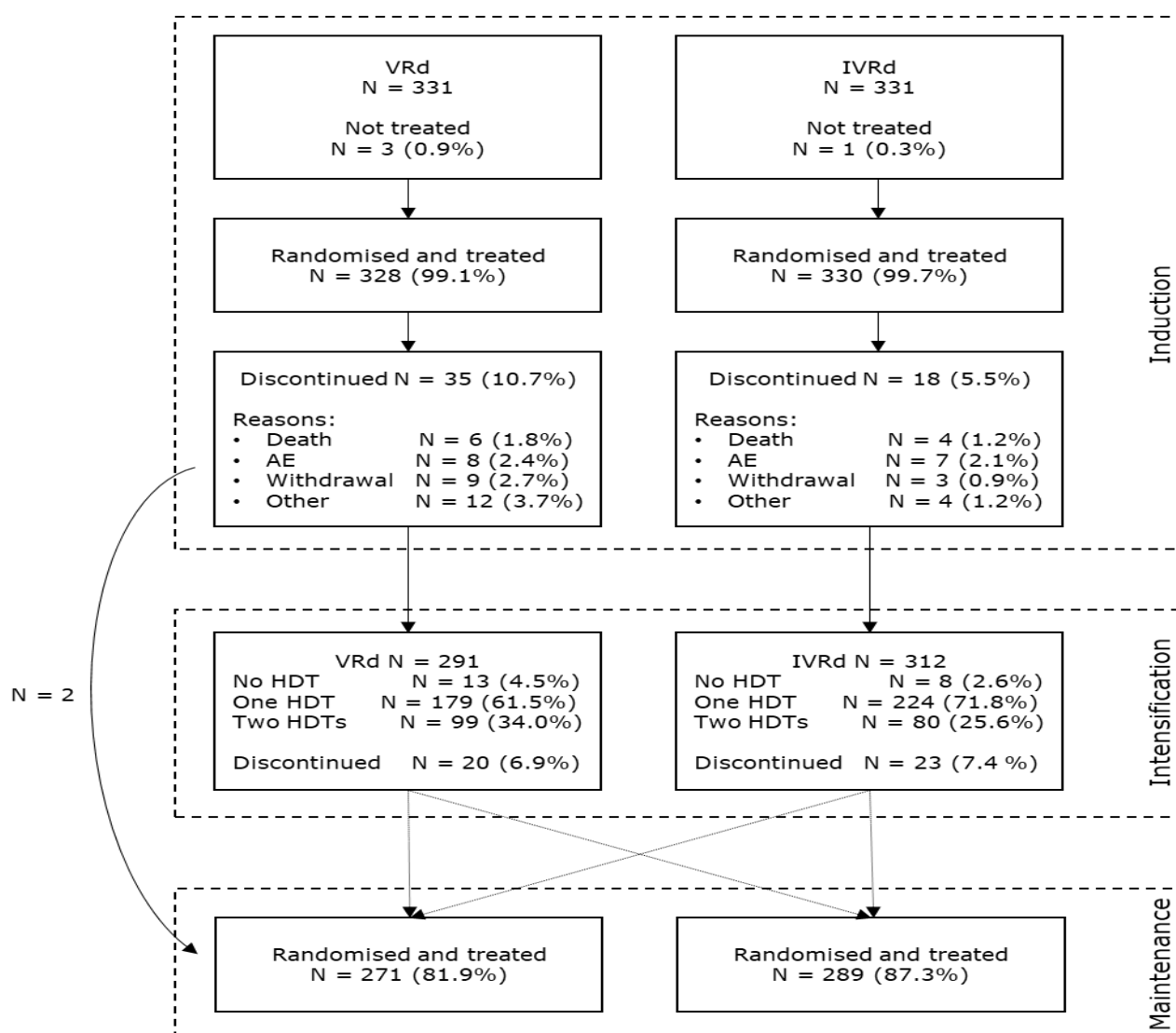


Table 6. Disposition for intensification phase - randomised population part 1 - study GMMG-HD7

	VRd (N=331)	IVRd (N=331)	All (N=662)
Randomised for induction and not treated during intensification	40 (12.1)	19 (5.7)	59 (8.9)
Randomised for induction and treated during intensification	291 (87.9)	312 (94.3)	603 (91.1)
Patients who completed mobilization	291 (87.9)	312 (94.3)	603 (91.1)
Patients who completed HDT1	278 (84.0)	304 (91.8)	582 (87.9)
Patients who completed HDT2	99 (29.9)	80 (24.2)	179 (27.0)
Patients still on intensification phase	0	0	0
Patients who completed mobilization phase and at least one HDT ^a	278 (84.0)	304 (91.8)	582 (87.9)
Patients with definitive discontinuation during mobilization	9 (2.7)	5 (1.5)	14 (2.1)
Confirmed progressive disease (PD) (after intensification or during maintenance)	0	0	0
Adverse Event	3 (0.9)	1 (0.3)	4 (0.6)
Patient's request or at request of the legal representative (withdrawal of consent)	2 (0.6)	0	2 (0.3)
Investigator's decision	2 (0.6)	4 (1.2)	6 (0.9)

	VRd (N=331)	IVRd (N=331)	All (N=662)
Pregnancy of female patient	0	0	0
Major protocol violations	0	0	0
Non-compliance of the patient	2 (0.6)	0	2 (0.3)
Non-eligibility for maintenance treatment	0	0	0
Death	0	0	0
Other	0	0	0
Patients with definitive discontinuation at the end of HDT1	11 (3.3)	14 (4.2)	25 (3.8)
Confirmed progressive disease (PD) (after intensification or during maintenance)	6 (1.8)	5 (1.5)	11 (1.7)
Adverse Event	0	1 (0.3)	1 (0.2)
Patient's request or at request of the legal representative (withdrawal of consent)	3 (0.9)	1 (0.3)	4 (0.6)
Investigator's decision	0	1 (0.3)	1 (0.2)
Pregnancy of female patient	0	0	0
Major protocol violations	0	0	0
Non-compliance of the patient	1 (0.3)	1 (0.3)	2 (0.3)
Non-eligibility for maintenance treatment	1 (0.3)	2 (0.6)	3 (0.5)
Death	0	3 (0.9)	3 (0.5)
Other	0	0	0
Patients with definitive discontinuation at the end of HDT2	2 (0.6)	4 (1.2)	6 (0.9)
Confirmed progressive disease (PD) (after intensification or during maintenance)	0	0	0
Adverse Event	0	1 (0.3)	1 (0.2)
Patient's request or at request of the legal representative (withdrawal of consent)	0	1 (0.3)	1 (0.2)
Investigator's decision	1 (0.3)	0	1 (0.2)
Pregnancy of female patient	0	0	0
Major protocol violations	0	0	0
Non-compliance of the patient	0	1 (0.3)	1 (0.2)
Non-eligibility for maintenance treatment	1 (0.3)	0	1 (0.2)
Death	0	1 (0.3)	1 (0.2)
Other	0	0	0
Patients with definitive discontinuation during intensification	22 (6.6)	23 (6.9)	45 (6.8)
Confirmed progressive disease (PD) (after intensification or during maintenance)	6 (1.8)	5 (1.5)	11 (1.7)
Adverse Event	3 (0.9)	3 (0.9)	6 (0.9)
Patient's request or at request of the legal representative (withdrawal of consent)	5 (1.5)	2 (0.6)	7 (1.1)
Investigator's decision	3 (0.9)	5 (1.5)	8 (1.2)
Pregnancy of female patient	0	0	0
Major protocol violations	0	0	0

	VRd (N=331)	IVRd (N=331)	All (N=662)
Non-compliance of the patient	3 (0.9)	2 (0.6)	5 (0.8)
Non-eligibility for maintenance treatment	2 (0.6)	2 (0.6)	4 (0.6)
Death	0	4 (1.2)	4 (0.6)
Other	0	0	0

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

^a Seven patients went directly in maintenance phase after mobilization (without any HDT)

Table 7. Stem cell Transplantations during HDT1 and HDT2 - Intensification safety population

	VRd (N=291)	IVRd (N=312)
Patients with		
Only one High dose/Stem cell transplantation	179 (61.5)	224 (71.8)
Indication for a 2nd high dose/SCT	96 (53.6)	109 (48.7)
Reason 2nd High dose/SCT not done		
Medical contraindication	14 (14.6)	14 (12.8)
Patient's decision	47 (49.0)	41 (37.6)
Other	35 (36.5)	54 (49.5)
Double High dose/Stem cell transplantation	99 (34.0)	80 (25.6)
Reason for 2nd High dose/SCT		
High risk patient	14 (14.1)	16 (20.0)
No complete response	60 (60.6)	38 (47.5)
High risk patient and no complete response	24 (24.2)	19 (23.8)
Other	1 (1.0)	7 (8.8)
No High dose/Stem cell transplantation	13 (4.5)	8 (2.6)

Recruitment

Study initiation date: 18 Oct 2018 (First Informed Consent) / 23 Oct 2018 (First Randomisation)

The study is ongoing.

The analyses presented in this report are based on a PFS data cut-off of 31 January 2024.

Conduct of the study

A total of 5 protocol versions were used during the executive phase of the study **Table 8**.

Table 8. Protocol version and number of patients included

Protocol version	Number of patients first randomized	Number of patients second randomized
Protocol 1.0 dated 23.05.2018	0	0
Protocol 1.1 dated 10.09.2018	0	0
Protocol 1.2 dated 27.12.2019	383	47
Protocol 1.3 dated 15.12.2022	662	560
Protocol 1.4 dated 02.06.2023	662	560

Enrolment for first randomisation (completed 22 September 2020) and second randomisation (21 January 2022) were both completed under protocol version 1.2. Under protocol version 1.2 it was decided that all high-risk patients should receive a second round of HDT, and Montelukast 10mg p.o. (30-60min prior to isatuximab infusion) was introduced as additional premedication on D1, D8 and D15 of the first cycle of induction and maintenance. Some changes were made to the secondary endpoints throughout the different versions of the protocol, and additional exploratory analyses were added.

Amendments of the Statistical Analysis Plan

The statistical analysis plan history (**Table 9**) gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan. **Table 10** shows the study timeline with all relevant events in chronological order.

Table 9. Statistical changes made to the Statistical Analysis Plan

SAP version	Approval date	Description of statistical changes	Rationale
5	27 SEP 2023	Addition of a sensitivity analysis of PFS from second randomisation to censor patients not responder at the end of intensification but second randomised in maintenance. Subgroups were added Sustained MRD for at least 6 months was added Minor updates	This sensitivity analysis has been added to assess if the responder status at the end of intensification impacts the occurrence of events during maintenance. The subgroups have been added to be consistent with other studies of the projects. The sustained MRD for at least 6 months has been added to be consistent with GMMG protocol. Clarification compared to previous versions
4	03 JUL 2023	PFS from second randomisation analyses timing was updated. The number of events for final analysis changed from 228 to 211 and the interim analysis was updated to be based on 75% IF instead of 70% IF. The following endpoint was added: - Renal response	Changes to GMMG protocol Additional endpoint was added to further characterize the efficacy of study treatment

		The quality of life will be analyzed on ITT population instead of safety population. Estimands were added Multiplicity control rules were updated to control for the primary and key secondary endpoints of both parts	The population has been updated to be consistent with other studies of the program According to EMA scientific Advice The overall study-wise Type-I error rate will be controlled using a graphical approach
3	21 APR 2021	The study was divided into two parts. All endpoints were defined separately for part 1 and part 2. Multiple key secondary endpoints have been added for each part of the study. The censoring rule for PFS endpoints on missed disease assessments was updated from 5.5/8 months to 7 months for the entire study. Some subgroups were updated and added. The comparison of induction arms (IA versus IB) regarding key secondary endpoints related to MRD will be done using logistic regression and Fisher test Update on the duration of exposure calculation Clarifications added Multiplicity rules have been updated to handle the primary and key secondary endpoints of both parts Futility OS analyses added at time of PFS from first randomisation IA and FA, and PFS from second	Due to the double randomisation scheme, the two study parts can be seen as two separate studies. The update will allow to treat each study part separately to first establish the induction effect using the data from the first randomisation and then to establish the maintenance effect using data from the second randomisation The censoring rule for the primary analysis of PFS was updated to handle events after missing scheduled assessments following FDA's guidance for industry document "Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics". The subgroups were updated/added to be consistent with other studies of the project The logistic regression method was added to be consistent with the method used to compare induction treatment arms regarding the MRD negativity after induction (assessed by NGF). The method of calculation was updated to consider the bridging cycles before transplant (due to COVID-19) Definitions related to kinetics response for ADAs clarified for treatment-boosted ADAs The family-wise Type-I error rate will be controlled using a hierarchical approach. Upon request from health authorities, futility OS analyses added and details on targeted

		randomisation FA. Details on the number of death events expected at each OS at interim and final analyses added.	number of death events expected at each analysis provided.
2	25 JUN 2021	The comparison of induction arms (IA versus IB) regarding the MRD negativity after induction assessed by NGS is moved from key secondary objectives/endpoints to further secondary objectives/endpoints The comparison of treatment arms regarding MRD[-] CR rate after intensification (by NGS) was moved from key secondary objectives/endpoints to further secondary objectives/endpoints The key secondary endpoint description of 'PFS from first randomisation to progression or death' remains the only key secondary endpoint, consistent with the study design and protocol description.	In GMMG protocol, MRD negativity by NGS is an exploratory endpoint only. During study implementation, NGS sample collection was not prioritized compared to sample collection for NGF and FISH cytogenetic testing (used as a stratification factor at baseline) when a limited amount of BMA material was available. Missing data are expected for the assessment of MRD negativity by NGS due to missing samples and to calibration failure also (with absence of ID clones at baseline). The comparison of the induction arms on the PFS from first randomisation to progression or death is considered of major interest and is the only key secondary endpoint in the study protocol. To prioritize this PFS key secondary endpoint analysis, analyses related to MRD negativity by NGS are moved from key secondary objectives/endpoints to further secondary objectives/endpoints

Table 10. Timeline of GMMG-HD7 data availability and updates to statistical analysis plan.

Date	Milestone
19 april 2021	Version 1 Sanofi Global SAP published
21 april 2021	Database lock date for MRD negativity after induction (Part 1)
25 june 2021	Version 2 Sanofi Global SAP published
30 june 2021	Topline results of MRD negativity after induction (Part 1) from GMMG
11 august 2021	Data transfer to Sanofi (MRD negativity after induction (Part 1))
21 april 2022	Ex-EU HA feedback necessitated a separate SAP for use in a particular country, therefore SAP Version 3 (version 1 for EMA submission) Sanofi EU SAP published
07 june 2022	Early pre-submission meeting with Rapporteur and Co-Rapporteur
13 october 2022	EU scientific advice letter issued ref: (EMA/SA/0000099699)
1 november 2022	GMMG-HD7 part 1 results (MRD negativity after induction) published in The Lancet Haematology
15 december 2022	Cut-off date for interim analysis of PFS from first randomisation (Part 1)
03 july 2023	Version 4 Sanofi EU SAP published to address issues raised in Scientific Advice letter

11 august 2023	Interim CSR prepared by Sanofi (MRD negativity after induction (Part 1))
1 september 2023	Database lock of interim analysis of PFS from first randomisation (Part 1) by GMMG
27 september 2023	Version 5 Sanofi EU SAP published to add a new sensitivity analysis and minor algorithm update
05 october 2023	DSMB meeting with review of the efficacy data for interim analysis of PFS from first randomisation (Part1) and decision to continue the study further without unblinding and data transfer to Sanofi
31 january 2024	Cut-off date for final analysis of PFS from first randomisation (Part 1)
22 may 2024	Database lock of final analysis of PFS from first randomisation (Part 1) by GMMG
01 july 2024	Top-line results of final analysis of PFS from first randomisation (Part 1) from GMMG Data transfer to Sanofi (final analysis of PFS from first randomisation (Part 1))

Changes following study unblinding/database lock and post-hoc analyses

The following analyses were added after database lock:

- Descriptive safety analyses by subgroups of age, gender, race, renal status, and hepatic status
- Descriptive safety analyses by subperiod of Part 1 (during induction/intensification/Part 1)
- Descriptive safety analyses of Grade 5 treatment emergent adverse events (TEAEs) during intensification period by system organ class (SOC) and preferred term (PT)
- Descriptive safety analyses of all deaths during Part 1 and during maintenance
- Efficacy analyses by subgroups:
 - MRD by NGF during intensification phase by subgroups (same subgroups as defined in the SAP for MRD by NGF at the end of induction)
 - PFS from first randomisation by entering maintenance (yes or no)
 - PFS from first randomisation by MRD status at end of induction by NGF and NGS, and by MRD status at end of intensification by NGF (negative/positive)
 - PFS from first randomisation by transplant status
 - PFS from first randomisation by response status at end of intensification (partial response [PR] or better, not responder)
 - PFS from first randomisation)
 - PFS from first randomisation by induction treatment policy (group IVRd R versus group VRd-R) by subgroups
- Efficacy sensitivity analyses of PFS from first randomisation censoring participant who were non-responder (PR or better) at end of intensification but second randomised
- Efficacy sensitivity analyses of PFS from first randomisation without any specific censoring rules for events occurring after further anti-myeloma therapy, or for late events

Protocol deviations

The main categories of the protocol deviations and incidence by treatment group included:

- HDT-related: VRd (2.4%) and IVRd (1.2%)
- IMP-related: VRd (1.8%) and IVRd (7.6%)
- Inclusion/exclusion-related: VRd (3.3%) and IVRd (4.2%)
- Intensification-related: IVRd (0.6%)
- Safety-related: VRd (0.3%)
- Induction schedule-related: VRd (0.6%) and IVRd (0.9%)
- Study conduct-related: VRd (2.1%) and IVRd (1.8%)

Baseline data

A detailed overview of baseline demographics in the ITT is provided in **Table 11** and **Table 12**.

Table 11. Summary of demographics at baseline of the ITT population – study GMMG-HD7

	VRd (N=331)	IVRd (N=331)	All (N=662)
Age (years)			
Number	331	331	662
Mean (SD)	58.69 (7.96)	58.28 (7.39)	58.49 (7.68)
Median	60.00	59.00	59.50
Q1 ; Q3	54.00 ; 65.00	54.00 ; 64.00	54.00 ; 64.00
Min ; Max	26.0 ; 70.0	37.0 ; 70.0	26.0 ; 70.0
Age group 1 (years) [n(%)]			
Number	331	331	662
<65 years	246 (74.3)	258 (77.9)	504 (76.1)
≥65 to <70 years	73 (22.1)	63 (19.0)	136 (20.5)
≥70 years	12 (3.6)	10 (3.0)	22 (3.3)
Sex [n(%)]			
Number	331	331	662
Male	207 (62.5)	204 (61.6)	411 (62.1)
Female	124 (37.5)	127 (38.4)	251 (37.9)
Race [n(%)]			
Number	331	331	662
Caucasian	329 (99.4)	327 (98.8)	656 (99.1)
African	1 (0.3)	1 (0.3)	2 (0.3)
Other	1 (0.3)	3 (0.9)	4 (0.6)

Table 12. WHO performance status at baseline - Induction intent-to-treat population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
WHO performance status at baseline		
0	169 (51.2)	158 (47.9)
1	130 (39.4)	137 (41.5)
2	30 (9.1)	35 (10.6)
3	1 (0.3)	0
4	0	0
5	0	0
Missing	1	1

Characterization of cytogenetic risk of the myeloma cells was performed by central laboratory FISH testing on plasma cells isolated from baseline bone marrow. 17.5% of participants in the IVRd group and 19.9% of participants in the VRd group were considered high-risk, defined as the presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16). An overview of other disease characteristics is provided in **Table 13**.

Table 13. Disease characteristics at study entry - Randomised population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)	All (N=662)
Diagnosis criteria [n(%)]			
Number	330	330	660
CRAB only	76 (23.0)	61 (18.5)	137 (20.8)
SLiM only	36 (10.9)	32 (9.7)	68 (10.3)
CRAB and SLiM	218 (66.1)	237 (71.8)	455 (68.9)
CRAB criteria			
Hypercalcaemia [n(%)]	331	331	662
Yes	29 (8.8)	26 (7.9)	55 (8.3)
No	301 (90.9)	305 (92.1)	606 (91.5)
Unknown	1 (0.3)	0	1 (0.2)
Renal insufficiency [n(%)]	331	331	662
Yes	23 (6.9)	19 (5.7)	42 (6.3)
No	308 (93.1)	312 (94.3)	620 (93.7)
Unknown	0	0	0
Anaemia [n(%)]	331	331	662
Yes	141 (42.6)	149 (45.0)	290 (43.8)
No	190 (57.4)	182 (55.0)	372 (56.2)
Unknown	0	0	0
Bone lesions [n(%)]	331	331	662
Yes	267 (80.7)	264 (79.8)	531 (80.2)
No	62 (18.7)	65 (19.6)	127 (19.2)
Unknown	2 (0.6)	2 (0.6)	4 (0.6)
SLiM criteria			
Bone marrow plasma cell $\geq$ 60%	331	331	662
Yes	133 (40.2)	169 (51.1)	302 (45.6)
No	195 (58.9)	160 (48.3)	355 (53.6)
Unknown	3 (0.9)	2 (0.6)	5 (0.8)

	VRd (N=331)	IVRd (N=331)	All (N=662)
Involved:uninvolved serum free light chain ratio ≥ 100 AND absolute involved SFLC ≥ 100 mg/l	331	331	662
Yes	188 (56.8)	175 (52.9)	363 (54.8)
No	143 (43.2)	156 (47.1)	299 (45.2)
Unknown	0	0	0
MRI >1 focal lesion	331	331	662
Yes	81 (24.5)	86 (26.0)	167 (25.2)
No	63 (19.0)	65 (19.6)	128 (19.3)
Unknown	187 (56.5)	180 (54.4)	367 (55.4)
MM subtype at study entry ^a [n(%)]			
Number	331	331	662
Ig G	194 (58.6)	194 (58.6)	388 (58.6)
Ig A	69 (20.8)	68 (20.5)	137 (20.7)
Ig M	3 (0.9)	1 (0.3)	4 (0.6)
Ig D	2 (0.6)	4 (1.2)	6 (0.9)
Ig E	0	0	0
Kappa light chain only	44 (13.3)	51 (15.4)	95 (14.4)
Lambda light chain only	19 (5.7)	13 (3.9)	32 (4.8)
Unknown/undetected	0	0	0
Biclonal status at study entry ^a [n(%)]			
Number	331	331	662
Yes	3 (0.9)	5 (1.5)	8 (1.2)
No	328 (99.1)	326 (98.5)	654 (98.8)
Beta 2-microglobulin (mg/L)			
Number	331	331	662
Mean (SD)	4.49 (6.40)	4.68 (3.88)	4.59 (5.29)
Median	3.27	3.60	3.40
Q1 ; Q3	2.30 ; 4.86	2.49 ; 5.20	2.40 ; 5.00
Min ; Max	1.0 ; 108.0	0.6 ; 26.0	0.6 ; 108.0
Beta 2-microglobulin (mg/L) [n(%)]			
Number	331	331	662
< 3.5	180 (54.4)	158 (47.7)	338 (51.1)
≥ 3.5 and <5.5	85 (25.7)	95 (28.7)	180 (27.2)
≥ 5.5	66 (19.9)	78 (23.6)	144 (21.8)
Albumin (g/L)			
Number	331	330	661
Mean (SD)	37.55 (6.93)	36.43 (7.51)	36.99 (7.24)
Median	38.00	37.00	38.00
Q1 ; Q3	33.00 ; 42.80	31.10 ; 42.00	32.00 ; 42.00
Min ; Max	15.6 ; 57.0	16.0 ; 62.1	15.6 ; 62.1
Albumin (g/L) [n(%)]			
Number	331	330	661
< 35	105 (31.7)	126 (38.2)	231 (34.9)
≥ 35	226 (68.3)	204 (61.8)	430 (65.1)
Serum LDH (IU/L)			
Number	331	331	662
Mean (SD)	192.14 (64.91)	201.19 (85.14)	196.66 (75.78)
Median	185.00	180.00	181.50
Q1 ; Q3	152.00 ; 220.00	149.00 ; 226.00	150.00 ; 223.00

	VRd (N=331)	IVRd (N=331)	All (N=662)
Min ; Max	67.0 ; 577.0	65.0 ; 849.0	65.0 ; 849.0
Serum LDH (IU/L)[n(%)]			
Number	331	331	662
≤ ULN	288 (87.0)	263 (79.5)	551 (83.2)
> ULN	43 (13.0)	68 (20.5)	111 (16.8)
ISS stage at study entry [n(%)]			
Number	331	331	662
Stage I	150 (45.3)	124 (37.5)	274 (41.4)
Stage II	115 (34.7)	129 (39.0)	244 (36.9)
Stage III	66 (19.9)	78 (23.6)	144 (21.8)
R-ISS stage at study entry [n(%)]			
Number	331	331	662
Stage I	99 (29.9)	77 (23.3)	176 (26.6)
Stage II	186 (56.2)	218 (65.9)	404 (61.0)
Stage III	26 (7.9)	27 (8.2)	53 (8.0)
Not classified	20 (6.0)	9 (2.7)	29 (4.4)
Fish done but risk not classified	20 (100)	9 (100)	29 (100)
Fish assessment missing	0	0	0
At least one biological assessment missing	0	0	0

^a: as per eCRF

MM: Multiple Myeloma, Ig: Immunoglobulin, LDH : Lactate Dehydrogenase, ULN : Upper Limit of Normal, ISS: International staging system, R-ISS: Revised International staging system

Numbers analysed

The number of participants included in each analysis population is provided in **Table 14**.

A total of 331 participants were randomised in each of the VRd and IVRd treatment groups. Of the participants randomised, 4 participants (3 participants in VRd and 1 participant in IVRd) did not start any treatments during the induction phase and 59 participants (40 participants in VRd and 19 participants in IVRd) did not start any treatment during the intensification phase.

Table 14. Analysis populations, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
Randomised population	331 (100)	331 (100)
Induction efficacy population: Induction Intent-To-Treat (ITT-IND)	331 (100)	331 (100)
Induction safety population (SAFE-IND)	328	330
Intensification safety population (SAFE-INT)	291	312
ADA population	0	37
PK population (Isatuximab)	0	37

Note: For the randomised and ITT populations, patients are tabulated according to their randomised treatment
For other populations patients are tabulated according to the treatment actually received (as treated)
No patients are randomised in a group and taking another study treatment

Outcomes and estimation

Primary endpoint MRD negativity rate

At the end of induction, MRD samples were collected for 90.5% of the study participants and MRD data were obtained for 87.3%. Participants without MRD assessment at the end of the induction period were scored as non-responders, i.e., MRD positive. The primary analysis of MRD negativity rate after induction was performed using the ITT-IND population.

At the end of induction, the MRD negativity rate (10^{-5} sensitivity level) in the ITT-IND population was statistically significantly higher in the IVRd group compared to the VRd group (50.5% [95% CI: 0.4493 to 0.5597] versus 35.6% [95% CI: 0.3049 to 0.4107]; OR=1.838 (95% CI: 1.346 to 2.511); $p<0.0001$).

MRD NGF results were missing for 84 participants at the end of induction: 50 participants in VRd group (15.1%) and 34 participants in IVRd group (10.3%). The reason for missing results was mainly "sample not done" (11.5% versus 7.6%, respectively), or "sample not evaluable".

Sensitivity Analyses

Tipping point analysis (**Figure 6** and **Figure 7**) and multiple imputation were conducted to assess the impact of missing data in the analysis of MRD negativity rate at the end of ITT IND population. In both analysis, participants who had PD or death during the induction period or who had MRD not evaluable ($<LOD$) were considered as MRD positive; the rest of missing data were imputed (30 in VRd group and 19 in IVRd group).

For the tipping point analysis, a matrix of all possible combinations of the number of imputations as MRD negative is displayed for the missing MRD values in VRd and IVRd group. A value of 0 means that 0 out of the all imputed values were scored as MRD negative, i.e. all missing values were imputed as MRD positive. Each combination is colour coded by whether it changes the conclusion about the treatment effect in terms of odds ratio (OR) and the statistical significance in terms of p-value.

Figure 6. Tipping point analysis - effect of imputed values on odds ratio, study GMMG-HD7

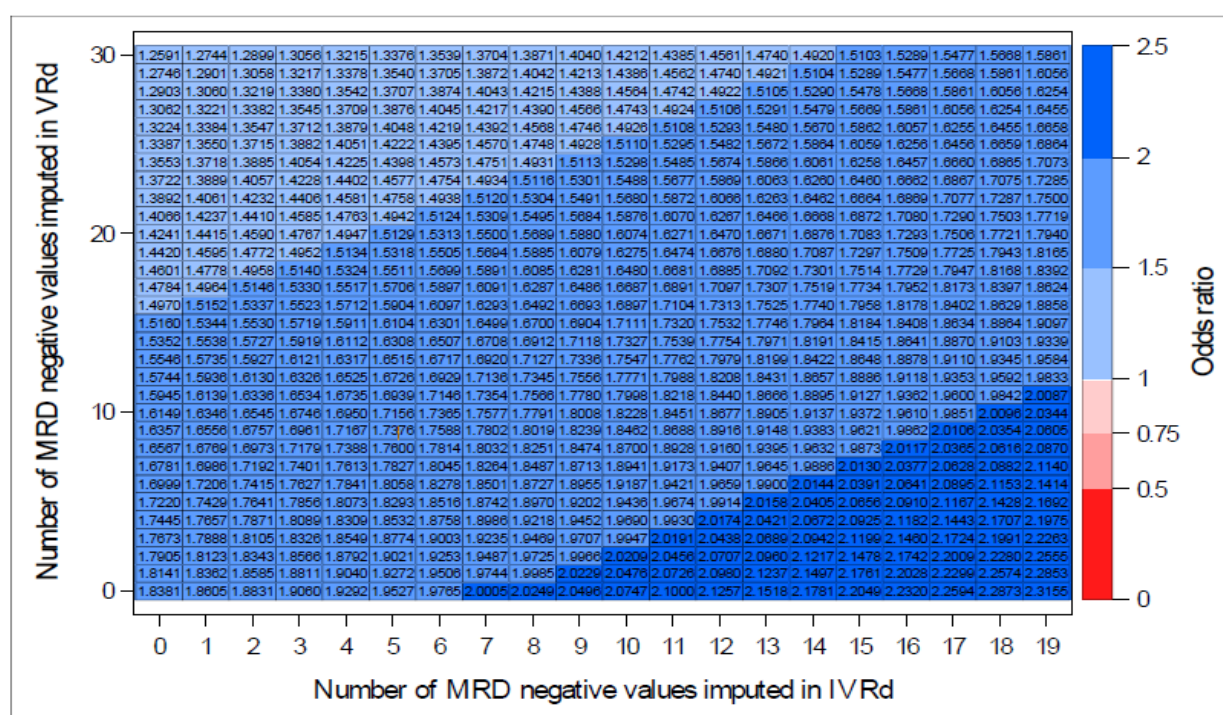
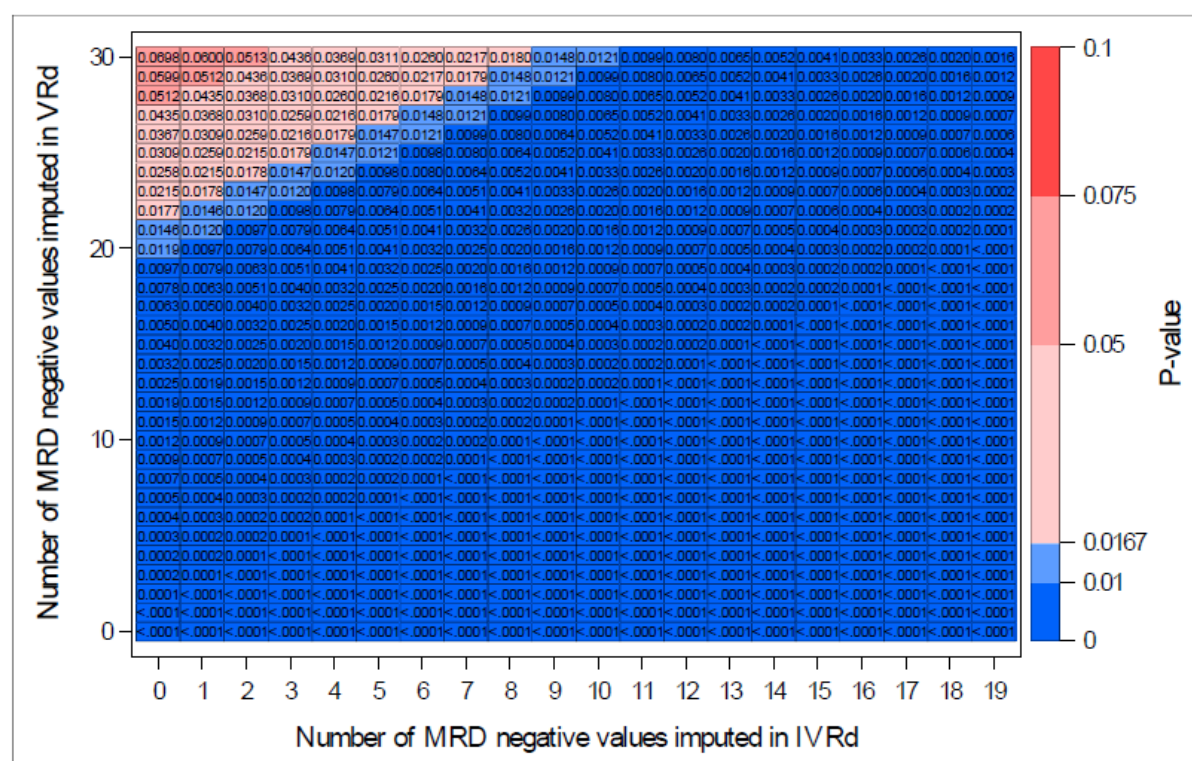


Figure 7. Tipping point analysis - effect of imputed values on p-value, study GMMG-HD7



The multiple imputation analysis is supportive of the primary analysis; the combined stratified OR for the MRD negativity rate (10^{-5} sensitivity level) is 1.769 [95% CI: 1.284 to 2.437, $p=0.0005$].

Supportive analysis

In this analysis, participants without MRD assessment at the end of induction were excluded (except participant dead or with PD event before end of induction who are counted as MRD positive). The OR is 1.759 (95% CI: 1.272 to 2.433, $p=0.0003$).

MRD by response rate

For determination of CR, including confirmed disappearance of all M protein by protein electrophoresis and immunofixation, the end of induction treatment (18 weeks) is a preliminary timepoint due to residual M protein presence in plasma or urine, despite potential tumour clearance in the bone marrow (MRD negativity). MRD negativity rate at the end of induction according to the best overall response during the induction period is summarized in **Table 15**.

Table 15. Summary of MRD negativity by NGF after induction phase - Induction intent-to-treat population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
Number (%) of patients		
With at least one evaluable sample at the end of induction phase	281 (84.9)	297 (89.7)
With MRD missing	50 (15.1)	34 (10.3)
Not evaluable	12 (3.6)	9 (2.7)
Not done	38 (11.5)	25 (7.6)
Number (%) of patients		
MRD negative at sensitivity level 1 in 10^{5a}	118 (35.6)	167 (50.5)
MRD positive at sensitivity level 1 in 10^{5a}	163 (49.2)	130 (39.3)
Number (%) ^b of patients with VGPR or better	212	264
with MRD negative (1 in 10^{5a})	107 (50.5)	159 (60.2)
with MRD positive (1 in 10^{5a})	84 (39.6)	89 (33.7)
with MRD missing	21 (9.9)	16 (6.1)
MRD sample not available	11 (5.2)	9 (3.4)
MRD sample non evaluable	10 (4.7)	7 (2.7)
Number (%) ^b of patients with VGPR or nCR	139	182
with MRD negative (1 in 10^{5a})	59 (42.4)	97 (53.3)
with MRD positive (1 in 10^{5a})	62 (44.6)	71 (39.0)
with MRD missing	18 (12.9)	14 (7.7)
MRD sample not available	11 (7.9)	8 (4.4)
MRD sample non evaluable	7 (5.0)	6 (3.3)
Number (%) ^b of patients with CR	73	82
with MRD negative (1 in 10^{5a})	48 (65.8)	62 (75.6)
with MRD positive (1 in 10^{5a})	22 (30.1)	18 (22.0)
with MRD missing	3 (4.1)	2 (2.4)
MRD sample not available	0	1 (1.2)
MRD sample non evaluable	3 (4.1)	1 (1.2)
Number (%) ^b of patients with PR	89	45
with MRD negative (1 in 10^{5a})	9 (10.1)	4 (8.9)
with MRD positive (1 in 10^{5a})	70 (78.7)	36 (80.0)
with MRD missing	10 (11.2)	5 (11.1)
MRD sample not available	9 (10.1)	4 (8.9)
MRD sample non evaluable	1 (1.1)	1 (2.2)
Number (%) ^b of patients with SD	4	1
with MRD negative (1 in 10^{5a})	0	0
with MRD positive (1 in 10^{5a})	3 (75.0)	1 (100)

	VRd (N=331)	IVRd (N=331)
with MRD missing	1 (25.0)	0
MRD sample not available	1 (25.0)	0
MRD sample non evaluable	0	0

MRD : Minimal residual disease

^a Respective minimum sensitivity of 1 in 10^x nucleated cells

^b Percentages are calculated on the number of patients with mentioned best overall response.

MRD subgroup analysis

Forrest plots of multiple subgroup analyses of the primary endpoint are shown in **Figure 8 - Figure 12**.

Figure 8. MRD negativity rate by NGF after induction phase - Subgroups analyses 1 (Forest plot) - Induction intent-to-treat population, study GMMG-HD7

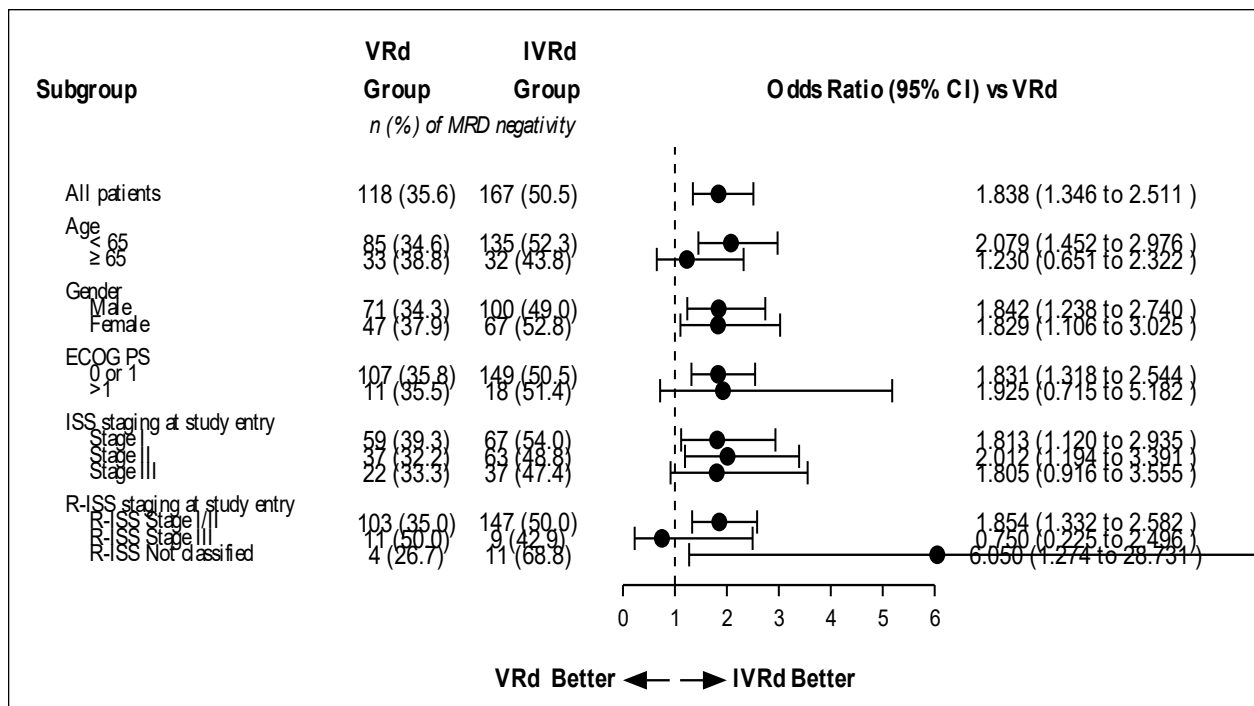


Figure 9. MRD negativity rate by NGF after induction phase - Subgroups analyses 2 (Forest plot) - Induction intent-to-treat population

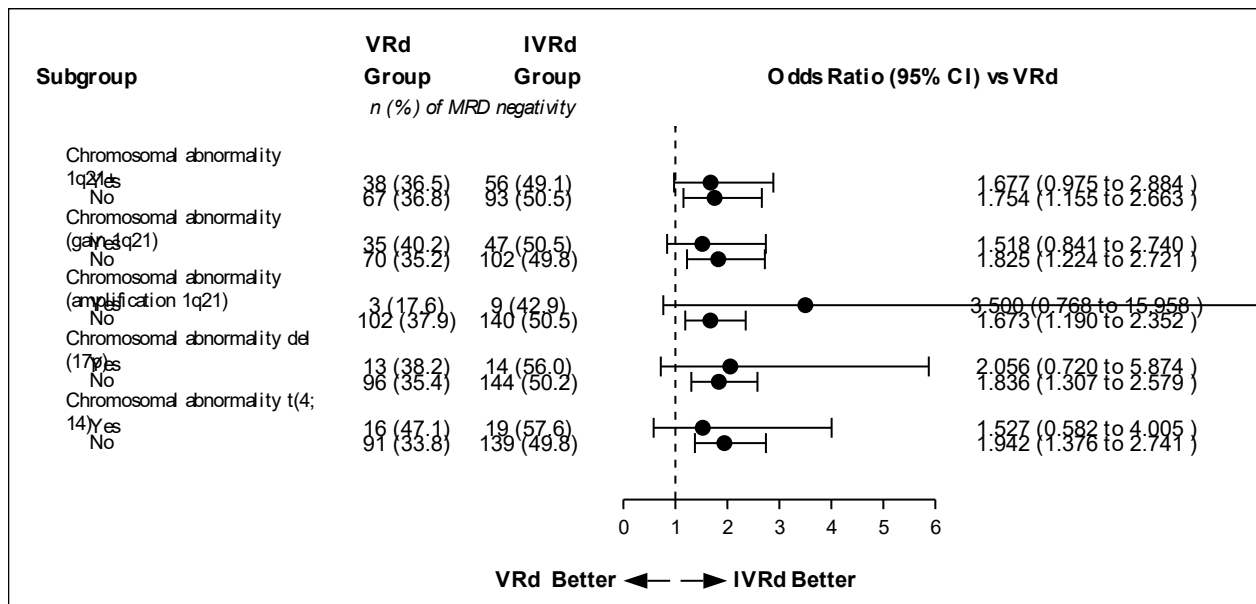


Figure 10. MRD negativity rate by NGF after induction phase - Subgroups analyses 3 (Forest plot) - Induction intent-to-treat population, study GMMG-HD7

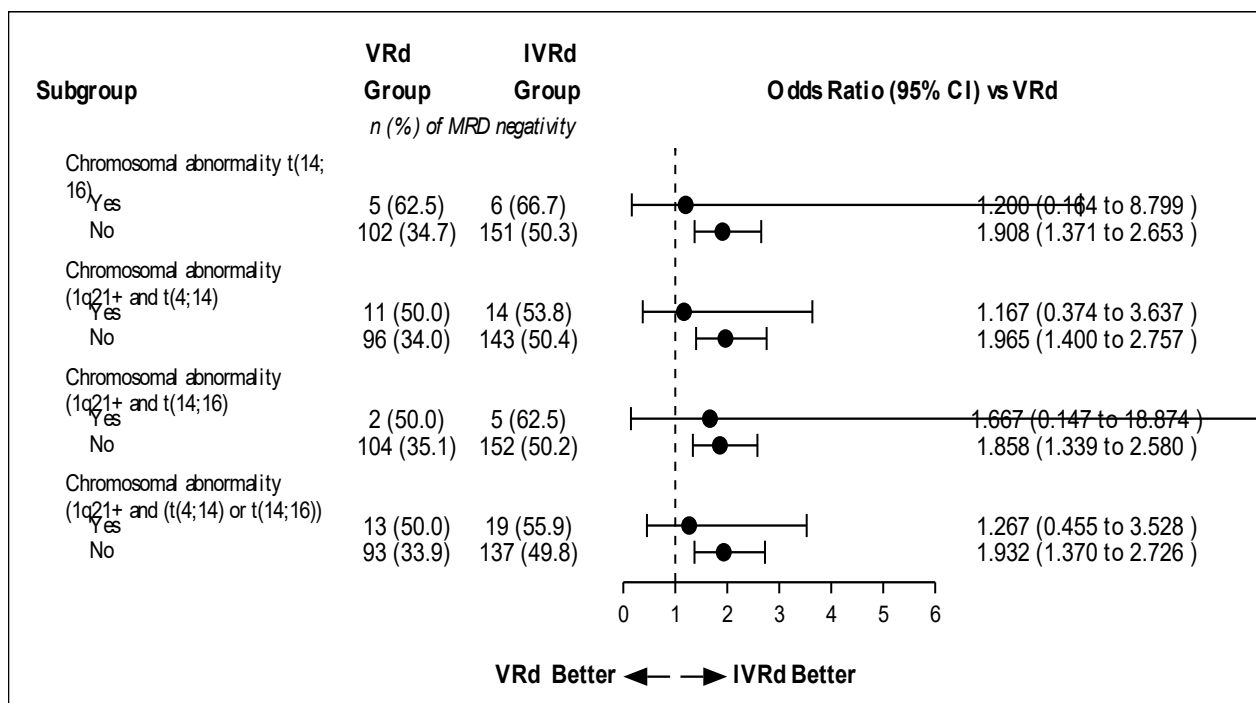


Figure 11. MRD negativity rate by NGF after induction phase - Subgroups analyses 4 (Forest plot) - Induction intent-to-treat population, study GMMG-HD7

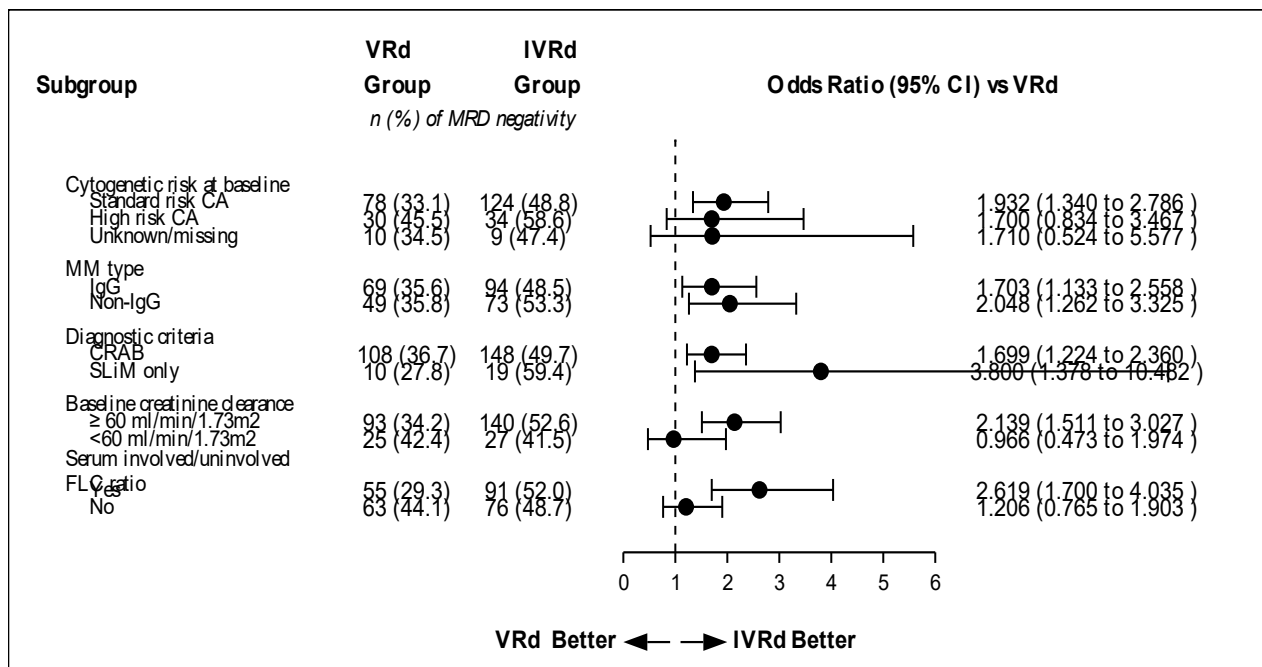
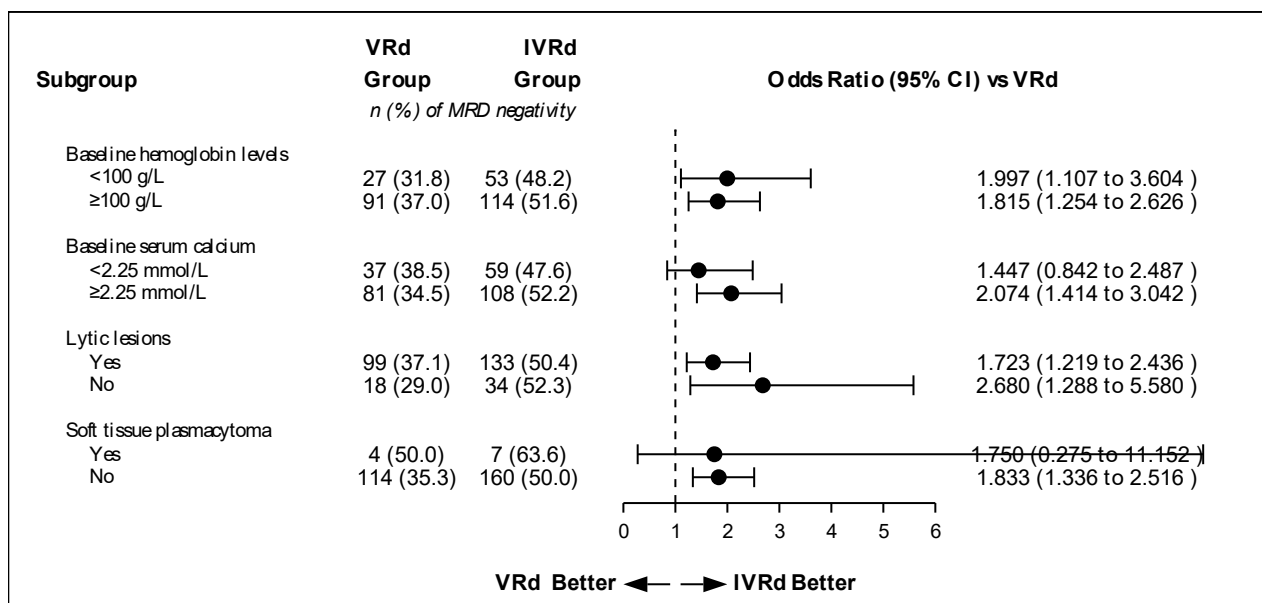


Figure 12. MRD negativity rate by NGF after induction phase - Subgroups analyses 5 (Forest plot) - Induction intent-to-treat population



BOR : Best Overall Response

Multivariate analysis

A multivariable analysis for MRD negativity was performed to identify prognostic factors among the demographic and baseline characteristic factors using logistic regression. The OR after adjustment is consistent with the primary analysis (adjusted OR 1.801 versus 1.838 for the primary analysis), and the p-values for baseline covariates were all greater than 0.2, suggesting that there were no confounding factors among the analysed covariates that may have influenced the treatment effect in the primary analysis of MRD negativity.

Progression-free survival from first randomisation regardless of second randomisation

PFS from first randomisation regardless of second randomisation are summarized in **Table 16**. At the time of the PFS cut-off, a total of 237 (71.6%) and 259 (78.2%) participants in the VRd and IVRd groups, respectively, did not have a PFS event and were censored. The reasons for censoring are summarised in **Table 17**.

Table 16. PFS from first randomisation regardless of second randomisation by treatment group - Induction intent-to-treat population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
Number (%) of events	94 (28.4)	72 (21.8)
Number (%) of patients censored	237 (71.6)	259 (78.2)
Kaplan-Meier estimates of PFS in months		
25% quantile (95% CI)	38.08 (27.565 to 47.836)	50.60 (42.283 to NC)
Median (95% CI)	NC (NC to NC)	NC (NC to NC)
75% quantile (95% CI)	NC (NC to NC)	NC (NC to NC)
Stratified ^a Log-Rank test p-value ^b		
vs VRd	-	0.0113
Stratified ^a Hazard ratio (95% CI)		
vs VRd	-	0.701 (0.516 to 0.953)
PFS probability (95% CI) ^c		
6 Months	0.917 (0.880 to 0.943)	0.960 (0.932 to 0.976)
12 Months	0.881 (0.839 to 0.912)	0.929 (0.894 to 0.952)
24 Months	0.830 (0.784 to 0.868)	0.864 (0.820 to 0.897)
36 Months	0.758 (0.706 to 0.803)	0.837 (0.791 to 0.873)
48 Months	0.695 (0.636 to 0.745)	0.770 (0.716 to 0.815)
60 Months	0.634 (0.558 to 0.699)	0.714 (0.640 to 0.776)
Number of patients at risk ^c		
6 Months	280 (84.6)	309 (93.4)
12 Months	265 (80.1)	291 (87.9)
24 Months	244 (73.7)	261 (78.9)
36 Months	215 (65.0)	246 (74.3)
48 Months	102 (30.8)	116 (35.0)
60 Months	7 (2.1)	6 (1.8)

PFS: Progression-free survival, CI: Confidence interval, NC: Not calculated, HR: Hazard ratio, IRT: Interactive Response Technology

Cut-off date: 31JAN2024 . Median follow-up time = 49.31 months. HR<1 favours IVRd arm

CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley

^a Stratified on randomisation factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

^b One-sided significance level is 0.014

^c Estimated using the Kaplan-Meier method

	VRd (N=331)	IVRd (N=331)
Events occurring more than 7 months after the last valid disease assessment are censored		

Table 17. PFS from first randomisation regardless of second randomisation - Description of censoring - Induction intent-to-treat population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
Number of patients censored [n(%)]	237 (71.6)	259 (78.2)
Reason of censoring		
Censored, follow-up ongoing	186 (56.2)	212 (64.0)
Censored, follow-up ended	51 (15.4)	47 (14.2)
No post-baseline assessment	8 (2.4)	4 (1.2)
Lost to follow-up	27 (8.2)	24 (7.3)
Events more than 7 months from last valid disease assessment	1 (0.3)	1 (0.3)
Progression disease	1 (0.3)	0
Death	0	1 (0.3)
Further anti-myeloma treatment	15 (4.5)	18 (5.4)

PFS: Progression-free survival

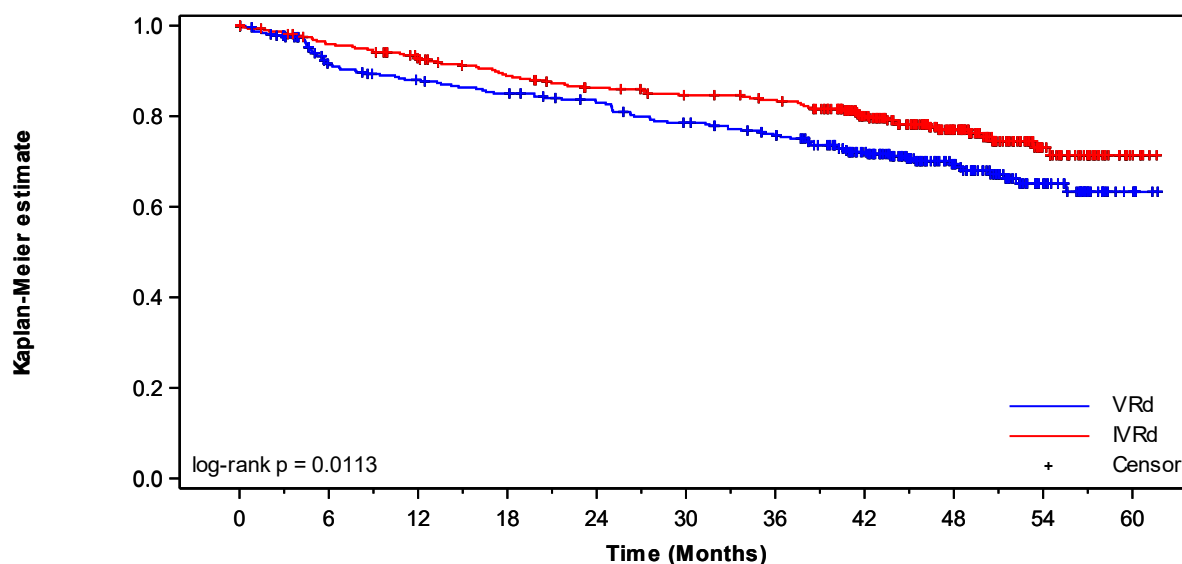
Cut-off date = 31JAN2024

Events occurring more than 7 months after the last valid disease assessment are censored

Patient is considered as Lost to follow up if the time between last disease assessment and cut off date is more than 7 months

A separation between the VRd and IVRd groups was observed from about 3 months onward in the PFS Kaplan-Meier curve (**Figure 13**).

Figure 13. PFS from first randomisation regardless of second randomisation - Kaplan Meier curves by treatment group - Induction intent-to-treat population, study GMMG-HD7



Number at Risk											
VRd	331	280	265	255	244	229	215	172	102	45	7
IVRd	331	309	291	274	261	252	246	189	116	44	6

Cut-off date = 31JAN2024

Median follow-up time = 49.31 months.

PFS: Progression-free survival, IRT: Interactive Response Technology

Log-Rank p value: Stratified on randomisation factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

One-sided significance level is 0.014

Events occurring more than 7 months after the last valid disease assessment are censored

A summary of the unweighted analyses is provided in **Table 18**, following the primary censoring rule (i.e., censoring for further anti-myeloma treatment and for progression or death occurring more than 7 months after the last valid disease assessment), and without any censoring rule (i.e., EMA censoring rule). In addition, the MAH performed additional sensitivity analyses for PFS by treatment sequence using IPW method without any censoring rule (i.e., EMA censoring rule).

Table 18. PFS from 1st randomisation by treatment sequence - Summary of inverse probability weight analysis and unweighted analysis

	Total number of events	VRd		IVRd		Hazard ratio (98.5% CI) vs VRd	P-value
		N (%) of events	Median (months) (95% CI)	N (%) of events	Median (months) (95% CI)		
PFS by treatment sequence (IVRd-R vs VRd-R)							
Main analysis by using IPW method: (FDA censoring rule) *	166	94 (28.4)	NC (55.556 to NC)	72 (21.8)	NC (NC to NC)	0.622 (0.424 to 0.912)	0.0066
IPW analysis with the EMA censoring rule	181	102 (30.8)	NC (51.351 to NC)	79 (23.9)	NC (NC to NC)	0.646 (0.448 to 0.931)	0.0085
Unweighted analysis with the FDA censoring rule	123	75 (22.7)	NC (51.351 to NC)	48 (14.5)	NC (NC to NC)	0.6 (0.417 to 0.862)	0.0026
Unweighted analysis without any censoring rule (EMA censoring rule)	135	80 (24.2)	NC (51.351 to NC)	55 (16.6)	NC (NC to NC)	0.643 (0.456 to 0.907)	0.0055
PFS by treatment sequence (IVRd-IR vs VRd-IR)							
Main analysis by using IPW method: (FDA censoring rule) *	166	94 (28.4)	NC (NC to NC)	72 (21.8)	NC (NC to NC)	0.791 (0.529 to 1.182)	0.1245
IPW analysis with the EMA censoring rule	181	102 (30.8)	NC (NC to NC)	79 (23.9)	NC (NC to NC)	0.765 (0.523 to 1.120)	0.0829
Unweighted analysis with the FDA censoring rule	108	60 (18.1)	NC (NC to NC)	48 (14.5)	NC (NC to NC)	0.727 (0.497 to 1.063)	0.0492
Unweighted analysis without any censoring rule (EMA censoring rule)	122	67 (20.2)	NC (NC to NC)	55 (16.6)	NC (NC to NC)	0.736 (0.515 to 1.052)	0.0459

PFS, progression-free survival; NC, not calculated; IPW, inverse probability weighting. Cut-off date = 31 January 2024

Note: FDA censoring rule means censoring PFS events for further anti-myeloma treatment and for progression or death occurring more than 7 months after the last valid disease assessment; EMA censoring rule means without censoring those PFS events.

PFS sensitivity analysis

The main PFS sensitivity analyses are summarized in **Table 19**.

Table 19. PFS from first randomisation regardless of second randomisation - Summary of main sensitivity analyses, study GMMG-HD7

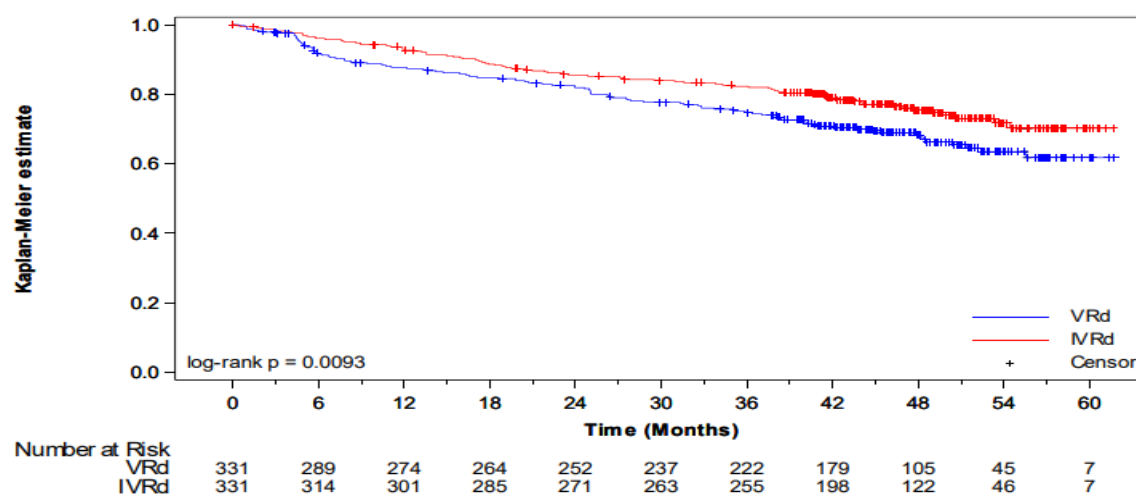
Sensitivity Analysis #		VRd		IVRd		Hazard ratio (95% CI) versus VRd	P-value
		N (%) of events	Median (months) (95% CI)	N (%) of events	Median (months) (95% CI)		
	PFS without censoring for further anti-myeloma treatment or censoring of progression or death occurring more than 7 months after the last valid disease assessment	102 (30.8)	NC (NC to NC)	79 (23.9)	NC (NC to NC)	0.704 (0.525 to 0.945)	0.0093
1	PFS without censoring for further anti-myeloma treatment	100 (30.2)	NC (NC to NC)	77 (23.3)	NC (NC to NC)	0.7 (0.52 to 0.943)	0.0091
2	PFS including initiation of further anti-myeloma treatment as an event	111 (33.5)	NC (NC to NC)	91 (27.5)	NC (NC to NC)	0.751 (0.569 to 0.991)	0.0209
3	PFS without censoring of progression or death occurring more than 7 months after the last valid disease assessment	95 (28.7)	NC (NC to NC)	73 (22.1)	NC (NC to NC)	0.703 (0.518 to 0.953)	0.0114
5	PFS using eCRF stratum R-ISS	94 (28.4)	NC (NC to NC)	72 (21.8)	NC (NC to NC)	0.689 (0.506 to 0.937)	0.0085
7	PFS censoring death events due to COVID-19 infections	93 (28.1)	NC (NC to NC)	69 (20.8)	NC (NC to NC)	0.679 (0.497 to 0.927)	0.0072
9a	PFS censoring participants randomised to receive isatuximab during maintenance (ie, group IIB) at second randomisation)	75 (22.7)	NC (NC to NC)	48 (14.5)	NC (NC to NC)	0.6 (0.417 to 0.862)	0.0026
9b	PFS censoring participants randomised to group IIB at second randomisation and without censoring events occurring more than 7 months after last valid assessment	75 (22.7)	NC (NC to NC)	49 (14.8)	NC (NC to NC)	0.612 (0.426 to 0.877)	0.0035

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; IVRd = VRd with isatuximab; N = number; NC = not calculated; PFS = progression-free survival; R-ISS = revised international staging system; VRd = induction therapy with lenalidomide/bortezomib/dexamethasone.

Kaplan-Meier curves for PFS from first randomisation regardless of maintenance without censoring for two or more missed visits or start of subsequent therapy (i.e. analyses according the EMA/CHMP/27994/2008/Rev.1) are shown in

Figure 14 to Figure 16.

Figure 14. PFS from first randomisation regardless of second randomisation without censoring for two or more missed visits or start of subsequent therapy - Kaplan Meier curves by treatment group - Induction ITT, study GMMG-HD7



Cut-off date = 31JAN2024

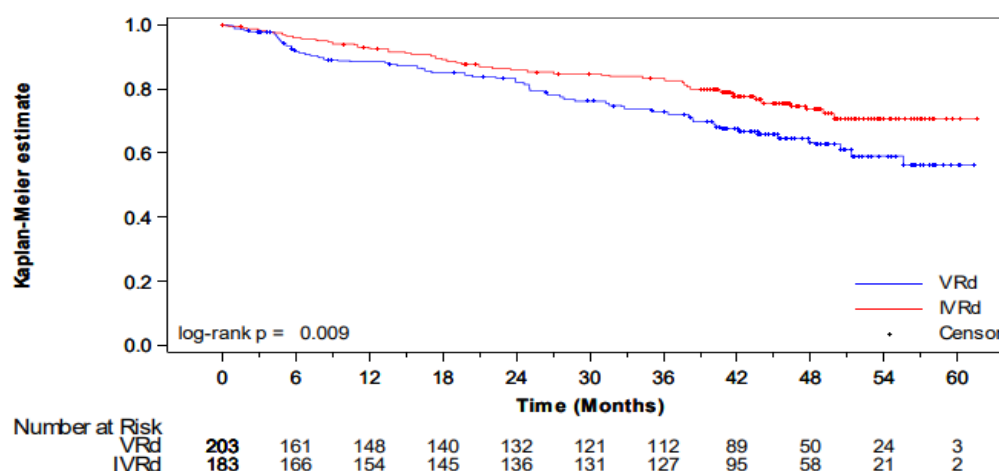
Median follow-up time = 49.31 months.

PFS: Progression-free survival, IRT: Interactive Response Technology

Log-Rank p value: Stratified on randomization factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

One-sided significance level is 0.014

Figure 15. PFS from first randomisation without censoring for two or more missed visits or start of subsequent therapy by induction treatment policy (arm IVRd-R vs arm VRd-R) - Inverse probability weighting - Weighted Kaplan Meier curves by treatment group - Induction ITT, study GMMG-HD7



Cut-off date = 31JAN2024

Median follow-up time = 49.31 months.

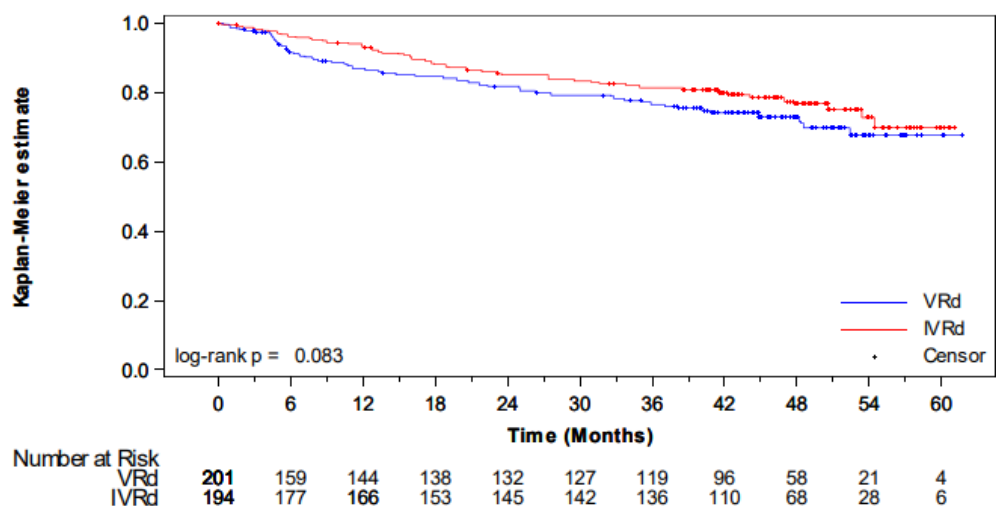
PFS: Progression-free survival, IRT: Interactive Response Technology, IPW : Inverse Probability Weighted

Weighted Log-Rank p value: Stratified on randomization factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

In this IPW analysis, weight is equal to 2 for patients randomized to receive treatment IIA during the maintenance period; weight is equal to 1 for patients who did not have the second randomization or who have an event before the second randomization (regardless the maintenance arm); and weight is equal to 0 for patients randomized to receive treatment IIB during the maintenance period.

Events occurring more than 7 months after the last valid disease assessment are censored

Figure 16. PFS from first randomisation without censoring for two or more missed visits or start of subsequent therapy by induction treatment policy (arm IVRd-IR vs arm VRd-IR) - Inverse probability weighting - Weighted Kaplan Meier curves by treatment group - Induction ITT, study GMMG-HD7

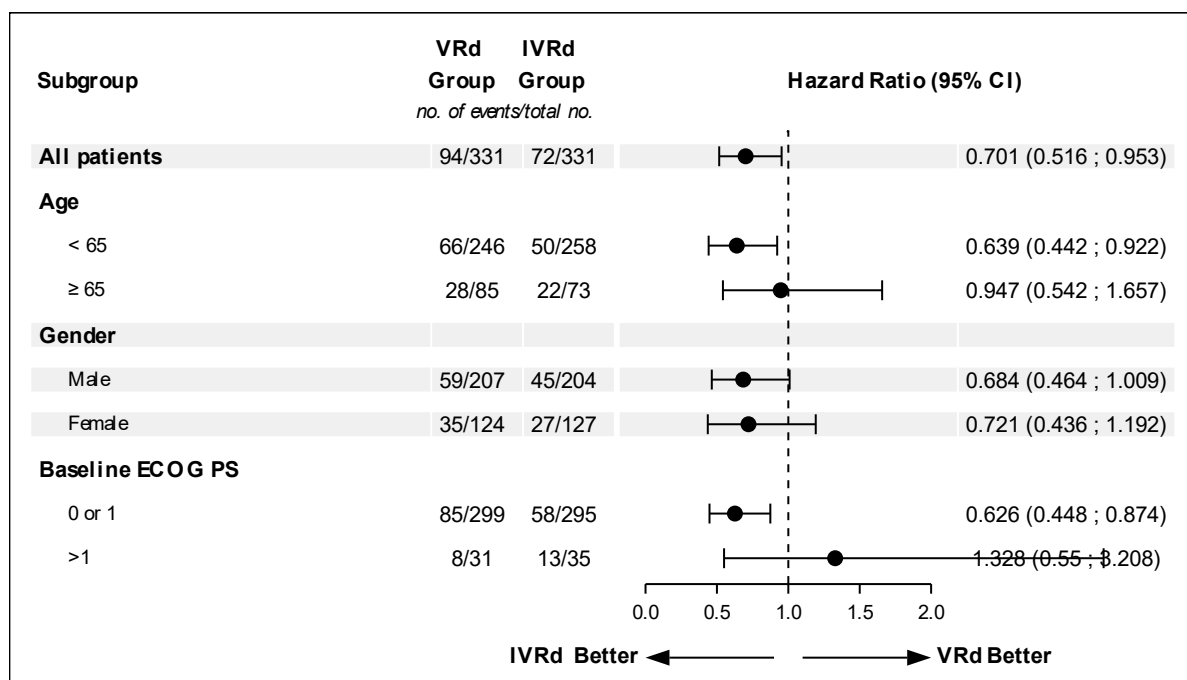


Cut-off date = 31JAN2024
 Median follow-up time = 49.31 months.
 PFS: Progression-free survival, IRT: Interactive Response Technology, IPW : Inverse Probability Weighted
 Weighted Log-Rank p value: Stratified on randomization factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).
 In this IPW analysis, weight is equal to 2 for patients randomized to receive treatment IIB during the maintenance period; weight is equal to 1 for patients who did not have the second randomization or who have an event before the second randomization (regardless the maintenance arm); and weight is equal to 0 for patients randomized to receive treatment IIA during the maintenance period.
 Events occurring more than 7 months after the last valid disease assessment are censored

PFS subgroup analysis

Forrest plots of multiple subgroup analyses of the primary endpoint are shown in Table 20.

Table 20. PFS from first randomisation regardless of second randomisation - Subgroups analyses 1 (Forest plot) by demographics/baseline characteristics - Induction intent-to-treat population, study GMMG-HD7



CI: Confidence interval, NC: Not calculated, PFS: Progression-free survival

Cut-off date = 31JAN2024

Events occurring more than 7 months after the last valid disease assessment are censored

PFS from first randomisation by induction treatment policy

Progression-free survival from first randomisation was analysed per the induction treatment policy (group IA-IIA versus group IB-IIA) to assess the treatment effect of addition of isatuximab to VRd induction in participants subsequently treated with standard-of-care lenalidomide maintenance. Such analysis was performed to mitigate a potential effect of second randomisation on the progression-free survival outcomes of induction treatment (**Table 21**).

Table 21. PFS from first randomisation by induction treatment policy (arm IVRd-R vs arm VRd-R) - Inverse probability weighting - Induction intent-to-treat population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
Number (%) of events	94 (28.4)	72 (21.8)
Number (%) of events during follow-up of patients not having second randomisation	8 (2.4)	5 (1.5)
Number (%) of events during induction or intensification	33 (10.0)	19 (5.7)
Number (%) of events during/after maintenance	53 (16.0)	48 (14.5)
Patients second randomised to arm R	34 (10.3)	24 (7.3)
Patients second randomised to arm IR	19 (5.7)	24 (7.3)
Number (%) of patients censored	237 (71.6)	259 (78.2)
Weighted Kaplan-Meier estimates of PFS in months		
25% quantile (95% CI)	31.573 (25.035 to 40.674)	49.018 (38.209 to NC)
Median (95% CI)	NC (55.556 to NC)	NC (NC to NC)

	VRd (N=331)	IVRd (N=331)
75% quantile (95% CI)	NC (NC to NC)	NC (NC to NC)
Stratified ^a IPW Log-Rank test p-value ^b vs VRd		0.0066
Stratified ^a IPW Hazard ratio ^d (95% CI) vs VRd		0.622 (0.424 to 0.912)
PFS probability (95% CI) ^c		
6 months	0.918 (0.882 to 0.943)	0.958 (0.930 to 0.976)
12 months	0.888 (0.849 to 0.918)	0.926 (0.889 to 0.951)
24 months	0.825 (0.773 to 0.866)	0.869 (0.818 to 0.906)
36 months	0.732 (0.672 to 0.782)	0.848 (0.794 to 0.889)
48 months	0.640 (0.574 to 0.698)	0.754 (0.686 to 0.809)
60 months	0.567 (0.488 to 0.639)	0.718 (0.642 to 0.781)
Number of patients at risk ^c		
6 months	153	161
12 months	140	144
24 months	124	128
36 months	105	119
48 months	48	53
60 months	3	1

PFS: Progression-free survival, CI: Confidence interval, NC: Not calculated, IPW : Inverse Probability Weighted, HR: Hazard ratio, IRT: Interactive Response Technology

Cut-off date: 31JAN2024 . Median follow-up time = 49.31 months. HR<1 favors IVRd arm. Events occurring more than 7 months after the last valid disease assessment are censored

CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley

In this IPW analysis, weight is equal to 2 for patients randomised to receive treatment IIA during the maintenance period; weight is equal to 1 for patients who did not have the second randomisation or who have an event before the second randomisation (regardless the maintenance arm); and weight is equal to 0 for patients randomised to receive treatment IIB during the maintenance period.

^a Stratified on randomisation factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

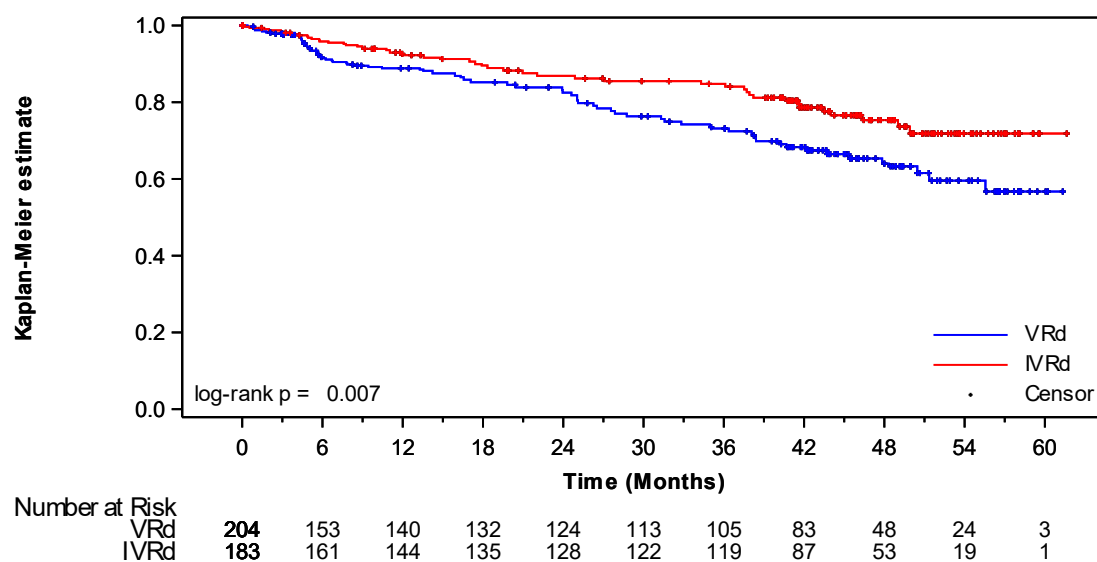
^b P-value from the inverse probability weighted log-rank test - One-sided significance level is 0.014

^c Estimated using the Kaplan-Meier method

^d The hazard ratio and its confidence interval will be estimated using the weighted Cox proportional hazards model.

The weighted Kaplan-Meier curves for PFS from first randomisation by induction treatment policy are provided in **Figure 17**.

Figure 17. PFS from first randomisation by induction treatment policy (arm IVRd-R vs arm VRd-R) - Inverse probability weighting - Weighted Kaplan Meier curves by treatment group - Induction intent-to-treat population, study GMMG-HD7



Cut-off date = 31JAN2024

Median follow-up time = 49.31 months.

PFS: Progression-free survival, IRT: Interactive Response Technology, IPW : Inverse Probability Weighted

Weighted Log-Rank p value: Stratified on randomisation factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

In this IPW analysis, weight is equal to 2 for patients randomised to receive treatment IIA during the maintenance period; weight is equal to 1 for patients who did not have the second randomisation or who have an event before the second randomisation (regardless the maintenance arm); and weight is equal to 0 for patients randomised to receive treatment IIB during the maintenance period.

Events occurring more than 7 months after the last valid disease assessment are censored

Overall survival from first randomisation regardless of second randomisation

Overall survival from first randomisation data are not yet mature and are planned to be formally tested only once at the final analysis of PFS from second randomisation (part 2) endpoint. OS data were summarised using descriptive statistics at time of PFS analysis (Table 22). The Kaplan-Meier OS curve is provided in Figure 18.

Table 22. Overall survival from first randomisation regardless of second randomisation by treatment group - Induction intent-to-treat population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
Number (%) of deaths	42 (12.7)	49 (14.8)
Number (%) of patients censored	289 (87.3)	282 (85.2)
Kaplan-Meier estimates of OS in months		
25% quantile (95% CI)	NC (NC to NC)	NC (NC to NC)
Median (95% CI)	NC (NC to NC)	NC (NC to NC)
75% quantile (95% CI)	NC (NC to NC)	NC (NC to NC)
Stratified ^a Hazard ratio (95% CI)		
vs VRd	-	1.138 (0.754 to 1.719)
Survival probability (95% CI) ^b		

	VRd (N=331)	IVRd (N=331)
6 Months	0.975 (0.951 to 0.988)	0.979 (0.956 to 0.990)
12 Months	0.959 (0.931 to 0.976)	0.951 (0.922 to 0.970)
24 Months	0.924 (0.889 to 0.948)	0.911 (0.875 to 0.937)
36 Months	0.891 (0.851 to 0.921)	0.880 (0.839 to 0.911)
48 Months	0.862 (0.817 to 0.897)	0.851 (0.806 to 0.886)
60 Months	0.855 (0.808 to 0.892)	0.833 (0.781 to 0.874)
Number of patients at risk ^b		
6 Months	310 (93.7)	322 (97.3)
12 Months	298 (90.0)	312 (94.3)
24 Months	286 (86.4)	291 (87.9)
36 Months	270 (81.6)	278 (84.0)
48 Months	154 (46.5)	165 (49.8)
60 Months	12 (3.6)	14 (4.2)

OS: Overall survival, CI: Confidence interval, NC: Not calculated, HR: Hazard ratio, IRT: Interactive Response Technology

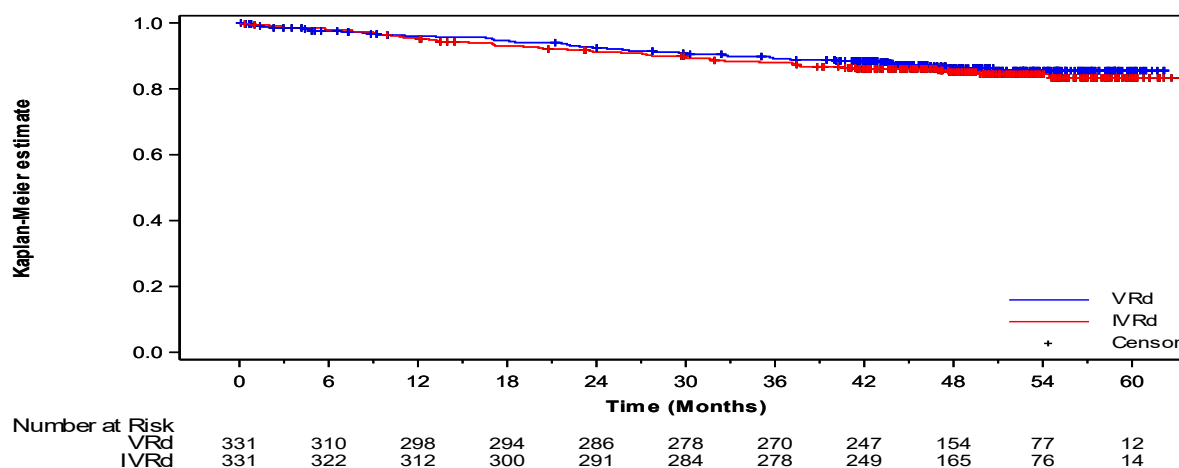
Cut-off date: 31JAN2024 . Median follow-up time = 49.31 months. HR<1 favours IVRd arm

CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley

^a Stratified on randomisation factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

^b Estimated using the Kaplan-Meier method

Figure 18. Overall survival from first randomisation regardless of second randomisation - Kaplan Meier curves by treatment group - Induction intent-to-treat population, study GMMG-HD7



Cut-off date = 31JAN2024

Overall survival from first randomisation by induction treatment policy (arm IVRd-R versus arm VRd-R)

With a median follow-up of 49.31 months by the cut-off date of 31 January 2024, the survival probability at 12 month (encompassing the induction and intensification periods) was 96% in VRd group and 95% in IVRd group (**Table 23**). Kaplan Meier curves are provided in **Figure 19**.

Table 23. OS from first randomisation by induction treatment policy (arm IVRd-R versus arm VRdR) - Inverse probability weighting - Induction intent-to-treat population, study GMMG-HD7

	VRd (N=331)	IVRd (N=331)
Number (%) of events	42 (12.7)	49 (14.8)
Number (%) of events during follow-up of patients not having second randomisation ^d	17 (5.1)	18 (5.4)
Number (%) of events during induction or intensification	4 (1.2)	6 (1.8)
Number (%) of events during/after maintenance	21 (6.3)	25 (7.6)
Patients second randomised to arm R	11 (3.3)	9 (2.7)
Patients second randomised to arm IR	10 (3.0)	16 (4.8)
Number (%) of patients censored	289 (87.3)	282 (85.2)
<i>Weighted Kaplan-Meier estimates of OS in months</i>		
25% quantile (95% CI)	NC (NC to NC)	NC (NC to NC)
Median (95% CI)	NC (NC to NC)	NC (NC to NC)
75% quantile (95% CI)	NC (NC to NC)	NC (NC to NC)
<i>Stratified^a IPW Hazard ratio^b (95% CI)</i>		
vs VRd		1.035 (0.617 to 1.737)
<i>OS probability (95% CI)^c</i>		
6 months	0.976 (0.953 to 0.988)	0.978 (0.954 to 0.989)
12 months	0.964 (0.937 to 0.979)	0.947 (0.913 to 0.967)
24 months	0.929 (0.891 to 0.954)	0.914 (0.872 to 0.943)
36 months	0.904 (0.859 to 0.935)	0.898 (0.853 to 0.929)
48 months	0.859 (0.802 to 0.900)	0.862 (0.811 to 0.901)
60 months	0.851 (0.794 to 0.894)	0.862 (0.811 to 0.901)
<i>Number of patients at risk ^c</i>		
6 months	179	172
12 months	169	162
24 months	160	150
36 months	150	143
48 months	86	83
60 months	8	3

OS: Overall survival, CI: Confidence interval, NC: Not calculated, IPW : Inverse Probability Weighted, HR: Hazard ratio, IRT: Interactive Response Technology

Cut-off date: 31JAN2024 . Median follow-up time = 49.31 months. HR<1 favors IVRd arm.

CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley

In this IPW analysis, weight is equal to 2 for patients randomised to receive treatment IIA during the maintenance period; weight is equal to 1 for patients who did not have the second randomisation; and weight is equal to 0 for patients randomised to receive treatment IIB during the maintenance period.

^a Stratified on randomisation factor according to IRT : Revised International Staging System (R-ISS) stage (I/II vs III vs Not classified).

^b The hazard ratio and its confidence interval will be estimated using the weighted Cox proportional hazards model

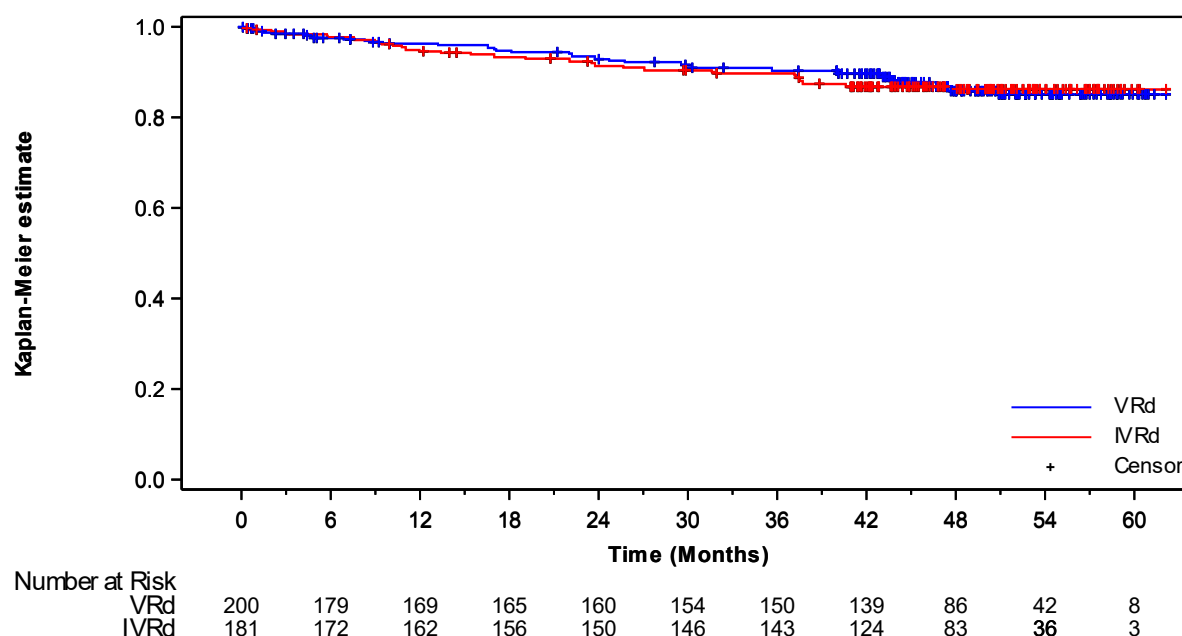
^c Estimated using the Kaplan-Meier method

**VRd
(N=331)**

**IVRd
(N=331)**

^d Includes one patient randomised in IVRd arm but not treated

Figure 19. OS from first randomisation by induction treatment policy (arm IVRd-R versus arm VRdR) - Inverse probability weighting - Weighted Kaplan Meier curves by treatment group - Induction intent-to-treat population, study GMMG-HD7



Cut-off date = 31JAN2024

Median follow-up time = 49.31 months.

OS: Overall survival, IRT: Interactive Response Technology, IPW : Inverse Probability Weighted

In this IPW analysis, weight is equal to 2 for patients randomised to receive treatment IIA during the maintenance period; weight is equal to 1 for patients who did not have the second randomisation; and weight is equal to 0 for patients randomised to receive treatment IIB during the maintenance period.

Other secondary endpoints

- PFS from first randomisation by induction treatment policy (group IA-IIB versus group IB-IIB)

For induction with IVRd compared to induction with VRd, followed by isatuximab+lenalidomide maintenance treatment in both groups, the IPW HR was 0.791 (95% CI: 0.529 to 1.182) at the cut-off date of 31 January 2024.

- MRD negativity rate at the end of intensification phase by NGF

In VRd, 163 (49.2% of VRd ITT) were MRD negative. In IVRd, 228 (68.9% of IVRd ITT) were MRD negative. The OR of IVRd over VRd was 2.281 (1.661 to 3.133) with one-sided p-value given for descriptive purpose being <0.0001. Where data were available at both timepoints, respectively 9 (2.7%) participants in VRd and 6 (1.8%) in IVRd lost their MRD negative status, and respectively 58 (17.5%) and 71 (21.5%) converted from MRD positive status after induction to MRD negative status after intensification.

- MRD[-] CR rate at the end of induction phase by NGF

After induction, 70 (21.1%) and 80 (24.2%) participants of the ITT-IND population were with CR and at least one evaluable sample for MRD assessment in VRd and IVRd, respectively. The MRD[-] CR rate was 14.5% (95% CI: 0.1089 to 0.1876) and 18.7% (95% CI: 0.1467 to 0.2336) of the ITT-IND population in VRd and IVRD, respectively. The OR was 1.360 (0.899 to 2.057) and the one-sided p-value provided for descriptive purpose was 0.0727.

- MRD[-] CR rate at the end of intensification phase by NGF

After intensification, 114 (34.4%) and 145 (43.8%) participants of the ITT-IND population were with CR and at least one evaluable sample for MRD assessment in VRd and IVRd respectively. the MRD[-] CR rate was 26.6% (95% CI: 0.2190 to 0.3169) and 40.5% (95% CI: 0.3515 to 0.4599) of the ITT-IND population in VRd and IVRD, respectively. The OR was 1.878 (1.353 to 2.607) and the one-sided p-value for descriptive purpose was $p < 0.0001$.

- Comparison of NGF results to NGS results

Participant samples at baseline were prioritized for MRD analysis by NGF (primary endpoint) and cytogenetics by iFISH (stratification factor information). As a result, the rate of NGS baseline missing samples was high and consequently, due to missing MRD data, concordance between the NGF and NGS methods was difficult to assess.

- CR at the end of induction

The CR data in this report were adjusted following the results of CE-IVD immunofixation Hydrashift 2/4 isatuximab IFE testing conducted by Labcorp Central Laboratory Services, Indianapolis, to remove isatuximab interference on M-protein measurement. CR was reached in 73 (22.1%) and 82 (24.8%) participants in the VRd and IVRd groups, respectively.

- CR at the end of intensification

With longer time for M-protein clearance and the impact of intensification, more participants in both groups had obtained a CR. A total of 123 (37.2%) (95% CI 0.3194 to 0.4261) in the VRd group and 154 (46.5%) (95% CI 0.4105 to 0.5206) in the IVRd group had CR as their best overall response after the intensification period.

- Time to first CR

the median (range) time to first CR during Part 1 was similar in both treatment groups: 159.5 days (111 to 482) in VRd group and 173 days (87 to 420) in IVRd group respectively

Ancillary analyses

Renal response

Complete renal response is defined in a participant with an eGFR < 50 mL/min/1.73m² at baseline as obtaining at least 1 eGFR assessment ≥ 60 mL/min/1.73m² during treatment. There was a trend towards a higher complete renal response rate in the IVRd group. Of the 39 participants in VRd group who had eGFR (MDRD) < 50 mL/min/1.73m² at baseline, 27 (69.2%) participants obtained a complete renal response while in the IVRd group, 33 out of 39 (84.6%) participants obtained a complete renal response. This completed renal response was durable (≥ 60 days) in 26/39 (66.7%) participants in VRd and 27/39 (69.2%) in IVRd, respectively.

Subsequent anti-myeloma treatment

Data on subsequent therapy are premature. As of the cut-off date, more participants in the VRd group (80 or 24.2%) had started subsequent therapy than in the IVRd group (56 or 16.9%). Of the participants receiving further antimyeloma therapy, most frequently used drug classes were Corticosteroids (85.0% in VRd, 67.9% in IVRd) and Proteasome Inhibitors (76.3% in VRd, 66.1% in IVRd) and IMiDs (65% in VRd, 73.2% in IVRd). Subsequent use of anti-CD38 was 68.8% in VRd and 51.8% in IVRd. Subsequent use of anti-BCMA was 10% in VRd and 5.4% in IVRd.

Patient-reported outcomes

Data were analysed at four time points to assess health-related quality of life (HRQoL) during the induction and intensification phases: at baseline, after Cycle 3, after last HDT, and at EOT. The EOT time point corresponds to participants who discontinued treatment during the induction or intensification phases and completed the questionnaire at the EOT visit. Only 24/331 (7.3%) and 15/331 (4.5%) participants in the VRd and IVRd groups, respectively, discontinued the induction or intensification treatment and completed the PRO questionnaires at EOT, therefore the results of the EOT timepoint are not interpretable at this time. Overall quality of life as measured by EORTC QLQ-C30 Global Health Score was maintained over time and similar in both treatment groups. Similarly, functioning, disease and treatment-related-symptoms, health status and health utility as measured by QLQ-C30, QLQ-MY20, and QLQ-EQ-5D-5L were maintained/did not significantly differ over time.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24. Summary of Efficacy for trial GMMG-HD7

Title: GMMG-HD7		
Study identifier	IIT15403	
Design	GMMG-HD7 is an ongoing prospective, multicentre (Germany), randomized, parallel group, open-label, Phase 3 clinical trial in transplant eligible NDMM patients evaluating the efficacy of Isatuximab combined with the approved triplet induction regimen bortezomib, lenalidomide + dexamethasone compared to the triplet induction regimen alone in.	
	Duration of main phase:	23 October 2018 (first patient enrolled) to 28 October 2024 (date of final PFS data analysis for Part 1; ongoing)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	IVRd induction (IB)	Isatuximab (10 mg/kg), bortezomib (1.3 mg/m ²), lenalidomide (25 mg), dexamethasone (20 mg) until disease progression, unacceptable toxicity, or participant's choice to discontinue (n = 331)
	VRd induction (IA)	Bortezomib (1.3 mg/m ²), lenalidomide (25 mg), dexamethasone (20 mg) until disease progression, unacceptable toxicity, or participant's choice to discontinue (n = 331)
	IR maintenance (IIB)	Isatuximab (10 mg/kg), lenalidomide (10 mg), dexamethasone (20 mg) until disease progression, unacceptable toxicity, or for a total of 3 years (n = 289)

	R maintenance (IIA)		Lenalidomide (10 mg), dexamethasone (20 mg) until disease progression, unacceptable toxicity, or for a total of 3 years (n = 271)
Endpoints and definitions	Primary endpoint	MRD negativity rate	MRD negativity after induction (assessed by NGF; sensitivity at least 10 ⁻⁵), defined as proportion of participants with negative MRD after induction
	Secondary endpoint	PFS regardless of maintenance	PFS, defined as time from first randomisation to date of first documented PD or date of death from any cause, whichever occurred first, regardless of second randomisation (overall group IA versus IB comparison)
	Secondary endpoint	PFS with standard R maintenance	PFS from first randomisation by induction treatment policy with standard maintenance (group IA-IIA versus group IB IIA)
	Secondary endpoint	OS with standard R maintenance	OS, defined as the time from first randomisation to time of death from any cause, by induction treatment policy with standard maintenance (group IA-IIA versus group IB IIA)
	Secondary endpoint	OS regardless of maintenance	OS regardless of second randomisation (overall group IA versus IB comparison)
Database lock	21-Apr-21 for MRD; 22-May-24 for final PFS analysis		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	VRd induction	IVRd induction
	Number of subject	331	331
	MRD negativity rate: n (%)	118 (35.6%)	167 (50.5%)
	95% CI	30.49 to 41.07	44.93 to 55.97
	Median PFS regardless of maintenance (months)	NC	NC
	95% CI	NC to NC	NC to NC
	Median PFS with standard R maintenance (months)	NC	NC
	95% CI	55.56 to NC	NC to NC
	Median OS with standard R maintenance (months)	NC	NC
	95% CI	NC to NC	NC to NC
	Median OS regardless of maintenance (months)	NC	NC
	95% CI	NC to NC	NC to NC

Effect estimate per comparison	Primary endpoint MRD negativity rate	Comparison groups	IA vs IB
		OR	1.84
		95% CI	1.35 to 2.51
		P-value	<0.0001 ^a
	Secondary endpoint Median PFS regardless of maintenance	Comparison groups	IA → IIA or IIB vs IB → IIA or IIB
		HR	0.700
		95% CI	0.52 to 0.95
		P-value	0.0113 ^b
	Secondary endpoint Median PFS with standard R maintenance	Comparison groups	IA → IIA vs IB → IIA
		HR	0.62
		95% CI	0.42 to 0.91
		P-value	0.0066 ^c
	Secondary endpoint Median OS with standard Rd maintenance	Comparison groups	IA → IIA vs IB → IIA
		HR	1.036
		95% CI	0.62 to 1.74
		P-value	NC
	Secondary endpoint Median OS regardless of maintenance	Comparison groups	IA → IIA or IIB vs IB → IIA or IIB
		HR	1.14
		95% CI	0.75 to 1.72
		P-value	NC
Notes	^a p-value from logistic regression including the randomisation factor from IRT, Revised International Staging System (R-ISS) stage (I or II versus III versus not classified). One-sided significance level is 0.01667. ^b Stratified on R-ISS, one-sided significance level is 0.014. ^c Stratified on R-ISS, p-value from the inverse probability weighted log-rank test. One-sided significance level is 0.014.		

Clinical studies in special populations

Patients older than 70 years of age were excluded from study entry, as the target population (transplant eligibility) is based on an age cut-off.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dosing – This is the first registration study in which isatuximab was added to an induction regimen preceding stem cell transplantation. Induction therapy was divided into three 42-day cycles, which falls within the four to six 28-day induction cycles recommended by the [ESMO Clinical Practice Guidelines](#). The dosing regimen that was selected for study GMMG-HD7 was based on previous experience from combination and monotherapy regimens in transplant ineligible patients across the isatuximab

developmental program. The dose of 10 mg/kg Q1W for 5 weeks in the first 6-week cycle, followed by once every 2 weeks in subsequent cycles was previously used in combination with bortezomib, lenalidomide + dexamethasone, pomalidomide + dexamethasone and carfilzomib + dexamethasone. After induction, patients received HDT-ASCT (without addition of the IMP). This was then followed by the maintenance phase; no consolidation with (I)VRd was given. This can be agreed, as VRd consolidation is not considered standard of care. During the 3-year maintenance phase after transplantation (39 cycles of 28 days/cycle), a similar regimen with receding frequency of isatuximab dosing was tested. Isatuximab was given at a dose of 10 mg/kg Q1W during the first cycle and Q2W in cycles 2 and 3. Starting with Cycle 4 of maintenance treatment, the schedule was again switched to a Q4W administration. For participants still in remission after 36 months of maintenance therapy, it was recommended to continue lenalidomide maintenance therapy until disease progression outside of the study protocol. While the duration of isatuximab treatment and the dosing interval during maintenance were not formally tested, and it is therefore unknown whether the most optimal regimen was selected, this strategy is not objected, since there is no strong consensus in the field on the duration of maintenance therapy, and similar strategies for other anti-CD38 mAbs have led to a positive B/R in other applications.

Study design – Study GMMG-HD7 is an ongoing phase 3, randomised, open-label, multicentre study comparing induction treatment with IVRd versus VRd (part 1) and maintenance treatment with IR versus R alone (Part 2) in participants with newly diagnosed MM who are eligible for ASCT. A screening phase of up to 21 days preceded inclusion into the study. The first randomisation before start of induction treatment was stratified by R-ISS (I/II versus III versus not classified). After the induction period and before second randomisation, participants followed a standard intensification phase (standard HDT + ASCT) without study-specific therapeutical intervention. Then, participants underwent a second randomisation (Part 2 of study) stratified by R-ISS I/II versus III versus not classified, and MRD negativity after HDT (no versus yes versus unknown).

One pivotal study could be acceptable if data from this study are statistically compelling and clinically relevant, and internal consistency is shown, amongst other prerequisites ([CPMP/EWP/2330/99](#)).

The study was investigator-initiated and was conducted according to a protocol and SAP that was drafted by the academic sponsor group. The current application, however, is based on the SAP for the EU that the MAH developed when the study was well underway. In general, the study design of pivotal study GMMG-HD7 is considered acceptable for assessing the add-on effect of isatuximab on top of the established VRd regimen during the induction phase (part 1) of the study.

The stratification factors (R-ISS stage and MRD negativity after HDT) have prognostic and predictive impact in this setting and are deemed appropriate.

Study GMMG-HD7 was only conducted in hospitals across Germany. It is generally not preferred to perform clinical trials in a single country, as this raises concerns about extrapolation of results to the general European population. However, it can be reasonably assumed that the treatment landscape of patients in the German trial sites is comparable to that of other European countries.

As patients entered the intensification phase, they could receive either a single transplant, or a tandem transplant, depending on whether a CR was achieved after the first transplant and whether the patient was considered high-risk. This introduces a potential bias in the results, as the number of tandem transplants was not balanced between the arms (34% in the VRd arm vs. 25.6% in the IVRd arm). Furthermore, every patient had a different time-to-randomisation for part 2, depending on when haematological recovery occurred after intensification (with a maximum of 90 days) and the patient was considered fit for maintenance. Taken together, there is significant heterogeneity in the duration

of the intensification phase, which may be of influence when assessing a time-to-event endpoint, like PFS. However, this bias is likely to be conservative.

Study participants – Inclusion and exclusion criteria adequately reflect newly diagnosed patients for whom HDT and ASCT would be part of the intended treatment plan. The diagnostic criteria for MM are acceptable and widely recognized (monoclonal plasma cells in the bone marrow $\geq 10\%$ or presence of a biopsy proven plasmacytoma and presence of at least one CRAB or SLiM CRAB criterion). Patients with severe cardiac, hepatic or renal comorbidities or with severe underlying infections were excluded from participation, which is endorsed, as these patients would not be considered transplant eligible.

For the second round of randomisation after intensification, patients had to pass a new set of inclusion criteria. These inclusion criteria encompass recovery of the haematopoietic system after transplant, which is endorsed. Cardiac, hepatic and renal function, and infections were listed as exclusion criteria for second randomisation and patients must have an ECOG PS ≤ 2 . Since only 4 patients failed inclusion criteria for maintenance therapy, indicating that there was no rigorous re-selection of fit patients, this issue is not pursued.

Treatments – A third of patients received emergency treatment with a cumulative dose of up to 160 mg of dexamethasone or equivalent before enrolment. The treatment schedule for the backbone treatment of the induction period of the study is identical to the previously authorized schedule in patient with NDMM ineligible to an ASCT and globally in line with current guidelines for induction therapy.

Objectives, endpoints – As outlined in the reflection paper on the use of measurable residual disease as a clinical endpoint in multiple myeloma studies adopted by CHMP in October 2021, MRD is not considered an acceptable surrogate endpoint for PFS/OS for regulatory purposes. It has not been demonstrated to what extent the difference in MRD negativity between the two treatment arms actually translates into a clinical benefit. Furthermore, it is unclear whether the chosen timepoint for measuring MRD (right after induction treatment, i.e. after about 4.5 months of treatment) is optimal ([Xu et al., Dynamics of MRD in MM](#)). Sustained MRD negativity may have more predictive power than determination of the MRD status of patients at a single point in time. The estimand strategies to handle intercurrent events for the MRD negativity endpoint are considered acceptable.

The MAH sought SA (EMA/SA/0000099699 issued in October 2022) and this SA stated that: "... a positive PFS result will be required at the time of MAA, as well as OS results showing no detrimental effect". Determination of the benefit of isatuximab during induction thus relies heavily on the secondary endpoint PFS. Two PFS comparisons were made: one where all patients were compared based on first randomisation, regardless of second randomisation, and one where PFS was compared based on first randomisation only in the patients that were re-randomised to the standard maintenance regime (i.e. maintenance without isatuximab). This latter analysis is most informative regarding the benefit of isatuximab addition to the induction regimen. The choice for PFS to support the main outcome variable is agreed, because of the long OS time that is expected in first-line MM patients.

Interpretation of the HRQoL endpoint is hindered by the open-label design of the study.

Sample size – A sample size calculation was made in the protocol for both primary endpoints, showing the need to recruit 514 patients for PFS from second randomisation and 662 patients for MRD negativity. The SAP added sample size information for a secondary endpoint, PFS from first randomisation, with the need to observe 159 PFS events. The sample size calculations are agreed.

Randomisation, blinding – Randomisation and stratification factors are considered acceptable. During the operational study conduct, there was no blinding of the investigators, due to the overt differences in the participant management in the treatment groups (pre-medication previous to

administration of isatuximab and additional IV infusions for isatuximab). A central laboratory was used to analyse all patient samples in a blinded fashion. The GMMG-HD7 trial was investigator-initiated and the MAH was not involved in the operational conduct of the study. Therefore, there was no central confirmation of a PFS event at the time that such an event was registered by the investigator. Instead, this central confirmation took place at a later timepoint after the operational part of the study (part 1) was already completed. Possible bias due to the unblinded investigator making the decision on whether or not to view and treat a patient as having PD, did not impact the results much as PFS by investigator and PFS by independent review were largely similar and for most part based on objective biochemical data (> 70%). Data were later transferred to the MAH in an unblinded fashion for performing the efficacy/safety analyses reported here. The topline results were presented by the team of investigators to the MAH (see below).

Statistical methods

Multiplicity

The academic sponsor protocol considered both study parts as independent studies, given the two randomisations, and consequently, controlled the type I error for each part separately (i.e. 0.025 one-sided for each part). When the study was well advanced (recruitment ended September 2020, second randomisation complete January 2022, data cut-off MRD in April 2021), the MAH proposed in their EU-SAP dated 21 April 2022 (original version of the statistical analysis plan was April 2021) a hierarchical testing strategy starting with an alpha split between the induction phase (two thirds of a one-sided 2.5% alpha) and the maintenance phase (one third of a one-sided 2.5% alpha). Two issues were raised regarding multiple testing across part 1 and 2, which was already highlighted in the CHMP scientific advice (received 13 October 2022).

Firstly, two randomisations for part 1 and part 2 in a study with the same patients do not automatically imply that regulatory decisions on the first part can be made independently of the second part or vice versa. Especially if the effect seen in part 1 is dependent on the treatment received in part 2 (i.e. induction by maintenance interaction). In that case, the full study would need to be completed in order to be able to judge the efficacy of the different treatment sequences that were applied, i.e. IA-IIA vs IA-IIB vs IB-IIA vs IB-IIB. It is questionable whether a (key) endpoint like PFS from part 1 (induction) regardless of part 2 (maintenance) can be interpreted in case of induction by maintenance interaction, or at all (the interpretation of "effect of induction combined with a 50% chance to get one or the other maintenance" may be questionable). Due to these issues, the MAH has agreed to submit the results from Part 2 of the study (i.e. the effect of addition of isatuximab to maintenance therapy) when available. Nonetheless, from a clinical point of view, addressing the add-on effect of a drug during induction and during maintenance treatment separately is welcomed.

The second issue is that key endpoints like PFS from first randomisation (induction + HDT) and PFS from second randomisation (maintenance) are likely correlated because they are based on the same patients and, partially, on the same PFS events, if a PFS event occurs after second randomisation. The scientific advice thus stated that a study-wise control of the type I error should be implemented. The updated (27 September 2023) EU-SAP follows this and sets one type I error ($\alpha=0.025$ one-sided) for the whole study (across induction and maintenance). However, more weight in testing was given to the induction part (2/3 of α) without motivation. Due to the open-label setting and possibly reasonably mature PFS after second randomisation data at the moment that the SAP was updated, it cannot be excluded that this amendment was data driven. This is, however, unlikely for the following reasons. Firstly, the MAH explained that they put more weight on the induction part of the study in order to have results for induction available earlier (as fewer events are needed with added weight), which is acknowledged. In addition, following the multiplicity testing strategy, α would be reallocated from the induction to maintenance part, which means that more than 1/3 α could be

allocated to the maintenance part in case induction PFS results were to be statistically significant. This appears to be sensible planning. Finally, the results were borderline statistically significant. It is unlikely that the MAH would jeopardise the study integrity where regardless of the choice of weights, statistical significance for critical endpoints would be borderline.

The rationale for the chosen order in which the endpoints were tested or for the chosen split of alpha between endpoints in each part of the study was not explained. However, an analysis under a conservative scenario (no alpha reallocation between the two study parts and equal alpha split between both parts: 1.25% one-sided), showed that results on PFS from first randomisation are similar (close under or above statistical significance), depending on the censoring rule (EMA or FDA) and adjudication (investigator or independent review).

An interim analysis was planned for PFS from first randomisation. It used O'Brien-Fleming alpha-spending rules for both interim and final analyses of this endpoint. Using this alpha spending function is agreed, although it should be noted that the use of an interim analysis for PFS is not recommended ([EMA/CHMP/27994/2008/Rev.1](#)). This concern is alleviated, as the study was not stopped at the interim analysis.

Statistical analysis

Primary endpoint: MRD negativity

The statistical analysis methods and missing data handling choices are considered appropriate for MRD negativity; nevertheless as explained above the key endpoint of interest is PFS.

Secondary endpoint: PFS from first randomisation

Due to the multiplicity issues described above, it is not clear if the following treatment comparisons (IA vs IB, IA-IIA vs IA-IIB, IB-IIA vs IB-IIB, IA-IIA vs IB-IIA, IA-IIB vs IB-IIB) are unbiased, as is the clinical relevance for such comparisons. As already indicated in the EMA scientific advice (EMA/SA/0000099699), the induction regardless of maintenance effect does not correspond to a clinically relevant estimand. A claim 'regardless of maintenance treatment by SoC or isatuximab' can only be based on a positive effect on both maintenance treatments separately, as the estimate would depend on the relative frequencies of use of each maintenance regimen, which are unknown. The most clinically relevant comparison is thus the induction treatments followed by standard maintenance (IA-IIA vs IB-IIA). Regarding estimation of this comparison, the analysis based on the IPW method replaces patients that were randomised to IIB (isatuximab add-on maintenance) by patients that were randomised to IIA (standard of care maintenance). This is at first sight reasonable given the counterfactual question ("what if the patients randomised to IIB were randomised to IIA"). However, for patients randomised to IIB, data after maintenance is missing data for the counterfactual ("what if the patients randomised to IIB were randomised to IIA"). Therefore, for these patients (randomised to IIB) no events after maintenance randomisation should be counted. The IPW-based analysis, however, does include events after maintenance for these patients, as they are replaced by patients randomised to IIA at maintenance, including their available follow-up during maintenance. Unweighted analyses that censor patients from the moment that they are randomised to the experimental maintenance therapy (IR), do not have this problem of counting events after maintenance for patients randomised to IIB. These analyses were requested, and are considered the most informative for decision making and the prescribers.

The preferred estimand for regulatory decision-making for PFS is without any specific censoring rules for events occurring after further anti-myeloma therapy and for late events. Although this was not the primary handling of intercurrent events, an analysis using these censoring rules yielded a hazard ratio similar to the MAH's main analysis for the 'regardless of maintenance' analyses and provided similar Kaplan-Meier curves (see the results section).

Secondary endpoint: OS from first randomisation

Aside from the question of comparison between the different treatment groups, statistical analysis choices for OS are in line with standard practice (treatment policy for all intercurrent events) and are, as such, acceptable. Fewer sensitivity analyses were conducted for this endpoint.

Conduct of the study – The study was performed according to the protocol drafted by the academic sponsor, GMMG and enrolment and both randomisations were completed under protocol version 1.2.

A total of 5 protocol versions were used during the executive phase of the study. During the recruitment period, only minimal changes to the inclusion/exclusion criteria were made (mostly clarifications). No changes were made to the primary endpoints' definition in any of the protocol amendments and other changes were minor and did not impact study conduct or outcome. As more than 86% of events for PFS and OS had already occurred before implementation of the major protocol changes in version 4, changes in the assessment of outcomes are considered unlikely.

The study initially had one statistical analysis plan but was later equipped with two additional statistical analysis plans, Sanofi-EU and Sanofi-US, to reflect the different choices of primary endpoints for different regulatory authorities. Each SAP has its own testing strategy. While this is not preferred, it is not prohibited in ICH E17 to have more than one statistical analysis plan as a separate document, if this is required by more than one regulatory authority

Efficacy data and additional analyses

Participant disposition - A total of 662 participants were enrolled in the study. Of these participants, 328 received induction treatment with VRd, and 330 patients received induction treatment with IVRd. After induction therapy, 603 (91.1%) participants (291 [87.9%] in VRd and 312 [94.3%] in IVRd) were treated during intensification. Two participants directly moved from induction treatment to maintenance without HDT, seven other participants were mobilized and moved into maintenance without any HDT. In total, 403 out of 603 (66.8%) participants received only 1 stem cell transplantation (HDT1) (179/291 [61.5%] participants in VRd and 224/312 [71.8%] participants in IVRd). More participants in the VRd group (99/291 [34%]) than in the IVRd group 80/312 [25.6%] received a second stem cell transplantation (HDT2). At the time of the cut-off for the final analysis for Part 1 of the study, all participants had completed the intensification phase. Overall, 60 (18.1%) in VRd and 42 (12.7%) in IVRd of the ITT-IND participants were not randomised into the maintenance phase, primarily due to treatment discontinuation during previous periods, i.e., 57 (17.2%) participants in VRd and 41 (12.4%) participants in IVRd, with the most common overall reasons being AE and withdrawal of consent.

Deviations – Protocol deviations were related to induction treatment, HDT/intensification, study treatment, inclusion/exclusion criteria, safety and study conduct.

Most of the critical or major protocol deviations were prevalent in low numbers overall and balanced between treatment groups, with no apparent distribution pattern, and, therefore, were unlikely to have any impact on the overall outcome of the study.

Baseline data – The baseline demographics and disease characteristics (including myeloma subtypes) are comparable across the two study arms ($\leq 10\%$ difference; only exception: baseline Bone marrow plasma cell $\geq 60\%$: 40.2 % in VRd arm and 51.1% in IVRd arm), and are representative of the target population, i.e. a rather fit patient population with NDMM with low levels of comorbidity that could go

through screening period without immediate need for initiation of anti-myeloma treatment. Interestingly, most of the known poor prognostic factors were over-represented in the IVRd arm, namely: Increased beta2 microglobulin / hypoalbuminemia / increased LDH, and a greater proportion of ISS and R-ISS grade 2 and above patients, however, this imbalance does not favour the treatment arm.

Outcomes – The study's primary endpoint, MRD negativity (sensitivity level of $\leq 10^{-5}$ with NGF) after induction, was met. The study demonstrated a significant improvement in MRD negativity for patients who received induction treatment with isatuximab in combination with VRd vs. VRd alone: OR = 1.84 (95% CI 1.35 to 2.51). The one sided p-value of <0.0001 met the pre-specified p-value boundary of 0.01667. At the end of induction, valid MRD data were obtained for 87.3% of patients. Participants without MRD assessment at the end of the induction period were considered non-responders (i.e. MRD positive). The MRD negativity rate at the end of induction in the IVRd group was 50.5% (95% CI: 0.4493 to 0.5597), compared to 35.6% (95% CI: 0.3049 to 0.4107) in the VRd group, demonstrating a 14.8% increase in MRD negativity upon addition of isatuximab to the VRd triplet. When participants without MRD assessment at the end of induction were excluded, the OR = 1.759 (95% CI: 1.272 to 2.433, p=0.0003). It is difficult to interpret whether this increase is clinically relevant, since MRD negativity has not been validated as a surrogate endpoint.

A tipping point analysis and multiple imputation analysis were conducted to assess the impact of missing data on the MRD negativity rate at the end of induction in the ITT IND population. These results were consistent with the primary analysis, thereby supporting the robustness of the conclusion.

The treatment effect remained in favour of the IVRd group (OR>1), regardless of how the values were imputed in both groups. In most cases, the p-value remained significant (p<0.017), except for cases where most missing data in the VRd group would have been MRD negative, while most missing data in the IVRd group would have been positive. Multivariable analysis for MRD negativity was performed suggesting that there were no confounding factors among the analysed covariates that may have influenced the treatment effect in the primary analysis of MRD negativity.

PFS regardless of maintenance treatment: At the time of the PFS cut-off, a total of 237 (71.6%) and 259 (78.2%) participants in the VRd and IVRd groups, respectively, did not have a PFS event and were censored. At a median follow-up of 49.31 months, in the ITT-IND population, 94 (28.4%) and 72 (21.8%) participants had PFS events (primarily disease progression) in the VRd and IVRd groups, respectively. The HR was 0.701 (95% CI: 0.516 to 0.953) and was higher than the treatment effect assumption (HRSAP (IVRd vs VRd) =0.58) as defined in the SAP. At 48 months, the PFS probability was 69.5% in the VRd group and 77.0% in the IVRd group. The one-sided stratified log rank test resulting from the comparison of PFS between the two groups was statistically significant with a p-value of 0.0113, which met the prespecified efficacy boundary of 0.014. A separation between the VRd and IVRd groups was observed from about 3 months onward in the PFS Kaplan-Meier curve. The IVRd line remained above the VRd line throughout follow up. For all of the sensitivity analyses, the findings suggest a positive treatment effect for the IVRd group. All HRs <1 (ranged from 0.6 to 0.751) and almost all were statistically significant (range of p-values 0.0026 to 0.0209). All subgroup analyses supported the IVRd regimen, except for baseline ECOG PS >1, however the number of patients in that subgroup was very small, and the CI did cross 1. In a sensitivity analysis, the HR and the Kaplan-Meier curves for PFS from first randomisation regardless of maintenance, and by treatment sequence were provided without censoring for two or more missed visits or start of subsequent therapy (in line with [EMA/CHMP/27994/2008/Rev.1](https://www.ema.europa.eu/en/medicines/human/CTX/CHMP/27994/2008/Rev.1)). These were in line with the corresponding curves for the analyses using the primary censoring rule.

PFS with SOC maintenance: The IPW HR was 0.622 (95% CI: 0.424 to 0.912). The one-sided stratified IPW log rank test resulting from the comparison of PFS between the 2 groups was statistically

significant with a p-value of 0.0066, which is less than the prespecified efficacy boundary of 0.014. The median weighted KM estimates of PFS were not reached in either group. For the induction followed by the SOC lenalidomide maintenance patients, the weighted PFS probability at 36-months was 84.8% in IVRd group versus 73.2% in VRd group. The KM PFS curve shows an early separation with the IVRd line remaining above the VRd line throughout the follow up period. The unweighted analysis based on the EMA censoring rules showed a HR of 0.643 (95% CI: 0.456 to 0.907).

OS data were very immature, with 87.3% and 85.2% of patients censored in the VRd and IVRd arm, respectively. This is in line with the long survival that is expected in NDMM patients. The KM curves mostly overlap. OS regardless of maintenance treatment: HR = 1.14 (95% CI 0.75 to 1.72; p-value NC); OS with SOC maintenance: HR = 1.036 (95% CI 0.62 to 1.74; p-value NC). At this point, an OS detriment cannot be ruled out. However this is not of major concern in light of the B/R analysis for this application, as the overall number of deaths during induction is low and the data are very immature. In addition, the safety profile of isatuximab is well known, and no new safety issues were identified (please refer to the clinical safety section). Nonetheless, the MAH has committed to providing results from the final analysis for OS for the GMMG-HD7 study post approval.

Other secondary endpoints included PFS after IR maintenance, MRD neg rate at the end of intensification, and MRD neg CR rates after intensification and induction.

For PFS in IVRd induction compared to VRd induction, followed by isatuximab + lenalidomide maintenance treatment, the IPW HR was 0.791 (95% CI: 0.529 to 1.182) at the cut-off date of 31 January 2024.

MRD negativity at the end of intensification was 49.2% for VRd 68.9% for IVRd. The OR of IVRd over VRd was 2.281 (1.661 to 3.133) with the one-sided p-value given for descriptive purpose being <0.0001. Where data were available at both timepoints, respectively 9 (2.7%) participants in VRd and 6 (1.8%) in IVRd lost their MRD negative status, and respectively 58 (17.5%) and 71 (21.5%) converted from MRD positive status after induction to MRD negative status after intensification, showing that the MRD rate had not stabilized after induction.

PFS from first randomisation regardless of second randomisation seem to show a link between MRD status and PFS event rate. Indeed, landmark analyses from end of induction showed longer PFS in patients achieving MRD- than MRD+ and PFS tended to be longer with Isa-RVd over RVd in MRD+ patients. However, this trend cannot be considered as an argument for MRD surrogacy.

After induction, The MRD[-] CR rate was 14.5% (95% CI: 0.1089 to 0.1876) and 18.7% (95% CI: 0.1467 to 0.2336) of the ITT-IND population in VRd and IVRD, respectively. After intensification, the MRD[-] CR rate was 26.6% (95% CI: 0.2190 to 0.3169) and 40.5% (95% CI: 0.3515 to 0.4599) of the ITT-IND population in VRd and IVRD, respectively.

Data on subsequent therapy are premature. As of the cut-off date, more participants in the VRd group (24.2%) had started subsequent therapy than in the IVRd group (16.9%). Of the participants receiving further antimyeloma therapy, most frequently used drug classes were corticosteroids (85.0% in VRd, 67.9% in IVRd) and Proteasome Inhibitors (76.3% in VRd, 66.1% in IVRd) and IMiDs (65% in VRd, 73.2% in IVRd). Subsequent use of anti-CD38 was 68.8% in VRd and 51.8% in IVRd. Subsequent use of anti-BCMA was 10% in VRd and 5.4% in IVRd.

There were no large differences in mean changes in EORTC QLQ-C30, QLQ-MY20, and QLQ-EQ-5D-5L Global Health Status scores between treatment arms. However, due to the lack of blinding and a predefined analysis plan, these data are difficult to interpret.

2.4.4. Conclusions on the clinical efficacy

Data from the pivotal study GMMG-HD7 indicate a statistically significant MRD negativity benefit of IVRd induction over VRd induction in patients with newly diagnosed multiple myeloma. These results are considered to be robust and consistent over almost all subgroups. However, the clinical relevance of MRD negativity is not established and can only be considered supportive. Importantly the study also showed a statistically significant effect on PFS in favour of patients treated with IVRd compared to patients treated with VRd during induction followed by ASCT and lenalidomide maintenance treatment. OS data are at this point not informative, and updated OS data will be provided post-marketing when available.

2.5. Clinical safety

Introduction

This submission is based primarily on the safety results from the Phase 3 pivotal study (GMMG-HD7) in participants with NDMM who were eligible for transplant. Only safety data before second randomisation (Part 1: induction and intensification) were provided. The maintenance period safety data up to the dossier cutoff date 31 January 2024 were not included in the study clinical study report or integrated analysis of safety.

There are 2 additional studies included in the safety population in participants with NDMM treated with the same IVRd regimen and who were not eligible for transplant or with no intent for immediate transplantation, which provide longer follow-up safety data for the combination. These studies consist of one Phase 3 study (EFC12522) and one Phase 1b/2 supportive study (TCD13983 (Part A and Part B)

Results of studies GMMG-HD7, EFC12522, and TCD13983 IVRd Part A (NDMM non eligible for transplantation) and Part B cohorts (NDMM non eligible for transplantation as a first intent) were pooled to provide the overall safety profiles of the IVRd regimen across the NDMM spectrum (i.e., transplant eligible, not eligible, and with no intent for immediate transplant) side by side with that of VRd in participants with NDMM.

Additionally, safety data from isatuximab clinical studies in participants with RRMM were combined with participants with NDMM (i.e., All-Isa group) to provide comprehensive supportive safety information for treatment with isatuximab.

Patient exposure

Pivotal Phase 3 study GMMG-HD7

A total of 662 participants were randomised (331 in each treatment group). A total of 328 (99.1%) participants were randomised and treated in the VRd group and 330 (99.7%) in the IVRd group. Overall, 292 (88.2%) participants in the VRd group and 312 (94.3%) in the IVRd group completed the induction phase. At the time of the cut-off date, there were no participants still in the induction phase.

The total median duration of exposure for all of Part 1 (including induction, mobilization, and 1 or 2 ASCT) was 45.07 weeks in the VRd group (Q1;Q3: 38.86;55.71) and 45.43 weeks in the IVRd group (Q1;Q3: 40.14;54.57). As the median exposure for induction was 18 weeks, by protocol, the remaining exposure is related to the intensification. Despite the fact that the duration of the transplant

procedure was not specified in the protocol, the duration of intensification period was similar in the two treatment groups.

Majority of the participants started at least 3 cycles (304/328 [92.7%] in the VRd group and 314/330 [95.2%] in the IVRd group (**Table 25**). The median and relative dose intensity (RDI) for isatuximab was 97.79% (interquartile range 91.32 to 100). The median RDIs for bortezomib (94.80% versus 93.18%), lenalidomide (95.24% versus 94.04%) and dexamethasone (97.67% versus 96.18%) in VRd and IVRd groups were similar in both treatment groups.

Because of the COVID-19 pandemic in March 2020, the sites were advised to omit cyclophosphamide-based stem cell mobilization and to postpone HDT/ASCT. To enable postponing HDT/ASCT, the sites were allowed to give up to 2 bridging cycles with VRd+/- Isatuximab depending on the first randomisation group based on the Investigator's discretion (including decision which of the medications to be given): this occurred in 19 (5.8%) participants in the VRd group and in 17 (5.2%) participants in the IVRd group. All participants except 2 in VRd group received only 1 bridging cycle. These bridging cycles were not taken into account for calculation of the cumulative dose, actual dose intensity, and RDI.

Table 25. Overall extent of exposure - Induction safety population, and relative dose intensity, study GMMG-HD7

	VRd (N=328)	IVRd (N=330)	All (N=658)
Total number of cycles started	966	982	1948
Cumulative exposure to treatment (patient-years)	115.94	119.89	235.8
Number of cycles started by patient			
Number	328	330	658
Mean (SD)	2.95 (0.53)	2.98 (0.43)	2.96 (0.48)
Median	3.00	3.00	3.00
Q1 ; Q3	3.00 ; 3.00	3.00 ; 3.00	3.00 ; 3.00
Min ; Max	1.0 ; 5.0	1.0 ; 4.0	1.0 ; 5.0
Number of cycles started by patient [n(%)]			
At least 1 cycle	328 (100)	330 (100)	658 (100)
At least 2 cycles	313 (95.4)	321 (97.3)	634 (96.4)
At least 3 cycles	304 (92.7)	314 (95.2)	618 (93.9)
At least 4 cycles	19 (5.8)	17 (5.2)	36 (5.5)
At least 5 cycles	2 (0.6)	0	2 (0.3)
Duration of exposure (weeks)			
Number	326	329	655
Mean (SD)	18.56 (4.87)	19.01 (4.56)	18.79 (4.72)
Median	18.00	18.00	18.00
Q1 ; Q3	18.00 ; 19.00	18.00 ; 19.14	18.00 ; 19.00
Min ; Max	2.0 ; 43.3	1.0 ; 44.9	1.0 ; 44.9

Dose modification

A total of 115/330 (34.8%) participants had a modified dose schedule for isatuximab; 59 (17.9%) involved a reduced number of applications (**Table 26**).

Table 26. Isatuximab dose modifications during induction phase - Induction safety population - Patients in IVRd arm, study GMMG-HD7

	IVRd (N=330)
Number of treated patients	330
Patients with at least one half cycle/bridging cycles with :	
Modified schedule	115 (34.8)
Reduced number of applications	59 (17.9)
Modified schedule+reduced applications	7 (2.1)
Drug not given	17 (5.2)
Dose reduction	6 (1.8)
Overdose	3 (0.9)
Number of half cycles/bridging cycles	2045
Number of half cycles/bridging cycles with :	
Modified schedule	168 (8.2)
Reduced number of applications	75 (3.7)
Modified schedule+reduced applications	9 (0.4)
Drug not given	22 (1.1)
Dose reduction	10 (0.5)
Overdose	5 (0.2)

Treatment-emergent AEs leading to an isatuximab dose temporarily discontinued during the induction period, were reported in 123 (37.3%) participants for all grades and 26.4% for Grade ≥ 3 in the IVRd group. The most frequently reported TEAEs leading to dose temporarily discontinued (all grades) were infusion related reaction (7.3%), neutropenia (6.4%), and pneumonia (3.6%).

Treatment-emergent AEs leading to a lenalidomide dose temporarily discontinued during the induction period, were reported in 107 (32.6%) of participants in the VRd group and 121 (36.7%) of participants in the IVRd group. The most frequently reported TEAEs leading to dose temporarily discontinued (all grades) were neutropenia (3.0% and 9.1% respectively for the VRd and IVRd groups), pneumonia (1.5% and 3.9% respectively for the VRd and IVRd groups), and neutrophil count decreased (1.2% and 3.6% respectively for the VRd and IVRd groups).

Dose reductions and omissions were permitted for lenalidomide, bortezomib, and dexamethasone. Dose reductions were not permitted for isatuximab, but dose omissions were permitted. In the induction period TEAEs leading to dose reduction include both to daily dose reduction as well as dose omissions that led to decrease in total dose administered in a cycle. Overall, the most common TEAEs (by SOC) were Investigations and Blood and Lymphatic system disorders. Investigations accounted for dose reductions in 3.0% of the VRd participants and 2.4% of the IVRd participants and Blood and lymphatic system disorders accounted for dose reductions in 0.9% of the VRd participants and 3.0% of the IVRd participants.

Treatment-emergent AEs leading to an isatuximab dose reduction during the induction period population were reported in 2.7% of the participants for all grades and 2.4% for Grade ≥ 3 in the IVRd group. The most frequently reported TEAEs leading to dose reduction (all grades) were neutrophil count decreased in 2 (0.6%) participants and infusion-related reaction, also in 2 (0.6%) participants.

Treatment-emergent AEs leading to a lenalidomide dose reduction during the induction period, were reported in 7.9% of participants in the VRd group and 8.8% of participants in the IVRd group. The most frequently reported TEAEs leading to dose reduction (all grades) were polyneuropathy (1.5% in VRd and 0.6%, in IVRd), thrombocytopenia (0% in VRd and 1.2% in IVRd), alanine aminotransferase increased (1.2% in VRd and 0.3% in IVRd), neutrophil count decreased (0.3% in VRd and 1.5% in IVRd), and neutropenia (0.6% in VRd and 1.2% in IVRd).

All-Isa pool

The total numbers of patients in each of the following treatment groups were: 521 (VRd), 692 (IVRd), and 1787 (All-Isa) (**Table 27**).

Table 27. Extent of overall exposure - All-Isa - Safety population

	NDMM		RRMM and NDMM
	VRd ^a (N=521)	IVRd ^b (N=692)	All-Isa ^c (N=1787)
Total number of cycles started	6994	15336	29966
Cumulative exposure to treatment (patient years)	634.13	1332.42	2498.18
Number of cycles started by patient			
Number	521	692	1787
Mean (SD)	13.4 (19.0)	22.2 (24.3)	16.8 (20.2)
Median	3.0	4.0	6.0
Q1 ; Q3	3.0 ; 16.0	3.0 ; 48.0	3.0 ; 23.0
Min ; Max	1 ; 69	1 ; 81	1 ; 91
Duration of exposure (months)			
Number	519	691	1786
Mean (SD)	14.66 (18.92)	23.14 (23.77)	16.79 (19.97)
Median	4.34	5.98	6.01
Q1 ; Q3	4.14 ; 17.71	4.14 ; 48.95	3.75 ; 23.29
Min ; Max	0.5 ; 67.2	0.2 ; 79.5	0.2 ; 87.2

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone.

a Include VRd treated NDMM patients from IIT15403 (induction and intensification periods) and EFC12522 (global portion and China expansion, excl. data after crossover).

b Include IVRd treated NDMM patients from IIT15403 (induction and intensification periods), EFC12522 (global portion and China expansion), and TCD13983.

c Include isatuximab treated patients from all MM studies including crossover patients receiving IRd and patients from China expansion part in EFC12522.

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

Dose modification

Overall, the number of participants with at least 1 infusion delayed was 15.5% in the IVRd group and 20.5% in the All-ISA group. The number of participants with at least 1 infusion omitted was 68.0% in the IVRd group and 40.6% in the All-ISA group.

A total of 21247 isatuximab infusions have been given in the IVRd group and a total of 50024 isatuximab infusions have been given in the All-Isa group. Of those, 0.9% and 1.4% of infusions, respectively, required an interruption.

TEAEs (all grades) leading to any dose modifications of isatuximab were reported in 64.7% participants in the IVRd NDMM group and 66.5% participants in the All-Isa group. The most frequent TEAEs leading to any isatuximab dose modification in the IVRd group and All-Isa group were: infusion related reaction (16.5% and 27.4%, respectively), neutropenia (14.7% and 13.4%), pneumonia (11.7% and 11.2%), and upper respiratory tract infection (8.5% and 10.7%).

TEAEs (all grades) leading to dose reductions of isatuximab were reported in 29.6% patients in the IVRd group and 28.3% participants in the All-Isa group. The most frequent TEAEs leading to isatuximab dose reductions in the IVRd group were pneumonia (4.6%), thrombocytopenia (4.6%), and upper respiratory tract infection (4.0%). In the All-Isa group, the most frequent TEAEs leading to isatuximab dose reductions were upper respiratory tract infection (5.6%), pneumonia (4.6%), and neutropenia (3.3%).

TEAEs (all grades) leading to dose interruption of isatuximab were reported in 30.8% participants in the IVRd group and 34.1% participants in the All-Isa group. The single most frequent TEAE leading to isatuximab dose interruption was infusion related reaction (16.2% and 27.2%, respectively).

TEAEs (all grades) leading to dose delays of isatuximab were reported in 36.8% participants in the IVRd group and 41.2% participants in the All-Isa group. The most frequent TEAE leading to isatuximab dose delays was neutropenia (10% participants and 10.2% participants, respectively).

Adverse events

Study GMMG-HD7

Induction Period (IND)

Table 28. Overview of induction phase Treatment-Emergent Adverse Events (IND-TEAEs) - Induction safety population, GMMG-HD7

	VRd (N=328)	IVRd (N=330)
Patients with any IND-TEAE	257 (78.4)	273 (82.7)
Patients with any grade ≥ 3 IND-TEAE	201 (61.3)	210 (63.6)
Patients with any grade 3-4 IND-TEAE	199 (60.7)	208 (63.0)
Patients with any grade 5 IND-TEAE ^a	7 (2.1)	4 (1.2)
Patients with any induction phase treatment emergent SAE	120 (36.6)	116 (35.2)
Patients with any IND-TEAE leading to definitive treatment discontinuation	14 (4.3)	10 (3.0)
Patients with any IND-TEAE leading to premature/partial discontinuation of one of the treatments	0	0
Patients with any induction phase AESI ^b	2 (0.6)	5 (1.5)
Patients with any IR of grade ≥ 3	0	2 (0.6)
Patients with any IND-TEAE leading to death	7 (2.1)	4 (1.2)
Patients with any treatment-related IND-TEAE ^c (any grade)	178 (54.3)	210 (63.6)
Patients with any treatment-related IND-TEAE ^c to isatuximab (any grade)	0	159 (48.2)
Patients with any treatment-related IND-TEAE ^c to lenalidomide (any grade)	178 (54.3)	196 (59.4)
Patients with any treatment-related grade ≥ 3 IND-TEAE	147 (44.8)	163 (49.4)
Patients with any serious treatment-related IND-TEAE	61 (18.6)	61 (18.5)

IND-TEAE: Induction phase treatment-emergent adverse events, AESI: Adverse event of special interest, SAE: Serious adverse event, IR: Infusion reaction

n (%) = number and percentage of patients with at least one IND-TEAE

^a IND-TEAE started during the induction treatment period with a fatal outcome

^b AESIs include IR of grade ≥ 3 , pregnancy, overdose and second primary malignancy

^c Treatment-related IND-TEAEs are IND-TEAEs related to at least one drug of the combination

Intensification period

Summary of TEAEs during intensification period is provided in **Table 29**.

Table 29. Overview of TEAEs by subperiod of part 1 by Primary SOC and PT (worst grade by patient) - Safety population, GMMG-HD7

	VRd (N=328) During induction	VRd (N=291) During intensification	VRd (N=328) During part1	IVRd (N=330) During induction	IVRd (N=312) During intensification	IVRd (N=330) During part1
Patients with any TEAE	257 (78.4)	65 (22.3)	270 (82.3)	273 (82.7)	71 (22.8)	283 (85.8)
Patients with any grade ≥ 3 TEAE	201 (61.3)	47 (16.2)	220 (67.1)	210 (63.6)	55 (17.6)	233 (70.6)
Patients with any grade 3-4 TEAE	199 (60.7)	47 (16.2)	218 (66.5)	208 (63.0)	53 (17.0)	231 (70.0)
Patients with any grade 5 TEAE ^a	7 (2.1)	1 (0.3)	8 (2.4)	4 (1.2)	3 (1.0)	7 (2.1)
Patients with any treatment emergent SAE ^b	120 (36.6)	57 (19.6)	151 (46.0)	116 (35.2)	63 (20.2)	154 (46.7)
Patients with any TEAE leading to definitive treatment discontinuation	14 (4.3)	1 (0.3)	15 (4.6)	10 (3.0)	0	10 (3.0)
Patients with any TEAE leading to premature/partial discontinuation of one of the treatments	0	0	0	0	0	0
Patients with any AESI ^c	2 (0.6)	3 (1.0)	5 (1.5)	5 (1.5)	0	5 (1.5)
Patients with any IR of grade ≥ 3	0	0	0	2 (0.6)	0	2 (0.6)
Patients with any TEAE leading to death	7 (2.1)	1 (0.3)	8 (2.4)	4 (1.2)	3 (1.0)	7 (2.1)
Patients with any treatment-related TEAE ^d (any grade)	178 (54.3)	10 (3.4)	182 (55.5)	210 (63.6)	13 (4.2)	213 (64.5)
Patients with any treatment-related TEAE ^d to isatuximab (any grade)	0	0	0	159 (48.2)	7 (2.2)	163 (49.4)
Patients with any treatment-related TEAE ^d to lenalidomide (any grade)	178 (54.3)	10 (3.4)	182 (55.5)	196 (59.4)	12 (3.8)	200 (60.6)
Patients with any treatment-related TEAE ≥ 3 TEAE	147 (44.8)	8 (2.7)	152 (46.3)	163 (49.4)	10 (3.2)	168 (50.9)
Patients with any serious treatment-related TEAE	61 (18.6)	8 (2.7)	65 (19.8)	61 (18.5)	6 (1.9)	66 (20.0)

TEAE: Treatment-emergent adverse events, AESI: Adverse event of special interest, SAE: serious adverse event, IR: infusion reaction

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

^a TEAE started during the treatment period with a fatal outcome

^b TEAEs with a start date before the operational Cut-off date and becoming serious after the operational Cut-off date were not counted as serious TEAE in this analysis

^c AESIs include IR of grade ≥ 3 , pregnancy, overdose and second primary malignancy

^d Treatment-related TEAEs are TEAEs related to at least one drug of the combination

Among participants who received 1 ASCT, the median time from the date of stem cells reinfusion to leucocytes recovery was 11 days in both groups. The median time from the date of stem cells reinfusion to platelets recovery was 13 and 16 days, respectively.

Among participants who received a second ASCT, the median time from the date of stem cells reinfusion to leucocytes recovery was 11 days in both groups. The median time from the date of stem cells reinfusion to platelets recovery was 12 and 14 days, respectively.

All-Isa pool

Summary of TEAEs in the All-Isa-Safety population is provided in **Table 30**.

Table 30. Overview of Treatment-Emergent Adverse Events - All-Isa - Safety population

N(%)	NDMM		RRMM and NDMM
	VRd ^a (N=521)	IVRd ^b (N=692)	All-Isa ^c (N=1787)
Patients with any TEAE (any grade)	447 (85.8)	633 (91.5)	1698 (95.0)
Patients with any treatment-related TEAE (any grade)	226 (43.4)	383 (55.3)	1253 (70.1)
Patients with any TEAE of grade ≥ 3	365 (70.1)	537 (77.6)	1302 (72.9)
Patients with any treatment-related TEAE of grade ≥ 3	169 (32.4)	301 (43.5)	729 (40.8)
Patients with any TEAE of grade 3-4	362 (69.5)	530 (76.6)	1272 (71.2)
Patients with any AESI	16 (3.1)	76 (11.0)	422 (23.6)
Patients with any AESI of grade ≥ 3	10 (1.9)	29 (4.2)	67 (3.7)
Patients with any IR (excluding symptoms)	0	146 (21.1)	642 (35.9)
Patients with any IR of grade ≥ 3 (excluding symptoms)	0	6 (0.9)	29 (1.6)
Patients with any serious TEAE	251 (48.2)	366 (52.9)	968 (54.2)
Patients with any serious treatment-related TEAE	89 (17.1)	145 (21.0)	366 (20.5)
Patients with any TEAE with fatal outcome during the treatment period	13 (2.5)	41 (5.9)	132 (7.4)
Patients with any treatment-related TEAE with fatal outcome during the treatment period	4 (0.8)	8 (1.2)	16 (0.9)
Patients with any TEAE leading to definitive discontinuation	63 (12.1)	91 (13.2)	200 (11.2)
Patients with any TEAE leading to premature discontinuation of isatuximab	-	9 (1.3)	15 (0.8)
Patients with any TEAE leading to premature discontinuation of bortezomib	17 (3.3)	45 (6.5)	45 (2.5)
Patients with any TEAE leading to premature discontinuation of lenalidomide	4 (0.8)	55 (7.9)	57 (3.2)
Patients with any TEAE leading to premature discontinuation of dexamethasone	31 (6.0)	25 (3.6)	66 (3.7)

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone.

a Include VRd treated NDMM patients from IIT15403 (induction and intensification periods) and EFC12522 (global portion and China expansion, excl. data after crossover).

b Include IVRd treated NDMM patients from IIT15403 (induction and intensification periods), EFC12522 (global portion and China expansion), and TCD13983.

c Include isatuximab treated patients from all MM studies including crossover patients receiving IRd and patients from China expansion part in EFC12522.

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

The following AE were considered AESI: DLT (for TCD14079), infusion reactions, pregnancy, overdose, and secondary primary malignancy.

Common adverse events

Induction period (IND)

The IND-TEAEs with an incidence $\geq 5\%$ in any treatment group by primary SOC and PT for the SAFE-IND population are included in **Table 31**.

Table 31. IND-TEAEs with an incidence $\geq 5\%$ in any treatment group by Primary SOC and PT (worst grade by patient) - Induction safety population, GMMG-HD7

Primary System Organ Class Preferred Term [n(%)]	VRd (N=328)		IVRd (N=330)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	257 (78.4)	201 (61.3)	273 (82.7)	210 (63.6)
Blood and lymphatic system disorders	56 (17.1)	55 (16.8)	85 (25.8)	85 (25.8)
Neutropenia	13 (4.0)	13 (4.0)	53 (16.1)	53 (16.1)
Anaemia	18 (5.5)	18 (5.5)	12 (3.6)	12 (3.6)
Lymphopenia	20 (6.1)	20 (6.1)	11 (3.3)	11 (3.3)
Nervous system disorders	115 (35.1)	33 (10.1)	96 (29.1)	27 (8.2)
Polyneuropathy	74 (22.6)	17 (5.2)	62 (18.8)	16 (4.8)
Peripheral sensory neuropathy	23 (7.0)	5 (1.5)	20 (6.1)	2 (0.6)
Investigations	82 (25.0)	77 (23.5)	82 (24.8)	79 (23.9)
Lymphocyte count decreased	45 (13.7)	45 (13.7)	37 (11.2)	37 (11.2)
Neutrophil count decreased	10 (3.0)	10 (3.0)	24 (7.3)	24 (7.3)
Platelet count decreased	15 (4.6)	15 (4.6)	19 (5.8)	18 (5.5)
White blood cell count decreased	11 (3.4)	11 (3.4)	17 (5.2)	17 (5.2)
Injury, poisoning and procedural complications	13 (4.0)	12 (3.7)	52 (15.8)	15 (4.5)
Infusion related reaction	0	0	41 (12.4)	2 (0.6)

IND-TEAE: Induction phase treatment emergent adverse event, SOC: System organ class, PT: Preferred term

MedDRA 26.1

n (%) = number and percentage of patients with at least one IND-TEAE

Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IVRd group

Only SOC with at least one PT $\geq 5\%$ in at least one treatment group are presented.

Treatment-related TEAEs

The most frequently reported related TEAEs during the induction period incidence at least 5% higher in the IVRd arm compared to the VRd arm were neutropenia and infusion reactions (any grade; 16.1% and 12.7%, Grade ≥ 3 16.1% and 0.9%, respectively).

Intensification period (INT)

The INT-TEAEs by primary SOC and PT for the SAFE-INT population are included in **Table 32**.

During the intensification period, 1 participant in the VRd group had a Grade 2 TEAE of an upper respiratory tract infection during the bridging cycle. In the IVRd group, 1 participant had a Grade 2 TEAE of polyneuropathy. Two participants in the IVRd group had Grade 3 TEAEs (transaminase increase in 1 participant, and alanine aminotransferase/gamma-glutamyltransferase increase in the other participant).

All-Isa pool

TEAEs with an incidence $\geq 10\%$ (all grades) or $\geq 5\%$ (grade ≥ 3) in any treatment group by primary SOC and PT are included in **Table 33**.

Table 32. INT-TEAEs by Primary SOC and PT (worst grade by patient) during intensification phase - Intensification safety population, GMMG-HD7

Primary System Organ Class Preferred Term [n(%)]	VRd (N=291)		IVRd (N=312)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	65 (22.3)	47 (16.2)	71 (22.8)	55 (17.6)
Infections and infestations	28 (9.6)	20 (6.9)	28 (9.0)	24 (7.7)
Covid-19	3 (1.0)	0	3 (1.0)	1 (0.3)
Pneumonia	3 (1.0)	3 (1.0)	3 (1.0)	3 (1.0)
Infection	3 (1.0)	2 (0.7)	2 (0.6)	2 (0.6)
Influenza	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Sepsis	7 (2.4)	7 (2.4)	2 (0.6)	2 (0.6)
Staphylococcal sepsis	0	0	2 (0.6)	2 (0.6)
Urinary tract infection	3 (1.0)	2 (0.7)	2 (0.6)	2 (0.6)
Appendicitis	0	0	1 (0.3)	1 (0.3)
Atypical pneumonia	0	0	1 (0.3)	1 (0.3)
Bacterial sepsis	0	0	1 (0.3)	1 (0.3)
Catheter site infection	0	0	1 (0.3)	1 (0.3)
Device related infection	0	0	1 (0.3)	1 (0.3)
Endocarditis	0	0	1 (0.3)	1 (0.3)
Epstein-barr virus infection reactivation	0	0	1 (0.3)	1 (0.3)
Escherichia infection	0	0	1 (0.3)	1 (0.3)
Herpes zoster	1 (0.3)	0	1 (0.3)	0
Meningitis	0	0	1 (0.3)	1 (0.3)
Norovirus infection	0	0	1 (0.3)	0
Oesophageal candidiasis	0	0	1 (0.3)	1 (0.3)
Oral herpes	0	0	1 (0.3)	0
Peritonitis	0	0	1 (0.3)	1 (0.3)
Pneumonia herpes viral	0	0	1 (0.3)	1 (0.3)
Septic shock	0	0	1 (0.3)	1 (0.3)
Subcutaneous abscess	0	0	1 (0.3)	1 (0.3)
Upper respiratory tract infection	2 (0.7)	0	1 (0.3)	0
Bronchitis	1 (0.3)	1 (0.3)	0	0
Covid-19 pneumonia	1 (0.3)	1 (0.3)	0	0
Diverticulitis	2 (0.7)	2 (0.7)	0	0
Febrile infection	1 (0.3)	1 (0.3)	0	0
Neutropenic sepsis	1 (0.3)	1 (0.3)	0	0
Vascular device infection	1 (0.3)	1 (0.3)	0	0
Vestibular neuronitis	1 (0.3)	1 (0.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	3 (1.0)	1 (0.3)	1 (0.3)
Myelodysplastic syndrome with single lineage dysplasia	0	0	1 (0.3)	1 (0.3)
Malignant peritoneal neoplasm	1 (0.3)	1 (0.3)	0	0
Plasmablastic lymphoma	1 (0.3)	1 (0.3)	0	0
Squamous cell carcinoma of skin	1 (0.3)	1 (0.3)	0	0
Blood and lymphatic system disorders	8 (2.7)	7 (2.4)	9 (2.9)	8 (2.6)
Febrile bone marrow aplasia	3 (1.0)	3 (1.0)	4 (1.3)	4 (1.3)
Febrile neutropenia	4 (1.4)	3 (1.0)	2 (0.6)	1 (0.3)
Bone marrow failure	0	0	1 (0.3)	1 (0.3)
Lymphopenia	0	0	1 (0.3)	1 (0.3)
Thrombocytopenia	0	0	1 (0.3)	1 (0.3)
Anaemia	1 (0.3)	1 (0.3)	0	0
Immune system disorders	1 (0.3)	0	0	0
Engraftment syndrome	1 (0.3)	0	0	0
Endocrine disorders	0	0	1 (0.3)	1 (0.3)
Goitre	0	0	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders	4 (1.4)	4 (1.4)	3 (1.0)	3 (1.0)
Cachexia	0	0	1 (0.3)	1 (0.3)
Decreased appetite	0	0	1 (0.3)	1 (0.3)
Hypocalcaemia	0	0	1 (0.3)	1 (0.3)
Dehydration	1 (0.3)	1 (0.3)	0	0
Hypokalaemia	2 (0.7)	2 (0.7)	0	0
Hyponatraemia	1 (0.3)	1 (0.3)	0	0

Primary System Organ Class Preferred Term [n(%)]	VRd (N=291)		IVRd (N=312)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Psychiatric disorders	0	0	1 (0.3)	1 (0.3)
Delirium	0	0	1 (0.3)	1 (0.3)
Nervous system disorders	7 (2.4)	4 (1.4)	6 (1.9)	3 (1.0)
Polyneuropathy	6 (2.1)	3 (1.0)	5 (1.6)	3 (1.0)
Facial paresis	0	0	1 (0.3)	0
Spinal cord compression	1 (0.3)	1 (0.3)	0	0
Cardiac disorders	2 (0.7)	1 (0.3)	6 (1.9)	4 (1.3)
Aortic valve incompetence	0	0	1 (0.3)	1 (0.3)
Atrial fibrillation	1 (0.3)	1 (0.3)	1 (0.3)	0
Atrial flutter	0	0	1 (0.3)	0
Cardiac failure	0	0	1 (0.3)	1 (0.3)
Giant cell myocarditis	0	0	1 (0.3)	1 (0.3)
Supraventricular tachycardia	0	0	1 (0.3)	1 (0.3)
Cardiomyopathy	1 (0.3)	0	0	0
Vascular disorders	1 (0.3)	0	1 (0.3)	0
Deep vein thrombosis	0	0	1 (0.3)	0
Thrombophlebitis	0	0	1 (0.3)	0
Aortic aneurysm	1 (0.3)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.3)	0	0
Pleurisy	1 (0.3)	1 (0.3)	0	0
Gastrointestinal disorders	12 (4.1)	11 (3.8)	12 (3.8)	7 (2.2)
Nausea	4 (1.4)	2 (0.7)	5 (1.6)	2 (0.6)
Vomiting	3 (1.0)	3 (1.0)	5 (1.6)	4 (1.3)
Diarrhoea	3 (1.0)	3 (1.0)	3 (1.0)	1 (0.3)
Gastrointestinal inflammation	0	0	1 (0.3)	1 (0.3)
Large intestine perforation	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Pancreatitis	0	0	1 (0.3)	0
Stomatitis	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)
Abdominal pain	1 (0.3)	1 (0.3)	0	0
Appendiceal mucocoele	1 (0.3)	1 (0.3)	0	0
Dysphagia	1 (0.3)	1 (0.3)	0	0
Hiatus hernia	1 (0.3)	1 (0.3)	0	0
Musculoskeletal and connective tissue disorders	4 (1.4)	3 (1.0)	2 (0.6)	2 (0.6)
Osteonecrosis of jaw	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Spinal instability	0	0	1 (0.3)	1 (0.3)
Back pain	2 (0.7)	1 (0.3)	0	0
Pain in extremity	1 (0.3)	1 (0.3)	0	0
Renal and urinary disorders	1 (0.3)	1 (0.3)	1 (0.3)	0
Urinary retention	0	0	1 (0.3)	0
Acute kidney injury	1 (0.3)	1 (0.3)	0	0
General disorders and administration site conditions	5 (1.7)	3 (1.0)	13 (4.2)	8 (2.6)
Pyrexia	3 (1.0)	1 (0.3)	9 (2.9)	6 (1.9)
Pain	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
General physical health deterioration	0	0	1 (0.3)	1 (0.3)
Influenza like illness	0	0	1 (0.3)	0
Mucosal inflammation	1 (0.3)	1 (0.3)	0	0
Investigations	3 (1.0)	1 (0.3)	3 (1.0)	3 (1.0)
Alanine aminotransferase increased	0	0	1 (0.3)	1 (0.3)
Gamma-glutamyltransferase increased	0	0	1 (0.3)	1 (0.3)
Neutrophil count decreased	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Transaminases increased	0	0	1 (0.3)	1 (0.3)
C-reactive protein increased	1 (0.3)	0	0	0
Platelet count decreased	1 (0.3)	1 (0.3)	0	0
Sars-cov-2 test positive	1 (0.3)	0	0	0
Injury, poisoning and procedural complications	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Ankle fracture	0	0	1 (0.3)	1 (0.3)
Skin injury	0	0	1 (0.3)	1 (0.3)
Wrist fracture	0	0	1 (0.3)	1 (0.3)
Post procedural complication	1 (0.3)	1 (0.3)	0	0
Surgical and medical procedures	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Tooth extraction	0	0	1 (0.3)	1 (0.3)
Thyroidectomy	1 (0.3)	1 (0.3)	0	0

INT-TEAE: treatment-emergent adverse events during intensification period, SOC: System organ class, PT: Preferred term
MedDRA 26.1

n (%) = number and percentage of patients with at least one INT-TEAE

Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IVRd group

Table 33. Number (%) of patients with TEAEs with an incidence $\geq 10\%$ (all grades) or $\geq 5\%$ (grade ≥ 3) by PT - All-Isa - Safety population

Preferred Term [n(%)]	NDMM				RRMM and NDMM	
	VRd ^a (N=521)		IVRd ^b (N=692)		All-Isa ^c (N=1787)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any event	447 (85.8)	365 (70.1)	633 (91.5)	537 (77.6)	1698 (95.0)	1302 (72.9)
Infusion related reaction	2 (0.4)	0	145 (21.0)	5 (0.7)	642 (35.9)	29 (1.6)
Diarrhoea	111 (21.3)	31 (6.0)	222 (32.1)	40 (5.8)	535 (29.9)	61 (3.4)
Upper respiratory tract infection	72 (13.8)	5 (1.0)	128 (18.5)	6 (0.9)	441 (24.7)	32 (1.8)
Fatigue	51 (9.8)	14 (2.7)	113 (16.3)	24 (3.5)	422 (23.6)	60 (3.4)
Neutropenia	52 (10.0)	50 (9.6)	152 (22.0)	148 (21.4)	341 (19.1)	326 (18.2)
Pneumonia	51 (9.8)	36 (6.9)	119 (17.2)	80 (11.6)	319 (17.9)	228 (12.8)
Peripheral sensory neuropathy	140 (26.9)	18 (3.5)	220 (31.8)	25 (3.6)	318 (17.8)	29 (1.6)
Constipation	84 (16.1)	6 (1.2)	162 (23.4)	13 (1.9)	309 (17.3)	16 (0.9)
Back pain	40 (7.7)	8 (1.5)	92 (13.3)	12 (1.7)	306 (17.1)	41 (2.3)
Oedema peripheral	66 (12.7)	3 (0.6)	130 (18.8)	3 (0.4)	273 (15.3)	8 (0.4)
Nausea	39 (7.5)	8 (1.5)	60 (8.7)	3 (0.4)	272 (15.2)	5 (0.3)
Insomnia	47 (9.0)	6 (1.2)	87 (12.6)	17 (2.5)	247 (13.8)	34 (1.9)
Cough	27 (5.2)	0	67 (9.7)	0	246 (13.8)	0
Arthralgia	38 (7.3)	4 (0.8)	71 (10.3)	2 (0.3)	244 (13.7)	19 (1.1)
Bronchitis	43 (8.3)	6 (1.2)	92 (13.3)	14 (2.0)	236 (13.2)	34 (1.9)
Pyrexia	38 (7.3)	5 (1.0)	74 (10.7)	7 (1.0)	223 (12.5)	20 (1.1)
Asthenia	46 (8.8)	5 (1.0)	110 (15.9)	16 (2.3)	221 (12.4)	30 (1.7)
Dyspnoea	28 (5.4)	8 (1.5)	49 (7.1)	7 (1.0)	211 (11.8)	35 (2.0)
Cataract	50 (9.6)	22 (4.2)	140 (20.2)	55 (7.9)	209 (11.7)	79 (4.4)
Headache	15 (2.9)	0	38 (5.5)	3 (0.4)	196 (11.0)	6 (0.3)
Nasopharyngitis	28 (5.4)	0	77 (11.1)	2 (0.3)	185 (10.4)	2 (0.1)
Hypertension	18 (3.5)	7 (1.3)	39 (5.6)	24 (3.5)	172 (9.6)	90 (5.0)
Anaemia	35 (6.7)	26 (5.0)	32 (4.6)	21 (3.0)	156 (8.7)	111 (6.2)
Thrombocytopenia	37 (7.1)	32 (6.1)	65 (9.4)	57 (8.2)	150 (8.4)	134 (7.5)

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone.

a Include VRd treated NDMM patients from IIT15403 (induction and intensification periods) and EFC12522 (global portion and China expansion, excl. data after crossover).

b Include IVRd treated NDMM patients from IIT15403 (induction and intensification periods), EFC12522 (global portion and China expansion), and TCD13983.

c Include isatuximab treated patients from all MM studies including crossover patients receiving IRd and patients from China expansion part in EFC12522.

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

Treatment-related TEAEs

The most frequently reported treatment-related TEAEs (all grades; at least 10% of participants in any treatment group) are listed below by PT and treatment group:

- Neutropenia (7.9% participants in VRd, 14.9% participants in IVRd, and 15.1% participants in All-Isa)
- Insomnia (5.8% participants in VRd, 9.2% participants in IVRd, and 10.0% participants in All-Isa)
- Peripheral sensory neuropathy (21.7% participants in VRd, 27.9% participants in IVRd, and 13.6% participants in All-Isa)
- Cataract (5.2% participants in VRd, 11.6% participants in IVRd, and 6.4% participants in All-Isa)
- Diarrhea (14.8% participants in VRd, 21.4% participants in IVRd, and 15.2% participants in All-Isa)
- Constipation (10.4% participants in VRd, 14.7% participants in IVRd, and 8.7% participants in All-Isa)
- Fatigue (7.7% participants in VRd, 11.8% participants in IVRd, and 14.4% participants in All-Isa)
- Oedema peripheral (7.3% participants in VRd, 10.0% participants in IVRd, and 7.2% participants in All-Isa)
- Asthenia (5.4% participants in VRd, 11.4% participants in IVRd, and 7.2% participants in All-Isa)

- Infusion related reaction (0.0% participants in VRd, 15.6% participants in IVRd, and 33.5% participants in All-Isa)

The most reported treatment-related Grade ≥ 3 TEAEs are listed below by PT and treatment group:

- Pneumonia (3.6% participants in VRd, 5.8% participants in IVRd, and 5.7% participants in All-Isa)
- Neutropenia (7.5% participants in VRd, 14.3% participants in IVRd, and 14.4% participants in All-Isa)
- Thrombocytopenia (4.4% participants in VRd, 6.4% participants in IVRd, and 5.1% participants in All-Isa)
- Peripheral sensory neuropathy (2.5% participants in VRd, 3.3% participants in IVRd, and 1.5% participants in All-Isa)
- Cataract (2.3% participants in VRd, 4.0% participants in IVRd, and 2.2% participants in All-Isa)
- Diarrhea (4.0% participants in VRd, 3.8% participants in IVRd, and 1.8% participants in All-Isa)

Serious adverse event/deaths/other significant events

Study GMMG-HD7

Induction period (IND)

SAEs with an incidence $\geq 2\%$ in any treatment group by primary SOC and PT are included in **Table 34**.

Table 34. Induction phase treatment emergent SAEs with an incidence $\geq 2\%$ in any treatment group by Primary SOC and PT (worst grade by patient) - Induction safety population, Study GMMG-HD7

Primary System Organ Class Preferred Term [n(%)]	VRd (N=328)		IVRd (N=330)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	120 (36.6)	99 (30.2)	116 (35.2)	94 (28.5)
Infections and infestations	39 (11.9)	28 (8.5)	43 (13.0)	34 (10.3)
Pneumonia	9 (2.7)	7 (2.1)	12 (3.6)	11 (3.3)
Nervous system disorders	18 (5.5)	12 (3.7)	10 (3.0)	8 (2.4)
Syncope	9 (2.7)	8 (2.4)	3 (0.9)	2 (0.6)
Gastrointestinal disorders	28 (8.5)	22 (6.7)	20 (6.1)	13 (3.9)
Diarrhoea	9 (2.7)	8 (2.4)	7 (2.1)	4 (1.2)
General disorders and administration site conditions	16 (4.9)	7 (2.1)	19 (5.8)	10 (3.0)
Pyrexia	11 (3.4)	4 (1.2)	11 (3.3)	4 (1.2)

SAE: Serious adverse event, SOC: System organ class, PT: Preferred term

MedDRA 26.1

n (%) = number and percentage of patients with at least one treatment emergent SAE

Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IVRd group
Only SOC with at least one PT $\geq 2\%$ in at least one treatment arm are presented

Intensification period

Serious TEAEs were reported with similar incidence in the VRd and IVRd treatment groups during intensification (**Table 35**).

Table 35. Intensification phase treatment emergent SAEs by Primary SOC and PT (worst grade by patient) - Intensification safety population, Study GMMG-HD7

Primary System Organ Class Preferred Term [n(%)]	VRd (N=291)		IVRd (N=312)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	57 (19.6)	43 (14.8)	63 (20.2)	48 (15.4)
Infections and infestations	24 (8.2)	19 (6.5)	27 (8.7)	23 (7.4)
Covid-19	3 (1.0)	0	3 (1.0)	1 (0.3)
Pneumonia	3 (1.0)	3 (1.0)	3 (1.0)	3 (1.0)
Infection	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Influenza	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Sepsis	7 (2.4)	7 (2.4)	2 (0.6)	2 (0.6)
Urinary tract infection	3 (1.0)	2 (0.7)	2 (0.6)	2 (0.6)
Appendicitis	0	0	1 (0.3)	1 (0.3)
Atypical pneumonia	0	0	1 (0.3)	1 (0.3)
Bacterial sepsis	0	0	1 (0.3)	1 (0.3)
Catheter site infection	0	0	1 (0.3)	1 (0.3)
Device related infection	0	0	1 (0.3)	1 (0.3)
Endocarditis	0	0	1 (0.3)	1 (0.3)
Epstein-barr virus infection reactivation	0	0	1 (0.3)	1 (0.3)
Escherichia infection	0	0	1 (0.3)	1 (0.3)
Meningitis	0	0	1 (0.3)	1 (0.3)
Norovirus infection	0	0	1 (0.3)	0
Oesophageal candidiasis	0	0	1 (0.3)	1 (0.3)
Peritonitis	0	0	1 (0.3)	1 (0.3)
Pneumonia herpes viral	0	0	1 (0.3)	1 (0.3)
Septic shock	0	0	1 (0.3)	1 (0.3)
Staphylococcal sepsis	0	0	1 (0.3)	1 (0.3)
Subcutaneous abscess	0	0	1 (0.3)	1 (0.3)
Upper respiratory tract infection	1 (0.3)	0	1 (0.3)	0
Bronchitis	1 (0.3)	1 (0.3)	0	0
Covid-19 pneumonia	1 (0.3)	1 (0.3)	0	0
Diverticulitis	2 (0.7)	2 (0.7)	0	0
Febrile infection	1 (0.3)	1 (0.3)	0	0
Neutropenic sepsis	1 (0.3)	1 (0.3)	0	0
Vascular device infection	1 (0.3)	1 (0.3)	0	0
Vestibular neuronitis	1 (0.3)	1 (0.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	3 (1.0)	1 (0.3)	1 (0.3)
Myelodysplastic syndrome with single lineage dysplasia	0	0	1 (0.3)	1 (0.3)
Malignant peritoneal neoplasm	1 (0.3)	1 (0.3)	0	0
Plasmablastic lymphoma	1 (0.3)	1 (0.3)	0	0
Squamous cell carcinoma of skin	1 (0.3)	1 (0.3)	0	0
Blood and lymphatic system disorders	7 (2.4)	6 (2.1)	6 (1.9)	5 (1.6)
Febrile bone marrow aplasia	3 (1.0)	3 (1.0)	4 (1.3)	4 (1.3)
Bone marrow failure	0	0	1 (0.3)	1 (0.3)
Febrile neutropenia	4 (1.4)	3 (1.0)	1 (0.3)	0
Immune system disorders	1 (0.3)	0	0	0
Engraftment syndrome	1 (0.3)	0	0	0
Endocrine disorders	0	0	1 (0.3)	1 (0.3)
Goitre	0	0	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders	4 (1.4)	4 (1.4)	3 (1.0)	3 (1.0)
Cachexia	0	0	1 (0.3)	1 (0.3)
Decreased appetite	0	0	1 (0.3)	1 (0.3)
Hypocalcaemia	0	0	1 (0.3)	1 (0.3)
Dehydration	1 (0.3)	1 (0.3)	0	0
Hypokalaemia	2 (0.7)	2 (0.7)	0	0
Hyponatraemia	1 (0.3)	1 (0.3)	0	0
Psychiatric disorders	0	0	1 (0.3)	1 (0.3)
Delirium	0	0	1 (0.3)	1 (0.3)

Primary System Organ Class Preferred Term [n(%)]	VRd (N=291)		IVRd (N=312)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Nervous system disorders	2 (0.7)	1 (0.3)	2 (0.6)	1 (0.3)
Facial paresis	0	0	1 (0.3)	0
Polyneuropathy	1 (0.3)	0	1 (0.3)	1 (0.3)
Spinal cord compression	1 (0.3)	1 (0.3)	0	0
Cardiac disorders	1 (0.3)	1 (0.3)	5 (1.6)	3 (1.0)
Atrial fibrillation	1 (0.3)	1 (0.3)	1 (0.3)	0
Atrial flutter	0	0	1 (0.3)	0
Cardiac failure	0	0	1 (0.3)	1 (0.3)
Giant cell myocarditis	0	0	1 (0.3)	1 (0.3)
Supraventricular tachycardia	0	0	1 (0.3)	1 (0.3)
Vascular disorders	1 (0.3)	0	0	0
Aortic aneurysm	1 (0.3)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.3)	0	0
Pleurisy	1 (0.3)	1 (0.3)	0	0
Gastrointestinal disorders	11 (3.8)	10 (3.4)	12 (3.8)	7 (2.2)
Nausea	4 (1.4)	2 (0.7)	5 (1.6)	2 (0.6)
Vomiting	3 (1.0)	3 (1.0)	5 (1.6)	4 (1.3)
Diarrhoea	3 (1.0)	3 (1.0)	3 (1.0)	1 (0.3)
Gastrointestinal inflammation	0	0	1 (0.3)	1 (0.3)
Large intestine perforation	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Pancreatitis	0	0	1 (0.3)	0
Stomatitis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Abdominal pain	1 (0.3)	1 (0.3)	0	0
Appendiceal mucocoele	1 (0.3)	1 (0.3)	0	0
Dysphagia	1 (0.3)	1 (0.3)	0	0
Hiatus hernia	1 (0.3)	1 (0.3)	0	0
Musculoskeletal and connective tissue disorders	4 (1.4)	3 (1.0)	2 (0.6)	2 (0.6)
Osteonecrosis of jaw	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Spinal instability	0	0	1 (0.3)	1 (0.3)
Back pain	2 (0.7)	1 (0.3)	0	0
Pain in extremity	1 (0.3)	1 (0.3)	0	0
Renal and urinary disorders	1 (0.3)	1 (0.3)	1 (0.3)	0
Urinary retention	0	0	1 (0.3)	0
Acute kidney injury	1 (0.3)	1 (0.3)	0	0
General disorders and administration site conditions	5 (1.7)	3 (1.0)	13 (4.2)	8 (2.6)
Pyrexia	3 (1.0)	1 (0.3)	9 (2.9)	6 (1.9)
Pain	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
General physical health deterioration	0	0	1 (0.3)	1 (0.3)
Influenza like illness	0	0	1 (0.3)	0
Mucosal inflammation	1 (0.3)	1 (0.3)	0	0
Investigations	2 (0.7)	0	0	0
C-reactive protein increased	1 (0.3)	0	0	0
Sars-cov-2 test positive	1 (0.3)	0	0	0
Injury, poisoning and procedural complications	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Ankle fracture	0	0	1 (0.3)	1 (0.3)
Skin injury	0	0	1 (0.3)	1 (0.3)
Wrist fracture	0	0	1 (0.3)	1 (0.3)
Post procedural complication	1 (0.3)	1 (0.3)	0	0
Surgical and medical procedures	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Tooth extraction	0	0	1 (0.3)	1 (0.3)
Thyroidectomy	1 (0.3)	1 (0.3)	0	0

SAE: Serious adverse event, SOC: System organ class, PT: Preferred term

MedDRA 26.1

n (%) = number and percentage of patients with at least one treatment emergent SAE

Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IVRd group

All-Isa pool

Serious TEAEs were experienced by 48.2% of participants in the VRd group and 52.9% of participants in the IVRd group (**Table 36**).

Table 36. Number (%) of patients with serious TEAEs with an incidence $\geq 2\%$ (all grades) by SOC and PT - All-Isa - Safety population

Primary System Organ Class Preferred Term [n(%)]	NDMM				RRMM and NDMM	
	VRd ^a (N=521)		IVRd ^b (N=692)		All-Isa ^c (N=1787)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any event	251 (48.2)	213 (40.9)	366 (52.9)	323 (46.7)	968 (54.2)	881 (49.3)
Infections and infestations	110 (21.1)	93 (17.9)	195 (28.2)	173 (25.0)	520 (29.1)	478 (26.7)
Pneumonia	36 (6.9)	31 (6.0)	78 (11.3)	72 (10.4)	226 (12.6)	210 (11.8)
Sepsis	10 (1.9)	10 (1.9)	11 (1.6)	11 (1.6)	38 (2.1)	38 (2.1)
Renal and urinary disorders	17 (3.3)	14 (2.7)	16 (2.3)	12 (1.7)	60 (3.4)	46 (2.6)
Acute kidney injury	8 (1.5)	6 (1.2)	9 (1.3)	7 (1.0)	40 (2.2)	31 (1.7)
General disorders and administration site conditions	31 (6.0)	15 (2.9)	44 (6.4)	28 (4.0)	141 (7.9)	109 (6.1)
Pyrexia	15 (2.9)	5 (1.0)	17 (2.5)	6 (0.9)	38 (2.1)	16 (0.9)
Disease progression	0	0	1 (0.1)	1 (0.1)	46 (2.6)	46 (2.6)

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone.

^a Include VRd treated NDMM patients from IIT15403 (induction and intensification periods) and EFC12522 (global portion and China expansion, excl. data after crossover).

^b Include IVRd treated NDMM patients from IIT15403 (induction and intensification periods), EFC12522 (global portion and China expansion), and TCD13983.

^c Include isatuximab treated patients from all MM studies including crossover patients receiving IRd and patients from China expansion part in EFC12522.

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

The number (%) of participants with any treatment-related serious TEAEs (all grades) in the VRd, IVRd, and All-Isa groups was 89 (17.1%) participants, 145 (21.0%) participants, and 366 (20.5%) participants, respectively. The most frequently reported treatment-related PT (all grades), and the only treatment-related PT with an incidence $\geq 2\%$, was pneumonia (16 [3.1%] participants in VRd group, 39 [5.6%] participants in IVRd group, and 103 [5.8%] participants in All-Isa pool). The percentage of participants with Grade ≥ 3 treatment-related serious TEAEs of pneumonia was higher in the IVRd group compared with the VRd group (5.3% versus 2.7%); the percentage in the All-Isa group was 5.4%.

Deaths

Study GMMG-HD7

For Study GMMG-HD7, deaths during the induction and intensification period prior to the second randomisation were reported, including those occurring during the follow-up period in participants who did not undergo the second randomisation (**Table 37**). Deaths during the maintenance period were not included, as the safety data after the second randomisation will be analysed along with the efficacy data after second randomisation in the future to ascertain the effect of isatuximab during maintenance treatment.

Table 37. Deaths by observation periods and cause of death - Induction safety population, Study GMMG-HD7

	VRd (N=328)	IVRd (N=330)
Deaths during all the study	42 (12.8)	48 (14.5)
IA - MM-dependent - MM-progression-related	16 (4.9)	14 (4.2)
IB - MM-dependent - therapy-related	10 (3.0)	14 (4.2)
IC - MM-dependent - not attributable to IA or IB	5 (1.5)	2 (0.6)
II - Multiple myeloma independent	1 (0.3)	3 (0.9)
III - Not attributable to I or II	4 (1.2)	8 (2.4)
IV - Unknown cause	6 (1.8)	7 (2.1)
Deaths during the induction phase or post-treatment induction period	14 (4.3)	10 (3.0)
IA - MM-dependent - MM-progression-related	4 (1.2)	2 (0.6)
IB - MM-dependent - therapy-related	4 (1.2)	3 (0.9)
IC - MM-dependent - not attributable to IA or IB	2 (0.6)	2 (0.6)
II - Multiple myeloma independent	0	0
III - Not attributable to I or II	1 (0.3)	1 (0.3)
IV - Unknown cause	3 (0.9)	2 (0.6)
Deaths during the induction phase ^a	4 (1.2)	4 (1.2)
IA - MM-dependent - MM-progression-related	0	0
IB - MM-dependent - therapy-related	0	2 (0.6)
IC - MM-dependent - not attributable to IA or IB	1 (0.3)	2 (0.6)
II - Multiple myeloma independent	0	0
III - Not attributable to I or II	1 (0.3)	0
IV - Unknown cause	2 (0.6)	0
Deaths during the post-treatment induction period ^b	10 (3.0)	6 (1.8)
IA - MM-dependent - MM-progression-related	4 (1.2)	2 (0.6)
IB - MM-dependent - therapy-related	4 (1.2)	1 (0.3)
IC - MM-dependent - not attributable to IA or IB	1 (0.3)	0
II - Multiple myeloma independent	0	0
III - Not attributable to I or II	0	1 (0.3)
IV - Unknown cause	1 (0.3)	2 (0.6)
Deaths within 60 days of first dose in induction phase	3 (0.9)	2 (0.6)
IA - MM-dependent - MM-progression-related	0	0
IB - MM-dependent - therapy-related	0	0
IC - MM-dependent - not attributable to IA or IB	0	2 (0.6)
II - Multiple myeloma independent	0	0
III - Not attributable to I or II	1 (0.3)	0
IV - Unknown cause	2 (0.6)	0
Deaths during the intensification phase or post-treatment intensification phase	7 (2.1)	13 (3.9)
IA - MM-dependent - MM-progression-related	3 (0.9)	4 (1.2)
IB - MM-dependent - therapy-related	2 (0.6)	5 (1.5)
IC - MM-dependent - not attributable to IA or IB	1 (0.3)	0
II - Multiple myeloma independent	0	2 (0.6)
III - Not attributable to I or II	1 (0.3)	1 (0.3)
IV - Unknown cause	0	1 (0.3)
Deaths during the intensification phase	0	2 (0.6)
IA - MM-dependent - MM-progression-related	0	0
IB - MM-dependent - therapy-related	0	2 (0.6)
IC - MM-dependent - not attributable to IA or IB	0	0
II - Multiple myeloma independent	0	0
III - Not attributable to I or II	0	0
IV - Unknown cause	0	0
Deaths during the post-treatment intensification phase ^c	7 (2.1)	11 (3.3)
IA - MM-dependent - MM-progression-related	3 (0.9)	4 (1.2)
IB - MM-dependent - therapy-related	2 (0.6)	3 (0.9)
IC - MM-dependent - not attributable to IA or IB	1 (0.3)	0
II - Multiple myeloma independent	0	2 (0.6)
III - Not attributable to I or II	1 (0.3)	1 (0.3)
IV - Unknown cause	0	1 (0.3)

The induction treatment period is defined as the time from the first dose of induction therapy to 30 days after the last administration of study treatments, start of intensification regimen, or upon the start of a new antimyeloma treatment (eg, relapse disease), whichever occurs first.

a Includes all deaths occurring during the induction treatment phase

b Includes all deaths occurring >30 days after the last dose of induction therapy and before start of intensification regimen,

c Includes all deaths occurring >30 days after the last dose of treatment during mobilization or last HDT for patients who did not second randomized

Deaths that occurred after the operational cut-off date are excluded from this analysis except for deaths due to an IND-TEAE starting before the operational cut-off date

There were 7 (2.1%) participants with Grade 5 IND-TEAEs in the VRd group and 4 (1.2%) in the IVRd group (**Table 38**). In addition, 2 (0.6%) participants experienced Grade 5 post-treatment AEs in the VRd group.

Table 38. IND-TEAEs leading to death by primary SOC and PT - Induction safety population, Study GMMG-HD7

Primary System Organ Class Preferred Term [n(%)]	VRd (N=328)		IVRd (N=330)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	7 (2.1)	7 (2.1)	4 (1.2)	4 (1.2)
Infections and infestations	0	0	3 (0.9)	3 (0.9)
Covid-19	0	0	1 (0.3)	1 (0.3)
Pneumonia influenzal	0	0	1 (0.3)	1 (0.3)
Septic shock	0	0	1 (0.3)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	1 (0.3)	0	0
Ovarian cancer	1 (0.3)	1 (0.3)	0	0
Nervous system disorders	0	0	1 (0.3)	1 (0.3)
Haemorrhage intracranial	0	0	1 (0.3)	1 (0.3)
Cardiac disorders	3 (0.9)	3 (0.9)	0	0
Cardiac arrest	1 (0.3)	1 (0.3)	0	0
Cardiac failure	1 (0.3)	1 (0.3)	0	0
Cardiac failure acute	1 (0.3)	1 (0.3)	0	0
Gastrointestinal disorders	1 (0.3)	1 (0.3)	0	0
Enteritis	1 (0.3)	1 (0.3)	0	0
Hepatobiliary disorders	1 (0.3)	1 (0.3)	0	0
Hepatorenal failure	1 (0.3)	1 (0.3)	0	0
General disorders and administration site conditions	1 (0.3)	1 (0.3)	0	0
Sudden death	1 (0.3)	1 (0.3)	0	0

IND-TEAE: Induction phase treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 26.1

n(%) = number and percentage of patients with at least one IND-TEAE leading to death

Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IVRd group

There were 4 Grade 5 TEAEs leading to death that occurred within 30 days of last treatment (i.e., after CAD mobilization or after stem cell infusion for HDT treatment period) during the intensification treatment period; 1 in the VRd and 3 in the IVRD group. Two participants died during the HDT1 treatment period in the IVRd group due to influenza infection and sepsis and 1 patient died in the post treatment period due to worsening of general condition, 28 days after stem cell infusion for ASCT. In the VRd group one patient died during the post treatment period, due to peritoneal carcinosis, this event started after CAD mobilization.

All-Isa pool

During the treatment period, deaths were reported for 13 (2.5%) participants in the VRd group, 41 (5.9%) participants in the IVRd group, and 132 (7.4%) participants in the All-Isa group (**Table 39**).

Table 39. Number (%) of deaths by study period and cause of death - All-Isa – Safety population

n(%)	NDMM	RRMM and NDMM	
	VRd ^a (N=521)	IVRd ^b (N=692)	All-Isa ^c (N=1787)
Death during the treatment period ^d	13 (2.5)	41 (5.9)	132 (7.4)
Disease progression	0	1 (0.1)	41 (2.3)
Adverse Event	10 (1.9)	35 (5.1)	81 (4.5)
Other	3 (0.6)	5 (0.7)	10 (0.6)
Death during post-treatment period	70 (13.4)	66 (9.5)	418 (23.4)
Disease progression	29 (5.6)	21 (3.0)	284 (15.9)
Adverse Event	13 (2.5)	17 (2.5)	21 (1.2)
Other	28 (5.4)	28 (4.0)	113 (6.3)
Death within 60 days from first dose	5 (1.0)	6 (0.9)	47 (2.6)
Disease progression	0	0	28 (1.6)
Adverse Event	3 (0.6)	5 (0.7)	15 (0.8)
Other	2 (0.4)	1 (0.1)	4 (0.2)

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone.

a Include VRd treated NDMM patients from IIT15403 (induction and intensification periods) and EFC12522 (global portion and China expansion, excl. data after crossover).

b Include IVRd treated NDMM patients from IIT15403 (induction and intensification periods), EFC12522 (global portion and China expansion), and TCD13983.

c Include isatuximab treated patients from all MM studies including crossover patients receiving IRd and patients from China expansion part in EFC12522.

d Deaths occurred during the crossover time period are counted in 'during the treatment period'.

Other significant Adverse Events

Infusion reactions

Study GMMG-HD7

As per protocol, only Grade 2 and above infusion reactions (IR) were collected. Overall, 42 (12.7%) participants experienced at least one infusion reaction in the IVRd group. Of those 42 infusion reactions, 39 (11.8%) were Grade 2, 2 (0.6%) were Grade 3 (dose reduction for 1 participant), and 1 (0.3%) was Grade 4 (drug withdrawn). None were of Grade 5.

The majority of participants with IRs had only 1 episode (33 [10%] participants), with 8 (2.4%) participants who had ≥ 2 episodes, 3 (0.9%) participants who had ≥ 3 episodes and 1 (0.3%) participant with at least 4 episodes. A total of 37 (11.2%) participants had infusion reactions at the first infusion, and 9 (2.7%) participants at the subsequent infusion.

All-Isa pool

For the All-Isa pooled data, analysis of IRs was performed according to the Investigator's reporting of IRs in eCRFs. Infusion reactions (all grades) were experienced by 146 (21.1%) participants in the IVRd group and 642 (35.9%) participants in the All-Isa group. The most frequently reported TEAE was infusion related reaction (21.0% in the IVRd group and 35.6% in the All-Isa group). A total of 6 (0.9%) participants in the IVRd group and 29 (1.6%) participants in the All-Isa group had TEAEs of Grade ≥ 3 .

The number of patients who experienced IR symptoms for any grade IRs was 105 (29.0%) participants in the IVRd group and 601 (41.2%) participants in the All-Isa group. Grade ≥ 3 IR symptoms were

experienced by 9 (2.5%) and 53 (3.6%) participants, respectively. The most frequent IR symptoms (any grade, in $\geq 3\%$ of participants) in participants in the IVRd group were dyspnoea (23 [6.4%]), chills (21 [5.8%]), cough (13 [3.6%]), vomiting (12 [3.3%]), and hypertension (11 [3.0%]). The most frequent IR symptoms (any grade, in $\geq 5\%$ of participants) in participants in the All-Isa group were: dyspnoea (156 [10.7%]), cough (107 [7.3%]), chills (104 [7.1%]), and nausea (90 [6.2%]). The most frequent Grade ≥ 3 IR symptom in the IVRd group was hypertension (6 [1.7%] participants), and in the All-Isa group they were hypertension (20 [1.4%] participants) and dyspnoea (14 [1.0%] participants).

Second primary malignancies

Study GMMG-HD7

During Part 1 of this study 4 participants in the VRd group and 2 participants in the IVRd group developed second primary malignancies (SPM).

During the induction period, 2 participants were assessed with second primary malignancies (i.e., ovarian cancer from the VRd group and pancreatic cancer from the IVRd group).

During mobilization, 1 (0.3%) participant in the VRd group was assessed with malignant peritoneal neoplasm. During HDT1, 2 participants in the VRd group were assessed with second primary malignancies (1 [0.3%] squamous cell carcinoma of the skin and 1 [0.3%] plasmablastic lymphoma) and 1 (0.3%) participant in the IVRd group was assessed with myelodysplastic syndrome with single lineage dysplasia. The ovarian cancer and the malignant peritoneal neoplasm were considered Grade 5 TEAEs. The participant with plasmablastic lymphoma died in post-treatment period, after receiving further anti-myeloma therapy.

All-Isa pool

Second primary malignancies that occurred during the treatment period or the post-treatment period were reported in 17 (3.3%) participants in the VRd group, 51 (7.4%) participants in the IVRd group, and 109 (6.1%) participants in All-Isa group. Among participants who had SPM, the median time (in months) from the 1st dose of study treatment to the onset of SPMs was 19.68, 25.30, and 19.29 months, respectively.

Second primary malignancies were skin cancers in 7 (1.3%) participants in the VRd group, 28 (4.0%) participants in the IVRd group, and 63 (3.5%) of participants in the All-Isa group. Solid tumors other than skin cancers occurred in 8 (1.5%) participants, 20 (2.9%) participants, and 44 (2.5%) participants, respectively.

Respiratory TEAEs

Study GMMG-HD7

During induction, there were a total of 3 (0.9%) lower respiratory TEAEs (dyspnoea, cough, pneumonitis) in the VRd group, of which 2 (0.6%) were Grade ≥ 3 . In the IVRd group, there were a total of 5 (1.5%) lower respiratory TEAEs, of which 2 (0.6%) were Grade ≥ 3 .

There were no lower respiratory TEAEs reported during the intensification period.

Respiratory infections were reported in 11.3% of participants in the VRd group and 15.8% of participants in the IVRd group. The most frequently reported TEAEs of respiratory infection (all grades) were pneumonia and bronchitis (2.7%, each) in the VRd group, and pneumonia (4.5%) and bronchitis and influenza (3.0%, each) in the IVRd group. For the VRd group, 4.3% of the events were Grade ≥ 3 versus 9.1% in the IVRd group.

All-Isa pool

There were a total of 74 (14.2%) lower respiratory TEAEs during the induction period, in the VRd group, of which 16 (3.1%) were Grade ≥ 3 . In the IVRd group, there were a total of 151 (21.8%) lower respiratory TEAEs, of which 23 (3.3%) were Grade ≥ 3 . In the All-Isa group, there were a total of 550 (30.8%) lower respiratory TEAEs, of which 81 (4.5%) were Grade ≥ 3 . The most frequently occurring PT was dyspnoea.

The most frequently reported respiratory infection TEAEs (by PT [all grades]) in both the VRd and IVRd groups were upper respiratory tract infection (13.8% and 18.5%, respectively), pneumonia (9.8% and 17.2%), bronchitis (8.3% and 13.3%), nasopharyngitis (5.4% and 11.1%), COVID-19 (6.7% and 12.7%), and influenza (2.7% and 5.6%). Incidences for these TEAEs were all numerically higher in the IVRd group. For Grade ≥ 3 , incidences were similar in the VRd and IVRd groups, with the exception of pneumonia which had a higher incidence in the IVRd group compared to the VRd group (VRd [6.9%] versus IVRd [11.6%]).

Neutropenia and neutropenic complications

Study GMMG-HD7

Neutropenia was reported when Grade 3 or above.

During the induction period, neutropenic infection was reported in 2 (0.6%) and 6 (1.8%) participants in the VRd and IVRd groups, respectively. Febrile neutropenia was reported in 2 (0.6%) and 3 (0.9%) participants in the VRd and IVRd groups, respectively.

All-Isa pool

Overall, in the VRd, IVRd, and All-Isa groups neutropenic complications (all grades) were experienced by 18 (3.5%) participants, 46 (6.6%) participants, and 120 (6.7%) participants, respectively.

The most frequently reported neutropenic complications (by PT) in the VRd, IVRd, and All-Isa groups were febrile neutropenia (1.2%, 1.7%, and 2.1%, respectively), and neutropenic infection (2.5%, 5.1%, and 5.2%, respectively).

Infections and antibiotic prophylaxis

Study GMMG-HD7

Overall, TEAEs in the SOC Infections and infestations were reported during the induction period in 75 (22.9%) and 88 (26.7%) of participants in the VRd and IVRd groups, respectively. The most frequently reported TEAEs in this SOC were infection (12 [3.7%] participants and 15 [4.5%] participants in the VRd and IVRd groups, respectively), pneumonia (9 [2.7%] participants and 15 [4.5%] participants), and bronchitis (9 [2.7%] participants and 10 [3.0%] participants).

Grade ≥ 3 events in the SOC Infections and infestations were reported in 33 (10.1%) and 43 (13.0%) of participants in the VRd and IVRd groups, respectively. The most frequently reported TEAEs in this SOC were pneumonia (7 [2.1%] participants and 13 [3.9%] participants in the VRd and IVRd groups, respectively), infection (4 [1.2%] participants in both groups), and influenza (2 [0.6%] participants and 6 [1.8%] participants in the VRd and IVRd groups, respectively).

As per study protocol, patients should have received antibioprophylaxis and anti-viral prophylaxis during the induction period. Antibioprophylaxis was received by 97.6% participants at any time during induction in both the VRd and IVRd groups, and 100% and 99.7% on participants received antiviral prophylaxis at any time during induction in the VRd and IVRd group, respectively.

All-Isa pool

In the VRd, IVRd, and All-Isa groups, 178 (34.2%) participants, 311 (44.9%) participants, and 884 (49.5%) participants, respectively, experienced at least 1 severe (all grades). For Grade ≥ 3 events, the number (%) of participants was 112 (21.5%), 200 (28.9%), and 544 (30.4%).

The most frequently reported PTs (all grades) in the VRd, IVRd, and All-Isa groups were upper respiratory tract infection (13.4%, 17.3%, and 22.5%, respectively), pneumonia (9.8%, 17.2%, and 17.8%, respectively), bronchitis (8.1%, 12.6%, and 12.4%, respectively).

For Grade ≥ 3 events, the most frequently reported PT was pneumonia in the VRd, IVRd, and All-Isa groups (6.9%, 11.6%, and 12.8%, respectively).

Thrombocytopenia and haemorrhages

Study GMMG-HD7

Data regarding thrombocytopenia and haemorrhages were not summarised for the GMMG-HD7 study in the same manner as the All-Isa pool.

All-Isa pool

A total of 47 (9.0%) participants in the VRd group, 84 (12.1%) participants in the IVRd group, and 246 (13.8%) participants in the All-Isa group had TEAEs of haemorrhages during the treatment period.

The most frequently reported TEAE (PT) for haemorrhages (all grades) in the VRd, IVRd, and All-Isa groups was contusion (11 [2.1%] participants, 16 [2.3%] participants, and 57 [3.2%] participants, respectively). None of the contusion events were rated Grade ≥ 3 .

Tumor lysis syndrome

Study GMMG-HD7

No events of tumor lysis syndrome (TLS) were reported in the induction period or intensification period of the study.

All-Isa pool

For in total 7 patients included in the All-Isa pool and treated with isatuximab TLS was reported. For one patient the outcome of the event was fatal, the event resolved in the other patients.

Haemolytic disorders

Study GMMG-HD7

Two adverse events of haemolytic anemia were reported in the VRd group (0.6%), both nonserious and Grade 3, which were reversible. No events were reported in the IVRd group.

All-Isa pool

There were no PTs for haemolytic disorders in the NDMM VRd or IVRd groups. In the All-Isa group, 1 (<0.1%) participant had an event of transfusion reaction, and it was not a Grade ≥ 3 event.

Autoimmune disorders

Study GMMG-HD7

One serious Grade 4 TEAE of Immune thrombocytopenia (0.3%) and 1 serious Grade 3 TEAE of Anaphylactic reaction (0.3%) were reported in the IVRd group, both reversible and possibly related to isatuximab, as per Investigator assessment.

All-Isa pool

For 24 patients in the All-Isa group an autoimmune disorder was reported. Most of these were grade 1 or 2, two patients experienced a grade 3 event.

Embolic and thrombotic TEAEs

Study GMMG-HD7

Embolic and thrombotic events, venous and/or arterial (excluding superficial thrombophlebitis or anal thrombosis), were reported at a slightly lower incidence in the VRd versus the IVRd group (3.4% and 6.1%) for all grades, with Grade ≥ 3 reported as 1.2% and 3.3%, respectively, for the VRd and IVRd groups. Most events were venous (2.4% and 4.5% in the VRd and IVRd groups, respectively). Among venous events, the most frequently reported PTs were pulmonary embolism (0.3% [Grade ≥ 3 : 0.3%] and 2.1% [Grade ≥ 3 : 2.1%] in the VRd and IVRd groups, respectively) and deep vein thrombosis (0.3% [Grade ≥ 3 : none] and 1.5% [Grade ≥ 3 : none]).

The incidence of arterial AEs reported was similar in the VRd and IVRd groups (0.9% and 1.5%, respectively, with Grade ≥ 3 : 0.3% and 1.2%, respectively). The most frequently reported arterial event was acute myocardial infarction (0.6% [Grade ≥ 3 : 0.6%] in the IVRd group and none in the VRd group).

All-Isa pool

Analysis of embolic and thrombotic adverse events for the All-Isa pool focused on the SMQ “Embolic and thrombotic events, venous” (narrow) and the SMQ “Embolic and thrombotic events, arterial” (narrow).

In the All-Isa pool, embolic and thrombotic events (all grades) had a numerically higher incidence in the IVRd group compared with the VRd group (13.7% versus 10.6%, respectively). However, for Grade ≥ 3 events incidences were similar (5.9% versus 4.8%, respectively). For the All-Isa group, incidences were 9.5% for All grade events and lower for Grade ≥ 3 events (4.1%).

The most frequently reported embolic events (all grades) in the VRd and IVRd groups were in the SOC of Respiratory, thoracic, and mediastinal disorders (15 [2.9%] participants and 23 [3.3%] participants, respectively). This SOC was reported for 38 (2.1%) of participants in the All-Isa pool. Within this SOC the most frequently reported embolic TEAE was pulmonary embolism (14 [2.7%] participants, 23 participants [3.3%], and 38 [2.1%] in VRd, IVRd, and All-Isa, respectively).

The most frequently reported thrombotic events (all grades) in the VRd and IVRd groups were in the SOC of Vascular disorders (28 [5.4%] participants and 54 [7.8%] participants, respectively). This SOC was reported for 97 (5.4%) of participants in the All-Isa pool. Within this SOC the most frequently reported thrombotic TEAE was deep vein thrombosis (21 [4.0%] participants in VRd group and 36 [5.2%] in IVRd group). This event occurred in 62 (3.5%) of participants from the All-Isa pool.

Nervous system disorders

Study GMMG-HD7

During the induction period, 115 (35.1%) participants in the VRd group and 96 (29.1%) participants in the IVRd group had any grade Nervous system disorders, including 10.1% and 8.2% Grade 3 and above, respectively. The PTs most frequently reported in the VRd and IVRd groups were polyneuropathy (22.6% versus 18.8%, respectively) and peripheral sensory neuropathy (7.0% versus 6.1%). The incidence of Grade ≥ 3 events was low in IVRd group: 2 (0.6%) for peripheral sensory neuropathies and 16 (4.8%) for polyneuropathy.

During the intensification period, 7 (2.4%) participants in the VRd group and 6 (1.9%) participants in the IVRd group had Nervous system disorder TEAEs of any grade, including 1.4% of participants in the

IVRd group and 1% of participants in the VRd group with Grade ≥ 3 TEAEs. The PT most frequently reported was polyneuropathy, with TEAEs in 2.1% of participants in the VRd group and 1.6% in the IVRd group.

All-Isa pool

A total of 235 (45.1%) participants in the VRd group, 321 (46.4%) participants in the IVRd group, and 440 (24.6%) participants in the All-Isa group had TEAEs of peripheral neuropathy during the treatment period; most events were not severe (Grade ≥ 3 : 7.9%, 7.8%, and 3.3%, respectively).

The most frequently reported TEAEs (all grades) in the VRd, IVRd, and All-Isa groups were peripheral sensory neuropathy (26.9%, 31.8%, and 17.8%, respectively) and polyneuropathy (14.2%, 9.2%, and 3.6%, respectively).

Cardiac events

Study GMMG-HD7

Overall, TEAEs in the SOC Cardiac disorders were reported during the induction period in 10 (3.0%) participants and 18 (5.5%) of participants in the VRd and IVRd groups, respectively. The most frequently reported TEAE in this SOC was atrial fibrillation (5 [1.5%] participants in both groups).

All-Isa pool

A total of 70 (13.4%) participants in the VRd group, 132 (19.1%) participants in the IVRd group, and 382 (21.4%) participants in the All-Isa group experienced any cardiac event during the treatment period; most events were not severe (Grade ≥ 3 : 6.7%, 9.2%, and 9.7%, respectively).

The most frequently reported events (all grades by PT) in the VRd, IVRd, and All-Isa groups were atrial fibrillation (4.0%, 4.6%, and 3.6%, respectively) in the Cardiac disorders SOC, and hypertension (3.5%, 5.6%, and 9.6%, respectively) in the Vascular disorders SOC. According to the applicant, the increased incidence of hypertension in the All-Isa group was due to an increased incidence in the isatuximab-carfilzomib-dexamethasone group of the EFC15246 (IKEMA) study. However, assessments of the mean and standard deviation of systolic and diastolic blood pressure over the course of the IKEMA study did not reveal a difference between the two groups.

COVID-19

Study GMMG-HD7

For part 1 of this study (including both the induction and intensification periods), the incidence of COVID-19 related events appears to be low. However, as the last participant was enrolled in the study in September 2020, the impact of COVID pandemic on the part 1 (treatment and posttreatment periods) may have been underestimated.

During the induction period 2 (0.6%) participants in the VRd group and 2 (0.6%) participants in the IVRd group had TEAEs related to COVID-19 illness. Only 1 (0.3%) participant in the IVRd group had a treatment-emergent event of Grade ≥ 3 which led to death.

During the intensification period 5 (1.7%) participants in the VRd group and 3 (1.0%) participants in the IVRd group had TEAEs related to COVID-19 illness during the intensification period. In the VRd and IVRd group, 1 (0.3%) participant each had a Grade ≥ 3 Covid-19 related TEAE (VRd: Covid-19 pneumonia; IVRd: COVID-19). None of these events led to treatment discontinuation or death.

All-Isa pool

A total of 43 (8.3%) participants in the VRd group, 112 (16.2%) participants in the IVRd group, and 161 (9.0%) participants in the All-Isa group experienced any COVID-19 event during the treatment period.

Laboratory findings

HAEMATOLOGY

Study GMMG-HD7

Induction period

The following Grade 3 or 4 hematologic values (worst grade) were reported during the induction period at the preplanned protocol time points:

- Anaemia: VRd (Grade 3: 0.9%); IVRd (Grade 3: 1.6%)
- Lymphocyte count decreased: VRd (Grade 3: 18.7% and Grade 4: 5.1%); IVRd (Grade 3: 15.6% and Grade 4: 2.2%)
- Neutrophil count decreased: VRd (Grade 3: 2.5% and Grade 4: 1.6%); IVRd (Grade 3: 3.1% and Grade 4: 2.8%)
- White blood cell decreased: VRd (Grade 3: 1.3%); IVRd (Grade 3: 1.3% and Grade 4: 0.3%)
- Platelet count decreased: VRd (Grade 3: 0.3%); IVRd (Grade 3: 0.6% and Grade 4: 0.9%)

In the VRd and IVRd groups, 227 (80.5%) and 206 (70.5%) participants, respectively, had no change from baseline in neutropenia grade, 21 (7.4%) and 31 (10.6%), respectively, had a 1 grade increase, 26 (9.2%) and 40 (13.7%), respectively, had a 2 grade increase, 3 (1.1%) and 8 (2.7%), respectively, had a 3 grade increase, and 5 (1.8%) and 7 (2.4%), respectively, had a 4 grade increase.

Two (0.6%) participants in the VRd group reported Grade 3 neutrophil count decreased at baseline; none were reported in the IVRd group.

In the VRd and IVRd groups: 231 (79.4%) and 225 (80.1%) participants, respectively, had no change from baseline in thrombocytopenia grade; 54 (18.6%) and 51 (18.1%), respectively, had a 1 grade increase; 5 (1.7%) and 1 (0.4%), respectively, had a 2 grade increase; 1 (0.3%) and 2 (0.7%), respectively, had a 3 grade increase; and none from the VRd group and 2 (0.7%) in the IVRd group had a 4 grade increase. Platelet count decreased at baseline were all Grade 1 (7.9% in the VRd group and 12.1% in the IVRd group).

Intensification period

The most frequent haematological abnormality was anaemia across different points of the intensification period (mobilization, 1st ASCT, and 2nd ASCT) for both groups, followed by lymphocyte count decreased and white blood cell decreased.

The following Grade 3 or 4 haematologic values were reported:

After mobilization:

- Anaemia: VRd (Grade 3: 1.1%); IVRd (Grade 3: 0.3%)
- Lymphocyte count decreased: VRd (Grade 3: 17.5% and Grade 4: 2.2%); IVRd (Grade 3: 22.5% and Grade 4: 3.4%)

- Neutrophil count decreased: VRd (Grade 3: 1.8% and Grade 4: 0.7%); IVRd (Grade 3: 0.7% and Grade 4: 1.7%)
- White blood cell decreased: VRd (Grade 3: 2.8%); IVRd (Grade 3: 1.3% and Grade 4: 0.3%)
- Platelet count decreased: VRd (Grade 3: 0.4% and Grade 4: 0.4%); IVRd (Grade 3: 1.0%)

After 1st ASCT:

- Anaemia: VRd (Grade 3: 0.7%); IVRd (Grade 3: 1.0%)
- Lymphocyte count decreased: VRd (Grade 3: 4.2% and Grade 4: 1.5%); IVRd (Grade 3: 2.7% and Grade 4: 3.1%)
- Neutrophil count decreased: VRd (Grade 3: 1.1% and Grade 4: 1.1%); IVRd (Grade 3: 0.7% and Grade 4: 2.0%)
- White blood cell decreased: VRd (Grade 4: 0.4%); IVRd (Grade 3: 1.0% and Grade 4: 0.3%)
- Platelet count decreased: VRd (Grade 3: 1.1%); IVRd (Grade 3: 0.3% and Grade 4: 0.3%)

After 2nd ASCT:

- Anaemia: VRd (Grade 3: 1.0%);
- Lymphocyte count decreased: VRd (Grade 3: 10.1% and Grade 4: 1.0%); IVRd (Grade 3: 5.3%)
- Neutrophil count decreased: VRd (Grade 4: 1.0%)
- White blood cell decreased: VRd (Grade 3: 1.0%)

All-Isa pool

Most participants in the VRd and IVRd groups experienced anaemia of all grades: VRd (441 [86.6%] participants); IVRd (615 [90.2%] participants); and All-Isa (1669 [94.7%] participants).

The haematology parameters that had the highest incidence of Grade 3 and Grade 4 abnormalities were the following:

Grade 3 and Grade 4 lymphocyte count decreased were reported in 133 (26.1%) and 45 (8.8%) participants in the VRd group, respectively, and 218 (32.0%) and 71 (10.4%) participants in the IVRd group, respectively. In the All-Isa group, incidences for Grade 3 and Grade 4 were 607 (34.4%) participants and 204 (11.6%) participants, respectively and were similar to those incidences in the IVRd group.

Grade 3 and Grade 4 neutrophil count decreased were reported in 62 (12.2%) and 21 (4.1%) participants in the VRd group respectively, and 138 (20.2%) and 70 (10.3%) participants in the IVRd group, respectively. In the All-Isa group, incidences for Grade 3 and Grade 4 were 350 (19.9%) participants and 254 (14.4%) participants, respectively, and were similar to those incidences in the IVRd group.

A numerically higher percentage of participants in the IVRd group had Grade 3 white cell count decreased compared with participants in the VRd group (15.4% versus 6.3%, respectively).

A numerically higher percentage of participants in the IVRd group had Grade 4 platelet count decreased compared with participants in the VRd group (9.1% versus 3.9%, respectively).

CLINICAL CHEMISTRY

Liver abnormalities

Study GMMG-HD7

Induction and intensification period

The reported incidence of Grade 3 and 4 liver function values (i.e., for abnormalities) was low and similar between treatment groups.

All-Isa pool

Grade 3 alanine aminotransferase increased was reported in 14 (2.8%) participants in the VRd group, 23 (3.4%) participants in the IVRd group, and 48 (2.7%) participants in All-Isa group.

Grade 3 blood bilirubin increased was reported in 4 (0.8%) participants in the VRd group, 12 (1.8%) participants in the IVRd group, and 22 (1.3%) participants in All-Isa group.

Electrolyte abnormalities

Study GMMG-HD7

Induction period

In Study GMMG-HD7, Grade 3 and 4 electrolyte values (worst grade) reported during the induction period were the following: Hyponatremia: VRd (Grade 3: none and Grade 4: 0.3%); IVRd (Grade 3: 0.6% and Grade 4: none); Hypokalemia: VRd (Grade 3: 1.0% and Grade 4: none); IVRd (Grade 3: 0.9% and Grade 4: none); Hyperkalemia: VRd (none); IVRd (Grade 3: 0.3% and Grade 4: none) and Hypercalcemia: VRd (Grade 3: 0.3% and Grade 4: none); IVRd (none).

Intensification period

The most common electrolyte abnormality during the intensification period was hypocalcemia (all grades). Hypocalcemia accounted for the majority of the electrolyte abnormalities for both the VRd and IVRd groups throughout parts of the intensification treatment (ie, after mobilization, after 1st ASCT, and after 2nd ASCT). No Grade 4 electrolyte abnormalities were observed during the intensification period.

All-Isa pool

Grade 3 hypophosphatemia was reported in 37 (19.2%) participants in the VRd group, 69 (19.2%) participants in the IVRd group, and 200 (14.0%) participants in All-Isa group.

Grade 3 hyponatremia was reported in 28 (5.5%) participants in the VRd group, 55 (8.1%) participants in the IVRd group, and 166 (9.4%) participants in All-Isa group.

Grade 3 hypokalemia was reported in 23 (4.5%) participants in the VRd group, 61 (9.0%) participants in the IVRd group, and 121 (6.9%) participants in All-Isa group.

Metabolic function abnormalities

Study GMMG-HD7

Induction period

Grade 3 metabolic function values (worst grade) reported during the induction period were: Hypoalbuminemia: VRd (Grade 3: none); IVRd (Grade 3: 0.3%) and C-Reactive Protein (>2 ULN or >10 mg/L, if ULN is not provided): VRd (29.3%); IVRd (35.4%).

No Grade 4 metabolic function abnormalities were observed in the SAFE-IND population (at baseline or during induction).

Intensification period

The highest grade of hypoalbuminemia observed (by worst grade) during the intensification period was Grade 3, which was observed in 0.7% of the participants in the IVRd group after ASCT1.

All- Isa pool

Grade 3 hyperglycemia was reported in 6 (3.6%) participants (with no Grade 4 events) in the VRd group and 19 (5.6%) participants (with 1 [0.3%] Grade 4 event) in the IVRd group. In the All-Isa group for hyperglycemia, 73 (5.3%) participants had Grade 3 and 10 (0.7%) participants had Grade 4 events.

Renal function abnormalities

Study GMMG-HD7

Induction period

The eGFR calculated by MDRD, indicated that majority of the participants had mild renal function abnormalities (ie, ≥ 60 - < 90 mL/min/1.73m²) at baseline (ie, 53.4% in VRd and 49.4% in IVRd). Additionally, 1.5% in VRd and 0.6% in IVRd participants had severe eGFR renal functional abnormalities values (ie, eGFR ≥ 15 - < 30 mL/min/1.73m²) at baseline. No participants were assessed with end stage renal disease in either group (ie, eGFR < 15 mL/min/1.73m²).

Relevant renal function values (worst stage and grade) reported during the induction period were;

- eGFR calculated by MDRD: VRd (Severe: 0.3%);
- Creatinine increased: VRd (Grade 3: none);
- Blood Urea Nitrogen: VRd (≥ 17 mmol/L: 0.3%); IVRd (≥ 17 mmol/L: none)
- Uric Acid: VRd (< 120 μ mol/L: 1.6% and > 408 μ mol/L: 5.8%); IVRd (< 120 μ mol/L: 5.1% and > 408 μ mol/L: 6.7%)

Among patients with eGFR < 50 mL/min/1.73m² at baseline, renal response was assessed. The renal Complete Response (eGFR < 50 mL/min/1.73m² at baseline and at least one assessment ≥ 60 mL/min/1.73m² during treatment) was higher in the IVRd group compared to the VRd group: 33/39 participants (84.6%) versus 27/39 participants (69.2%).

Intensification period

Renal function abnormalities, as assessed by eGFR calculated by MDRD, during the intensification period were primarily mild (≥ 60 - < 90 mL/min/1.73m²), i.e., $> 42\%$ of participants in each treatment group, and across the intensification period. Severe (i.e., eGFR ≥ 15 - < 30 mL/min/1.73m²) renal abnormality was observed in 0.7% participants in IVRd group after the 1st ASCT and 1% participants in the VRd group during 2nd ASCT. No end stage renal disease was observed in either treatment groups during the intensification period.

All-Isa pool

Grade 3 creatinine increased was reported in 5 (1.0%) participants in the VRd group, 13 (1.9%) participants in the IVRd group, and 52 (2.9%) participants in All-Isa group.

Calculated mean creatinine clearance was similar in the VRd and IVRd groups (70.48 and 66.15 mL/min/1.73m²). Calculated mean creatinine clearance was numerically lower in the All- Isa group (59.94 mL/min/1.73m²).

Calculated creatinine clearance by renal status during the treatment period for most of the participants in the VRd, IVRd, and All-Isa groups was rated as normal or mildly impaired (66.5%, 61.9%, and 49.8%, respectively). Severe renal impairment was experienced by 20 (4.2%) participants, 27 (4.3%) participants, and 126 (7.8%) participants, respectively.

End stage renal disease (ie, GFR <15 mL/min/1.73m²) was reported in a few participants in the VRd and IVRd groups (4 [0.8%] participants and 10 [1.6%] participants, respectively). In the All-Isa group a total of 47 (2.9%) participants had end stage renal disease.

Safety in special populations

Age

GMMG-HD7

Of note, 73 (22.1%) participants were ≥65 years of age and <70 years of age in the IVRd group.

Age had some impact on the safety outcomes for the IVRd group, in which 59.7% of participants <65 years of age had Grade ≥3 IND-TEAEs, compared to 77.8% of participants ≥65 years of age. This difference was not observed in participants treated with the VRd combination (61.5% of participants <65 years of age and 60.7% of participants ≥65 years of age had Grade ≥3 IND-TEAEs), so incidence of Grade ≥3 IND-TEAEs appeared lower in the VRd group in older participants as compared to the IVRd group.

In the IVRd group, differences in Grade ≥3 IND-TEAEs between participants <65 years of age and participants ≥65 years of age were observed in the following SOC:

- Nervous system disorders: 14 (5.4%) and 13 (18.1%)
- Cardiac disorders: 5 (1.9%) and 8 (11.1%)
- Respiratory, thoracic and mediastinal disorders: 4 (1.6%) and 5 (6.9%)
- Gastrointestinal disorders: 16 (6.2%) and 9 (12.5%)
- Injury, poisoning and procedural complications: 9 (3.5%) and 6 (8.3%)

In the IVRd group, both the incidence of Grade 3 and Grade 4 TEAEs was increased in older participants (154 [59.7%] participants <65 years of age versus 56 [77.8%] participants ≥65 years of age), as well as the incidence of Grade 5 TEAEs (2 [0.8%] participants <65 years of age versus 2 [2.8%] participants ≥65 years of age). The same trend in Grade 5 TEAEs was observed for the VRd group (3 [1.2%] participants <65 years of age and 4 [4.8%] participants ≥65 years of age) and remained higher in the VRd group compared to the IVRd group in both age subgroups.

The incidence of SAEs in the IVRd group was also increased in older participants (78 [30.2%] participants <65 years old versus 38 [52.8%] participants ≥65 years old). A similar trend for SAEs was observed for the VRd group (81 [33.2%] participants <65 years of age and 39 [46.4%] participants ≥65 years of age) and remained comparable between the two treatment groups in both age subgroups. Additionally, the incidence of AEs leading to definitive discontinuation in the IVRd group was increased in older participants (4 [1.6%] participants <65 years old versus 6 [8.3%] participants ≥65 years old). This trend in AEs leading to definitive discontinuation was not observed in the VRd group (11 [4.5%] participants <65 years of age and 3 [3.6%] participants ≥65 years of age).

All-Isa pool

Age categories for Group 1 were <65, 65-74, and ≥75 years. In both the VRd and IVRd groups, the incidence of Grade ≥3 TEAEs increased with age, and the incidence of serious TEAEs was higher in participants ≥75 years old. Definitive treatment discontinuations increased by age in both treatment groups.

Age categories for Group 3 were <65, 65-70, 71-80, and >80 (**Table 40**). In both the VRd and IVRd groups, incidences for any TEAEs, Grade ≥3 TEAEs, treatment-emergent SAEs, and definitive treatment discontinuations all increased in participants who were >65 years of age, with incidences highest in the 71- 80 years of age category. Due to the small number of participants who were >80 years of age in the IVRd group (n=4), meaningful conclusions cannot be made in this age category.

Table 40. Overview of treatment-emergent adverse events by age group 1 - All-Isa – Safety population

AE groups Age group 1 in years, n(%)	NDMM		RRMM and NDMM
	VRd ^a (N=521)	IVRd ^b (N=692)	All-Isa ^c (N=1787)
Patients with any TEAE			
<65	204/255 (80.0)	232/281 (82.6)	705/763 (92.4)
65-74	185/207 (89.4)	316/326 (96.9)	753/772 (97.5)
≥75	58/59 (98.3)	85/85 (100)	240/252 (95.2)

Patients with any treatment-related TEAE				
<65	39/255 (15.3)	41/281 (14.6)	429/763 (56.2)	
65-74	130/207 (62.8)	258/326 (79.1)	618/772 (80.1)	
≥75	57/59 (96.6)	84/85 (98.8)	206/252 (81.7)	
Patients with any grade ≥3 TEAE				
<65	161/255 (63.1)	173/281 (61.6)	494/763 (64.7)	
65-74	154/207 (74.4)	283/326 (86.8)	615/772 (79.7)	
≥75	50/59 (84.7)	81/85 (95.3)	193/252 (76.6)	
Patients with any treatment-related grade ≥3 TEAE				
<65	34/255 (13.3)	30/281 (10.7)	201/763 (26.3)	
65-74	95/207 (45.9)	201/326 (61.7)	395/772 (51.2)	
≥75	40/59 (67.8)	70/85 (82.4)	133/252 (52.8)	
Patients with any grade 5 TEAE with a fatal outcome during treatment period				
<65	3/255 (1.2)	4/281 (1.4)	43/763 (5.6)	
65-74	8/207 (3.9)	25/326 (7.7)	58/772 (7.5)	
≥75	2/59 (3.4)	12/85 (14.1)	31/252 (12.3)	
Patients with any treatment-related grade 5 TEAE with a fatal outcome during treatment period				
<65	1/255 (0.4)	3/281 (1.1)	7/763 (0.9)	
65-74	3/207 (1.4)	3/326 (0.9)	6/772 (0.8)	
≥75	0/59	2/85 (2.4)	3/252 (1.2)	
Patients with any serious TEAE				
<65	89/255 (34.9)	93/281 (33.1)	356/763 (46.7)	
65-74	122/207 (58.9)	210/326 (64.4)	458/772 (59.3)	
≥75	40/59 (67.8)	63/85 (74.1)	154/252 (61.1)	
Patients with any treatment-related serious TEAE				
<65	16/255 (6.3)	21/281 (7.5)	107/763 (14.0)	
65-74	51/207 (24.6)	96/326 (29.4)	196/772 (25.4)	
≥75	22/59 (37.3)	28/85 (32.9)	63/252 (25.0)	
Patients with any TEAE leading to definitive treatment discontinuation				
<65	14/255 (5.5)	8/281 (2.8)	49/763 (6.4)	
65-74	35/207 (16.9)	62/326 (19.0)	111/772 (14.4)	
≥75	14/59 (23.7)	21/85 (24.7)	40/252 (15.9)	

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone.

- a Include VRd treated NDMM patients from IIT15403 (induction and intensification periods) and EFC12522 (global portion and China expansion, excl. data after crossover).
- b Include IVRd treated NDMM patients from IIT15403 (induction and intensification periods), EFC12522 (global portion and China expansion), and TCD13983.
- c Include isatuximab treated patients from all MM studies including crossover patients receiving IRd and patients from China expansion part in EFC12522.

Gender

GMMG-HD7

For gender, there were no relevant differences in safety profile observed between treatment groups.

All-Isa pool

Females in the NDMM IVRd group had a higher incidence of TEAEs, treatment-related TEAEs, and any Grade ≥3 TEAEs compared with male participants (93.7% vs 89.7%; 60.6% vs 51.3%; 81.5% vs 74.6%, respectively).

Race

GMMG-HD7

For race, there were no relevant differences in safety profile observed between treatment groups; however, the analyses according to race should be interpreted with caution due to the low number of non-Caucasian participants (6) as compared to Caucasian participants (652).

All-Isa pool

There was an imbalance in the number of Caucasian (VRd: 457 participants and IVRd: 566 participants) versus non-Caucasian participants (VRd: 35 participants and IVRd: 69 participants). The number of non-Caucasian participants (compared with Caucasian participants) were too few to draw any meaningful conclusions on TEAE incidences.

Hepatic status

GMMG-HD7

For hepatic status, there were no relevant differences in safety profile observed between treatment groups.

All-Isa pool

There were no trends observed in the incidence of TEAEs in participants based on hepatic status. However, data needed to be interpreted with caution as there were fewer participants with mild/moderate/severe hepatic status at baseline in the VRd and IVRd groups (62 and 76 participants, respectively) compared with participants with normal hepatic status (448 and 605 participants, respectively).

Renal status

GMMG-HD7

Subgroup analysis according to renal status indicated that, in both treatment groups, there was a consistent trend toward higher Grade ≥ 3 TEAE rates and SAE rates in participants with baseline eGFR <60 mL/min/1.73 m² compared to ≥ 60 mL/min/1.73 m². Incidence of Grade ≥ 3 TEAEs in the VRd group was 67.2% and 60% for participants with baseline eGFR <60 mL/min/1.73 m² and ≥ 60 mL/min/1.73 m², respectively, and in the IVRd group was 66.2% and 63%, respectively. Incidence of SAEs in the VRd group was 46.6% and 34.4% for participants with baseline eGFR <60 mL/min/1.73 m² and ≥ 60 mL/min/1.73 m², respectively, and in the IVRd group was 43.1% and 33.2%, respectively. For discontinuations due to AE or for AE leading to death, no differences were observed according to renal status in either treatment group.

All-Isa pool

In the VRd group participants with eGFR <60 mL/min/1.73 m² had a higher incidence of treatment-emergent SAEs versus participants with eGFR ≥ 60 mL/min/1.73 m² (59.7% versus 44.0%) and also for Grade ≥ 3 TEAEs (79.8% versus 68.4%).

In the IVRd group participants with eGFR <60 mL/min/1.73 m² had a higher incidence of treatment-emergent SAEs versus participants with eGFR ≥ 60 mL/min/1.73 m² (60.4% versus 50.4%) and also for TEAEs leading to definitive treatment discontinuation (18.7% versus 11.1%).

In the All-Isa group incidences for participants with treatment-emergent SAEs with eGFR <60 mL/min/1.73 m² and ≥ 60 mL/min/1.73 m² were 60.5% versus 51.7%, respectively.

The safety profile based on renal status indicate similar tolerance between the VRd group, the IVRd group, and the All-Isa group in participants with impaired renal function (eGFR <60 mL/min/1.73 m²), regarding Grade ≥ 3 TEAEs, SAEs, and TEAEs leading to definitive treatment discontinuation. However, the incidence of Grade 5 TEAEs differed for participants in the All-Isa group (4.2% in the VRd group, 9.4% in the IVRd group, and 11.5% in the All-Isa group), primarily associated with the late stage of disease in RRMM participants.

Geographic region

GMMG-HD7

Not applicable, as all study sites were located in Germany.

All-Isa pool

In the VRd and IVRd groups, most of the participants were in Western and Eastern Europe (434 participants and 571 participants, respectively). There were far fewer participants in the other regions and thus the comparison focuses on data from Western and Eastern Europe.

In the All-Isa group, there were no marked or consistent differences across different geographic regions in the incidences of TEAEs.

Long-term exposure

A total of 259 patients with NDMM have been treated with IVRd regimen for more than 24 months, and a total of 433 patients with NDMM or RRMM have been treated with an isatuximab-containing regimen for more than 24 months.

Incidence of any TEAE of Grade ≥ 3 in the IVRd group and the All-Isa group was lower in the >24 months of time period (52.1% and 50.6%, respectively) compared with the ≤ 24 month time period (81.9% and 81.3%, respectively). With the exception of the SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps), the incidence of TEAE of Grade ≥ 3 in most SOCs were also lower in >24 months exposure in IVRd group and all-Isa group, as compared to ≤ 24 months.

Incidence of treatment-emergent SAEs (any grade) by SOC and PT, and by period of first onset of SAE in participants with more than 24 months isatuximab exposure. Incidence of any treatment-emergent SAE in the IVRd group and the All-Isa group was lower in the >24 months of exposure time period (40.5% and 40.9%, respectively) compared with the ≤ 24 month exposure time period (48.6% and 49.4%, respectively). With the exception of several SOCs (Neoplasms benign, malignant and unspecified [incl cysts and polyps]; Eye disorders; Hepatobiliary disorders; Skin and subcutaneous tissue disorders; Renal and urinary disorders [Acute kidney injury only]; and Injury, poisoning and procedural complications), the incidence of SAEs in most SOCs were lower in the >24 months exposure time period in the IVRd group and All-Isa group, as compared to during the ≤ 24 months exposure time period.

Incidence of Grade 5 TEAEs by SOC and PT (and by period of first onset) in participants with more than 24 months isatuximab exposure. In the >24 months exposure population, there were 14 (5.4%) Grade 5 TEAEs in the IVRd group and 25 (5.8%) Grade 5 TEAEs in the All-Isa group. For comparison, in all participants (regardless of length of isatuximab exposure), the total incidence of Grade 5 TEAEs with a fatal outcome during the treatment or post-treatment period was 7.4% (51 of 692 participants) in the IVRd group and 9.2% (165 of 1787 participants) in the All-Isa group.

The majority of Grade 5 TEAEs in the >24 month time period occurred in the SOC Infestations and infestations (10 [3.9%] participants in the IVRd group and 18 [4.2%] participants in the All-Isa group), in which COVID-19 pneumonia was the predominant PT (7 [2.7%] participants in the IVRd group and 10 [2.3%] participants in the All-Isa group).

As cumulative treatment-emergent incidence rates are influenced by the duration of exposure, exposure-adjusted incidence rates were also calculated. In the pooled NDMM studies, there was a trend towards higher exposure-adjusted rates per patient year in the VRd group as compared to the IVRd group for SAEs (0.672 in VRd versus 0.483 in IVRd) and for TEAEs leading to definitive treatment discontinuation (0.096 in VRd versus 0.067 in IVRd). An opposite trend was seen for any TEAEs (6.634 in VRd versus 9.604 in IVRd). Exposure-adjusted rates were similar in the VRd group and the IVRd group for Grade ≥ 3 TEAEs (1.674 in VRd and 1.632 in IVRd) and for Grade 5 TEAEs (0.026 in VRd and 0.030 in IVRd).

In the All-Isa group, the exposure-adjusted rate per patient year for any TEAE was 12.689, which was higher compared with the VRd and IVRd groups in the NDMM studies (6.634 and 9.604, respectively). Exposure-adjusted rate per PY in the All-Isa group were similar to those of VRd and IVRd listed in other categories (eg, participants with any Grade ≥ 3 TEAE).

Discontinuation due to adverse events

Study GMMG-HD7

Induction period

Overall, during induction, 14 (4.3%) and 10 (3.0%) participants in the VRd and IVRd groups, respectively, had TEAEs leading to definitive treatment discontinuation. Definitive treatment discontinuation during induction was most frequently due to sepsis (2 [0.6%] participants) and enteritis (2 [0.6%] participants), in the VRd group. In the IVRd group at the PT level, the highest frequency of a specific event leading to discontinuation of treatment was 1. At the SOC level, the most common causes of definitive discontinuation were Nervous system disorders (eg, autonomic neuropathy, Guillain-Barré syndrome, paraplegia), which occurred in 2 (0.6%) participants in VRd and 6 (1.8%) in IVRd, and Gastrointestinal disorders (eg, nausea and vomiting), which occurred in 5 (1.5%) in VRd and 2 (0.6%) in IVRd.

Among 14 participants in the VRd group, the main reason for treatment discontinuation during induction was selected as AE for 8 participants, withdrawn informed consent for 2 participants, Investigator's decision for 1 participant, and death for 1 participant. One participant developed ovarian cancer (action taken drug withdrawn), but discontinuation was registered for intensification period.

Among 10 participants in the IVRd group, the reason for treatment discontinuation during induction was selected as AE for 6 participants, Investigator's decision for 1 participant for adverse drug reactions, and death for 3 participants.

The 2 patients in the IVRD group had an AE leading to premature discontinuation of either isatuximab or lenalidomide. One patient had a Grade 4 anaphylactic reaction (induction Cycle 1) leading to discontinuation of isatuximab. The other patient had a Grade 3 hypercalcemia (induction Cycle 3) leading to discontinuation of lenalidomide.

Intensification period

During the intensification period, 1 (0.3%) participant in the VRd group definitively discontinued the study treatment due to a TEAE of plasmablastic lymphoma. No participants definitively discontinued treatment from the IVRd group.

All-Isa pool

In the All-Isa pool, TEAEs (all grades) leading to definitive treatment discontinuation were reported in similar incidences in the treatment groups: 63 (12.1%) participants in the VRd group, 91 (13.2%) participants in the IVRd group, and 200 (11.2%) participants in the All-Isa pool. The same was observed for TEAEs of Grade ≥ 3 (10.0%, 11.8%, and 10.0%, respectively).

The most frequently reported TEAEs (all grades) that led to definitive treatment discontinuation in the VRd group were diarrhea (5 [1.0%] participants), pneumonia (4 [0.8%] participants), sepsis (3 [0.6%] participants), and COVID-19 (3 [0.6%] participants).

The most frequently reported TEAEs (all grades) that led to definitive treatment discontinuation in the IVRd group were COVID-19 pneumonia (9 [1.3%] participants), pneumonia (7 [1.0%] participants), and sepsis and sudden death (4 [0.6%] participants, each).

The most frequently reported TEAEs (all grades) that led to definitive treatment discontinuation in the All-Isa pool were infusion related reaction (20 [1.1%] participants), pneumonia (19 [1.1%] participants), COVID-19 pneumonia (13 [0.7%] participants), and sepsis (8 [0.4%] participants).

Post marketing experience

Sarclisa was first approved on 02 March 2020 for Relapsed Refractory Multiple Myeloma.

Since the last (Periodic Benefit-Risk Evaluation Report) PBRER with the reporting interval of 02 March 2023 to 01 March 2024 did not identify any new safety concerns, the MAH reviewed new data between the data lock point of that PBRER and the data lock point of this submission and did not identify any new safety signals.

2.5.1. Discussion on clinical safety

For safety, this submission is based primarily on the safety results from a Phase 3 pivotal study (GMMG-HD7) in participants with NDMM who were eligible for transplant. Only safety data before second randomisation (part 1: induction and intensification) was provided.

In Study GMMG-HD7, only AEs CTCAE Grades 3, 4 and 5 were required to be recorded for the study. Since some specific occurrences were evaluated with respect to their frequency during induction and maintenance treatment, they were documented also at CTCAE Grade 2. So not all AEs were reported, which is considered acceptable, as the general safety profile of isatuximab is already known from previous studies.

There are two additional studies included in the safety population in participants with NDMM treated with the same IVRd regimen and who were not eligible for transplant or with no intent for immediate transplantation: one Phase 3 study (EFC12522) and one Phase 1b/2 supportive study (TCD13983 (Part A and Part B)). These studies provide supportive safety and provide longer follow-up safety data for the combination.

In the pivotal GMMG-HD7 study, a total of 328 (99.1%) participants were randomised and treated in the VRd group and 330 (99.7%) in the IVRd group. Overall, 88.2% participants in the VRd group and 94.3% in the IVRd group completed the induction phase, 10.6% of the participants in the VRd group and 18.5.4% in IVRd group definitively discontinued the study treatment during the induction period. At the time of the cut-off date, there were no participants still in the induction phase. The main reason for definitive treatment discontinuation was AE, which accounted for approximately 2% in each group. After induction therapy, 87.9% in VRd group and 94.3% in IVRd group received treatment during intensification period.

The total median duration of exposure for all of Part 1 (including induction, mobilization, and 1 or 2 ASCT) was 45.1 weeks in the VRd group (Q1;Q3: 38.96;55.7) and 45.4 weeks in the IVRd group (Q1;Q3: 40.1;54.6). The median exposure for induction was 18 weeks, as planned by protocol, the remaining exposure is mainly related to the intensification period. A majority of the participants started at least 3 cycles (92.7% in the VRd group and 95.2% in the IVRd group). The median RDI for isatuximab was 97.8% (interquartile range 91.3 to 100). The median RDIs for bortezomib (94.8% versus 93.2%), lenalidomide (95.2% versus 94.0%) and dexamethasone (97.7% versus 96.2%) in VRd and IVRd groups were similar in both treatment groups.

In the All Isa-pool analysis, a total of 15336 IVRd cycles have been started in 692 patients with NDMM, and a total of 29966 isatuximab cycles have been started in 1787 patients with NDMM or RRMM. The cumulative exposure to treatment was 634.13 patient-years in the VRd group and 1332.42 patient-years in the IVRd group, and 2498.18 patient-years in the All-Isa group. While the median number of cycles started per participant for the VRd, IVRd, and All-Isa groups were 3.0, 4.0, and 6.0, respectively, there was difference in the mean number of cycles started per patient in the IVRd group (22.2 cycles) compared to the VRd group (13.4 cycles) driven by the longer exposure to IVRd treatment in the EFC12522 (IMROZ) study. The number of patients exposed to isatuximab for ≥ 24 months was 259 of 692 total participants (37.4%) in the IVRd group and 433 of 1787 total participants (24.2%) in the All-Isa group.

Adverse events

Study GMMG-HD7

Overall, 78.4% in the VRd group and 82.7% in the IVRd group had at least 1 TEAE during the induction period (IND). Addition of isatuximab to VRd during the induction period did not increase the incidence of Grade ≥ 3 IND-TEAEs (61.3% and 63.6%, respectively), nor the incidence of treatment-emergent SAEs (36.6% and 35.2%, respectively), or IND-TEAEs leading to death (7 [2.1%] participants and 4 [1.2%] participants, respectively), or of IND-TEAEs leading to study discontinuation (4.3% and 3.0%, respectively).

The most frequently reported TEAEs during the induction period (at least 10% of participants in any treatment group for either of the following paired terms) were: polyneuropathy (22.6% VRd, 18.8% IVRd), peripheral sensory neuropathy (7.0% VRd and 6.1% IVRd); lymphocyte count decreased (13.7% VRd and 11.2% IVRd, all Grade 3), lymphopenia (6.1% VRd and 3.3% IVRd, all Grade 3); neutropenia (4.0% VRd and 16.1% IVRd, all Grade 3), neutrophil count decreased (3.0% VRd and 7.3% IVRd, all Grade 3) and infusion related reaction (0% VRd and 12.4% IVRd). The most frequently reported Grade ≥ 3 TEAEs during the induction period (at least 10% of participants in any treatment group) were Neutropenia (4.0% VRd and 16.1% IVRd) and Lymphocyte count decreased (13.7% VRd and 11.2% IVRd).

The most frequently reported treatment-related TEAEs during the induction period (at least 10% of participants in any treatment group for either of the following paired terms) were: neutropenia (4.0% VRd and 14.8% IVRd, all Grade ≥ 3), neutrophil count decreased (3.0% VRd and 7.0% IVRd, all Grade ≥ 3), lymphocyte count decreased (13.4% VRd and 10.6% IVRd, all Grade ≥ 3), lymphopenia (5.2% VRd and 3.3% IVRd, all Grade ≥ 3) and infusion related reaction (0% VRd and 12.1% IVRd).

During the induction period, the highest difference in incidence for AEs between VRd and IVRd treated patients, was seen for neutropenia/neutrophil count decreased, which is a known side effect of isatuximab.

During the intensification period, 22.3% in the VRd group and 22.8% in the IVRd group had TEAEs of any class, of which 16.2% in the VRd group and 17.6% in the IVRd group had any class of TEAEs Grade ≥ 3 . Most of the events reported during the intensification period were SAEs; 19.6% in the VRd group and 20.2% in the IVRd group. 9.6% of VRd and 9.0% of IVRd participants experienced infections and infestations, and 6.9% in VRd and 7.7% in IVRd experienced infections and infestations of Grade ≥ 3 . Considering all grades, Gastrointestinal disorders were observed in 4.1% of participants in the VRd group and 3.8% in the IVRd group, Blood and lymphatic system disorders of all grades were observed in 2.7% of participants in the VRd group and 2.9% in the IVRd group, and General disorders and administration site conditions were observed in 1.7% of participants in the VRd group and 4.2% in the IVRd group. The most common TEAEs of all grades (ie, occurring in at least 7

participants in either group) were sepsis (2.4% in VRd and 0.6% in IVRd) and pyrexia (1.0% in VRd and 2.9% in IVRd).

Overall, TEAEs were well-balanced between the VRd and IVRd groups. During intensification period the incidence of pyrexia was higher in the IVRd group, but absolute numbers were low.

Embolic and thrombotic events, venous and/or arterial, were reported at a slightly lower incidence in the VRd group versus the IVRd group (3.4% and 6.1% for all grades, with Grade ≥ 3 reported as 1.2% and 3.3%, for the VRd and IVRd groups, respectively). Most events were venous (2.4% and 4.5% in the VRd and IVRd groups, respectively). Arterial AEs reported were similar in the VRd and IVRd groups (all grades: 0.9% and 1.5%, respectively, with Grade ≥ 3 : 0.3% and 1.2%, respectively).

Addition of isatuximab to VRd did not increase leucocyte recovery after ASCT, but platelets recovery was slightly longer in the IVRd group compared to the VRd group. Among participants who received 1 ASCT, the median time from the date of stem cells reinfusion to leucocytes recovery was 11 days in both groups. The median time from the date of stem cells reinfusion to platelets recovery was 13 and 16 days, respectively. Among participants who received a second ASCT, the median time from the date of stem cells reinfusion to leucocytes recovery was 11 days in both groups. The median time from the date of stem cells reinfusion to platelets recovery was 12 and 14 days, respectively.

All-Isa pool

85.8% of participants in the VRd group, 91.5% participants in the IVRd group, and 95.0% participants in the All-Isa group had at least 1 TEAE. Grade ≥ 3 TEAEs were reported by 70.1% of participants in the VRd group, 77.6% participants in the IVRd group, and 72.9% participants in the All-Isa group. Serious TEAEs were reported by 48.2% of participants in the VRd group, 52.9% participants in the IVRd group, and 54.2% participants in the All-Isa group or including 17.1% of participants in the VRd group, 21.0% participants in the IVRd group, and 20.5% participants in the All-Isa group, who had a Serious TEAE that were reported as treatment related.

The most frequently reported TEAEs ($\geq 50\%$ of participants [all grades] in either group) by primary SOC in the VRd and IVRd groups were Infections and infestations (46.8% participants and 59.7% participants, respectively) and Nervous system disorders (52.2% and 57.2%, respectively).

The most frequently reported TEAEs ($\geq 20\%$ for all grades) in either the VRd and IVRd groups were: diarrhea (21.3% participants and 32.1% participants, respectively), peripheral sensory neuropathy (26.9% and 31.8%), constipation (16.1% and 23.4%), neutropenia (10.0% and 22.0%), infusion related reaction (0.4% and 21.0%), and cataract (9.6% and 20.2%).

The most frequently reported TEAEs ($\geq 20\%$ for all grades) in the All-Isa group were infusion related reaction (642 [35.9%] participants), diarrhea (535 [29.9%]), upper respiratory tract infection (441 [24.7%]), and fatigue (422 [23.6%]).

A total of 259 patients with NDMM have been treated with IVRd regimen for more than 24 months, and a total of 433 patients with NDMM or RRMM have been treated with an isatuximab-containing regimen for more than 24 months. Presented results do not indicate evidence of cumulative toxicity by isatuximab nor increased incidence of death upon long term exposure in a large data set of 692 participants, when adding isatuximab to the standard of care VRd.

Serious Adverse events

Study GMMG-HD7

In the induction period, the most frequently (at least 2% of participants) reported serious TEAEs were for following the SOC: Infections and infestations (11.9% VRd and 13.0% IVRd); Gastrointestinal

disorders (8.5% VRd and 6.1% IVRd); General disorders and administration site conditions (4.9% VRd and 5.8% IVRd); and Nervous system disorders (5.5% VRd and 3.0% IVRd). The most frequently reported serious TEAEs during the induction period (at least 2% of participants) were: pneumonia (2.7% VRd and 3.6% IVRd); pyrexia (3.4% VRd and 3.3% IVRd); diarrhea (2.7% VRd and 2.1% IVRd); and syncope (2.7% VRd and 0.9% IVRd).

The most frequently reported serious TEAE (>2% of participants in either group, all grades, regardless of causal relationship) by primary PT were sepsis (2.4% in the VRd group and 0.6% in the IVRd group) and pyrexia (1.0% in the VRd group and 2.9% in the IVRd group).

In total, 7 patients in the VRd group and 3 patients in the IVRd group developed a second primary malignancies. As the current submission presents data only from part 1 (including induction and intensification), conclusions regarding SPM incidence in Study GMMG-HD7 cannot be drawn.

During induction, 4.3% and 3.0% in the VRd and IVRd groups, respectively, had TEAEs leading to definitive treatment discontinuation. Definitive treatment discontinuation during induction was most frequently due to sepsis (2 [0.6%] participants) and enteritis (2 [0.6%] participants), in the VRd group. In the IVRd group at the PT level, the highest frequency of a specific event leading to discontinuation of treatment was 1. At the SOC level, the most common causes of definitive discontinuation were Nervous system disorders (eg, autonomic neuropathy, Guillain-Barré syndrome, paraplegia), which occurred in 0.6% participants in VRd and 1.8% in IVRd, and Gastrointestinal disorders (eg, nausea and vomiting), which occurred in 1.5% in VRd and 0.6% in IVRd.

During the intensification period, 1 (0.3%) participant in the VRd group definitively discontinued the study treatment due to a TEAE of plasmablastic lymphoma. No participants definitively discontinued treatment from the IVRd group.

A total of 44 deaths occurred in both groups during induction and intensification periods: 21 in the VRd group and 23 in the IVRd group. Among the 21 deaths in the VRd group, 14 occurred during the induction period and 7 occurred during the intensification period. Among 23 deaths in the IVRd group, 10 occurred during the induction period and 13 occurred during the intensification period. The incidence of death due to AEs that was assessed as related to study treatment was 1.2% for the IVRd group and 2.1% for the VRd group. In the VRd group TEAEs leading to death included cardiac arrest, cardiac failure, enteritis, and hepatorenal failure. In the IVRd group, 1 death was considered related to study treatment; septic shock.

Of the patients who did not receive further maintenance therapy, and who were treated with standard-of-care mobilization and intensification, in total, 7 (2.4%) and 13 (4.2%) died during the intensification period in the VRd and IVRd groups, respectively, in either the treatment period (2 events in the IVRd group) or the post-treatment period (7 (2.4%) and 11(3.5%) events in the VRd and IVRd groups, respectively).

In participants who did not receive further intensification and maintenance therapy, there were 10 (3.0%) deaths in the VRd group and 6 (1.8%) in the IVRd group during the post-treatment induction period. Eleven death events occurred in the context of disease progression and/or further anti-myeloma therapies (6 participants in the VRd group and 5 participants in the IVRd group). The remaining 5 deaths events occurred in the post-treatment induction period (4 in the VRd group [hepatorenal failure, sepsis, enteritis, and urosepsis] and 1 in the IVRd group [COVID-19]).

No symptomatic overdose was reported during Part 1 of the study.

All-Isa pool

Serious TEAEs were experienced by 48.2% of participants in the VRd group and 52.9% of participants in the IVRd group. The most frequently reported serious TEAEs in the VRd group and the IVRd group were pneumonia (6.9% versus 11.3%, respectively), pyrexia (2.9% versus 2.5%), sepsis (1.9% versus 1.6%), and acute kidney injury (1.5% versus 1.3%).

A numerically higher percentage of participants in the IVRd group had Grade 3 white cell count decreased and Grade 4 platelet count decreases, compared with participants in the VRd group (15.4% versus 6.3% and 9.1% versus 3.9%, respectively). During the treatment period, deaths were reported for 2.5% participants in the VRd group, 5.9% participants in the IVRd group, and 7.4% participants in the All-Isa group. Ten (1.9%) participants in the VRd group, 5.1% participants in the IVRd group, and 4.5% participants in the All-Isa pool presented with AEs leading to death during the treatment period.

Second primary malignancies that occurred during the treatment period or the post-treatment period were reported more frequently in patients who received isatuximab; 3.3% participants in the VRd group, 7.4% participants in the IVRd group, and 6.1% participants in All-Isa group. The risk of developing second primary malignancies is included in section 4.4 of the SmPC.

TEAEs leading to definitive treatment discontinuation were reported by 12.1% of participants in the VRd group, 13.2% participants in the IVRd group, and 11.2% participants in the All-Isa group.

Deaths during the post-treatment period were reported for 13.4% participants in the VRd group, 9.5% participants in the IVRd group, and 23.4% participants in the All-Isa group. During the post-treatment period, the most frequent cause of death in the All-Isa pool and the VRd group was Disease progression (15.9% and 5.6%, respectively), while the most frequent cause in the IVRd group was Other (4.0%). The category of Other mainly consisted of adverse events on subsequent therapy.

Laboratory findings

For haematology parameters, the results for the 2 treatment groups were similar across all the haematology parameters. For the induction period, the most frequent abnormalities were anaemia (79.7% in the VRd group and 80.0% in the IVRd group) and lymphocyte count decreased (67.7% in the VRd group and 54.4% in the IVRd group). The incidence of Grade 3 and 4 haematological laboratory abnormalities at the fixed timepoints required per protocol during the induction period was low, demonstrating good haematological tolerance of induction IVRd treatment in the transplant eligible population..

Safety in special populations

Results of study GMMG-HD7 suggest that age had some impact on the safety for the IVRd group, in which 59.7% of participants <65 years of age had Grade ≥ 3 IND-TEAEs, compared to 77.8% of participants ≥ 65 years of age. This difference was not observed in participants treated with the VRd combination (61.5% of participants <65 years of age and 60.7% of participants ≥ 65 years of age had Grade ≥ 3 IND-TEAEs).

More Grade 5 TEAEs were reported in participants ≥ 65 years of age treated with IVRd (0.8% versus 2.8 %). The same trend was seen in the VRd group (1.2% participants <65 years of age and 4.8% participants ≥ 65 years of age). The incidence of Grade 5 events were higher in the VRd group compared to the IVRd group in both age subgroups.

In the IVRd group the incidence of AEs leading to definitive discontinuation in the IVRd group was increased in older participants (1.6% participants <65 years old versus 8.3% participants ≥ 65 years old). This trend in AEs leading to definitive discontinuation was not observed in the VRd group (4.5% participants <65 years of age and 3.6% participants ≥ 65 years of age).

For patients older than 65 the incidence of grade 3 or higher TEAEs including grade 5 TEAEs and AEs leading to definitive discontinuation of the IVRd treatment was higher compared to the younger patients.

In the pooled All-Isa analysis both for the VRd and IVRd groups, incidences for any TEAEs, Grade ≥ 3 TEAEs, treatment-emergent SAEs, and definitive treatment discontinuations all increased in participants who were >65 years of age, with incidences highest in the 71- 80 years of age category. Due to the small number of participants who were >80 years of age in the IVRd group ($n=4$), meaningful conclusions cannot be made in this age category.

Regarding gender; in the All-Isa pool analysis, females in the NDMM IVRd group had a higher incidence of TEAEs, treatment-related TEAEs, and any Grade ≥ 3 TEAEs compared with male participants (93.7% vs 89.7%; 60.6% vs 51.3%; 81.5% vs 74.6%, respectively).

Due to limited number of non-Caucasian patients and with mild/moderate/severe hepatic status at baseline no conclusion can be drawn regarding safety profile for race or hepatic status. Available data do not suggest differences in toxicity per geographic region. For the pivotal safety data set, subgroup analysis according to renal status indicated that, in both treatment groups, there was a consistent trend toward higher Grade ≥ 3 TEAE rates and SAE rates in participants with baseline eGFR <60 mL/min/1.73 m² compared to ≥ 60 mL/min/1.73 m². For discontinuations due to TEAEs or for TEAEs leading to death, no differences were observed according to renal status in either treatment group. The All Isa pool, a higher incidence of treatment emergent SAEs in both VRd group and IVRd group was also seen. However, the safety profile based on renal status indicate similar tolerance between the VRd group, the IVRd group, and the All-Isa group in participants with impaired renal function (eGFR <60 mL/min/1.73 m²).

ADR reporting in the SmPC

Section 4.8 of the SmPC, in relation to this application, includes reported incidence of adverse reactions during the 3 cycles of the induction period. It was decided to not report on ADRs during the intensification phase, as isatuximab is not part of the treatment in this phase. Anaphylactic reactions, second primary malignancies, anaemia, thrombocytopenia, lymphopenia and pneumonia were also added for consistency with safety tables of isatuximab in combination with other drugs or transplant ineligible patients. Neutrophil count decreased was added to complement information on neutropenia.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of isatuximab in addition to VRd induction therapy in patients with newly diagnosed multiple myeloma, was consistent with the known safety profile of isatuximab combination therapy, and with the safety profile as seen for other approved anti-CD38 products. Addition of isatuximab to VRd did not increase overall incidence of Grade 3 or higher AEs, SAEs, discontinuation due to AE or death due to AE during induction period. Furthermore, the safety profile of intensification treatment was generally similar for patients who did or did not receive isatuximab during induction treatment in addition to VRd. No new safety signals were identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set

out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the MAH's assessment is that the additional information pertaining to this application included in the PL are minor, and do not require additional consultation beyond those already performed for previously approved indications.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication is:

"Sarclisa (isatuximab) in combination with bortezomib, lenalidomide and dexamethasone is indicated for the induction treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT)."

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

3.1.2. Available therapies and unmet medical need

Patients with NDMM are typically categorised into two subpopulations: eligible for ASCT or transplant ineligible. Eligibility is usually defined by age and suitability for intensive treatment. Patients eligible for ASCT will typically receive an induction regimen followed by intensification (high-dose chemo + ASCT), sometimes followed by consolidation therapy and often followed by maintenance treatment. VRd, along with quadruplet regimen DaraVTd (daratumumab-bortezomib-thalidomide-dexamethasone), is one of the preferred induction regimens recommended by NCCN and ESMO treatment guidelines for the primary therapy of patients with NDMM who are transplant candidates (Kumar 2023; Dimopoulos 2021). More recently, daratumumab in combination with VRd during induction and consolidation treatment, and in combination with R during maintenance treatment received authorisation in transplant eligible NDMM patients (EMA/CHMP/494023/2024).

Despite the significant progress that has been made in the management of multiple myeloma, it remains an incurable malignancy, and thus there is an unmet need (e.g. prolonged disease control), particularly in the high-risk patients.

3.1.3. Main clinical studies

The pivotal study, GMMG-HD7 (IIT15403) is a randomised, open-label Phase 3 study in NDMM patients who are eligible for ASCT. In this study, isatuximab, bortezomib, lenalidomide and dexamethasone (IVRd) induction treatment was compared to VRd induction alone (part 1) and maintenance treatment with isatuximab, lenalidomide and dexamethasone (IRd) was compared to maintenance with lenalidomide and dexamethasone (Rd) alone (part 2). IVRd and VRd were given for an induction period of 18 weeks (three 42-day cycles), followed by intensification (HDT + ASCT). After intensification, a second randomisation took place and patients received maintenance treatment in 28-day cycles for up to 39 cycles. The current extension of indication is restricted to part 1 of the study, i.e. the added benefit of isatuximab during induction treatment.

Patients were randomised in a 1:1 ratio to VRd (N=331) or IVRd (N=331). Randomisation was stratified by R-ISS (I or II versus III versus not classified).

Efficacy was analysed in the ITT population. The primary endpoint was MRD negativity at the 10^{-5} level, supported by PFS and OS analyses including or excluding patients that received isatuximab during maintenance treatment.

3.2. Favourable effects

At the cut-off date and with a median follow-up time of 49.31 months, the study demonstrated a significant improvement in MRD negativity for patients who received induction treatment with isatuximab in combination with VRd vs. VRd alone: OR = 1.84 (95% CI: 1.35 to 2.51; $p < 0.0001$). The MRD negativity rate at the end of induction in the IVRd group was 50.5% (95% CI: 0.4493 to 0.5597), compared to 35.6% (95% CI: 0.3049 to 0.4107) in the VRd group, demonstrating a 14.8% increase in MRD negativity upon addition of isatuximab to the VRd triplet. MRD negativity is robust in sensitivity analyses and the effect is consistent in most subgroups.

A hierarchical testing procedure was carried out for the key secondary endpoint PFS and OS. Both endpoints were analysed within the entire induction treatment group, (1) regardless of which maintenance treatment they received, and (2) only in the patients who received SOC maintenance treatment (Rd) without isatuximab.

PFS regardless of maintenance treatment: At a median follow-up of 49.31 months, in the ITT-IND population, 94 (28.4%) and 72 (21.8%) participants had PFS events (primarily disease progression) in the VRd and IVRd groups, respectively. The HR was 0.701 (95% CI: 0.516 to 0.953, $p = 0.0113$). The median PFS was not reached in either group. At 48 months, the PFS probability was 69.5% in the VRd group and 77.0% in the IVRd group. PFS regardless of maintenance treatment is robust in sensitivity analyses and the effect is consistent in most subgroups.

PFS with SOC maintenance: The IPW HR was 0.622 (95% CI: 0.424 to 0.912; $p = 0.0066$). The median weighted KM estimates of PFS were not reached in either group. The weighted PFS probability

at 36-months was 84.8% in IVRd group versus 73.2% in VRd group. The unweighted analysis based on the EMA censoring rules showed a HR of 0.643 (95% CI: 0.456 to 0.907).

OS data were very immature, with 87.3% and 85.2% of patients censored in the VRd and IVRd arm, respectively. This is in line with the long survival that is expected in NDMM patients. OS regardless of maintenance treatment: HR = 1.14 (95% CI 0.75 to 1.72; p-value NC); OS with SOC maintenance: HR = 1.036 (95% CI 0.62 to 1.74; p-value NC).

3.3. Uncertainties and limitations about favourable effects

Since MRD negativity is not validated as a surrogate endpoint, the clinical benefit of the observed 14.8% increase in MRD negativity upon addition of isatuximab to the VRd triplet during induction is difficult to interpret. While it indicates that more patients achieve a deeper response with IVRd treatment, it is not yet known how this metric correlates with the preferred endpoints of PFS and OS. Furthermore, this MRD negativity was determined at a single timepoint (namely after induction), whereas it may be more informative to assess how long the MRD negative status is retained in patients, thereby adding a time-to-event component to the endpoint. Lastly, it is unclear whether 4.5 months is long enough for MRD negativity to develop. Some scientific data suggest that roughly 50% of patients may take longer to achieve an MRD negative status.

Investigators and the MAH were unblinded and changes were made to the protocol and in the SAP after the open-label study had already started and the study was well-advanced. Post-hoc explanations from the MAH have largely mitigated concerns that these decisions were data-driven. Firstly, it was in the MAH's best interest to deviate from the protocol and put more weight on testing for the induction phase than for the maintenance phase, as this would allow the study to finish earlier. Secondly, the choice of weights had minimal impact on statistical significance of the PFS analyses which were already at the border of statistical significance, sometimes significant or sometimes not depending on the scenario (weight, adjudication by investigator or independent review, treatment comparison, censoring rule). For the clinically relevant comparison of PFS with SoC maintenance, top line results of the academic sponsor and the MAH were similar.

As OS data are currently immature, the CHMP recommended the submission of the final OS analysis once available.

3.4. Unfavourable effects

This submission is based primarily on the safety results from the Phase 3 pivotal study (GMMG-HD7) in participants with newly diagnosed multiple myeloma (NDMM) who were eligible for transplant. Only safety data before second randomisation (part 1: induction and intensification) were provided.

A total of 328 participants were randomised and treated in the VRd group and 330 in the IVRd group. The total median duration of exposure for all of Part 1 (including induction, mobilization, and 1 or 2 ASCT) was 45.1 weeks in the VRd group (Q1;Q3: 38.9;55.7) and 45.4 weeks in the IVRd group (Q1;Q3: 40.1;54.6). The median exposure for induction was 18 weeks, as planned by protocol, the remaining exposure is mainly related to the intensification.

Overall, 257 (78.4%) of participants in the VRd group and 273 (82.7%) participants in the IVRd group had at least 1 TEAE during the induction period (IND). The most frequently reported TEAEs during the induction period (at least 10% of participants in any treatment group for either of the following paired terms) were: polyneuropathy/peripheral sensory neuropathy (22.6%/7.0% VRd and 18.8%/6.1%

IVRd); lymphocyte count decreased/lymphopenia (13.7%/6.1% VRd and 11.2%/3.3% IVRd, all Grade 3); neutropenia/neutrophil count decreased (4.0%/3.0% VRd and 16.1%/7.3% IVRd, all Grade 3); and infusion related reaction (0% VRd and 12.4% IVRd).

The most frequently reported Grade ≥3 TEAEs during the induction period (at least 10% of participants in any treatment group) were Neutropenia (4.0% VRd and 16.1% IVRd) and Lymphocyte count decreased (13.7% VRd and 11.2% IVRd).

In the induction period, the most frequently reported serious TEAEs (at least 2% of participants) were: pneumonia (2.7% VRd and 3.6% IVRd); pyrexia (3.4% VRd and 3.3% IVRd); diarrhea (2.7% VRd and 2.1% IVRd); and syncope (2.7% VRd and 0.9% IVRd).

During induction, 14 (4.3%) and 10 (3.0%) participants in the VRd and IVRd groups, respectively, had TEAEs leading to definitive treatment discontinuation. Definitive treatment discontinuation during induction was most frequently due to sepsis (2 [0.6%] participants) and enteritis (2 [0.6%] participants), in the VRd group. In the IVRd group at the PT level, the highest frequency of a specific event leading to discontinuation of treatment was 1.

A total of 44 deaths occurred in both groups during induction and intensification periods: 21 in the VRd group and 23 in the IVRd group. During the inducing period the incidence of TEAEs leading to death was 1.2% for the IVRd group and 2.1% for the VRd group. In the VRd group 4 deaths were assessed as related to study treatment including cardiac arrest, cardiac failure, enteritis, and hepatorenal failure. In the IVRd group, 1 death from septic shock was considered related to study treatment.

3.5. Uncertainties and limitations about unfavourable effects

In Study GMMG-HD7, only AEs CTCAE Grades 3, 4 and 5 were required to be recorded for the study. Since some specific occurrences were evaluated with respect to their frequency during induction and maintenance treatment, they were documented also at CTCAE Grade 2. So not all grade 2 or lower AEs were reported, which is considered acceptable as the general safety profile of isatuximab is already known from previous studies.

In the pooled All-Isa analysis both for the VRd and IVRd groups, incidences for any TEAEs, Grade ≥3 TEAEs, treatment-emergent SAEs, and definitive treatment discontinuations all increased in participants who were >65 years of age, with incidences highest in the 71- 80 years of age category. However, due to the small number of participants who were >80 years of age in the IVRd group (n=4), no robust conclusions regarding to the safety profile in patients>80 years can be drawn.

3.6. Effects Table

Table 41. Effects Table for induction treatment with isatuximab in combination with VRd in participants with NDMM who are eligible for ASCT (data cut-off: 31 January 2024)

Effect	Short description	Unit	IVRd	VRd	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	IVRd	VRd	Uncertainties / Strength of evidence	References
PFS	Progression free survival defined as median time from randomisation to first disease progression (according to the IMWG response criteria) or death in patients with induction treatment followed by SOC maintenance	Months (95% CI)	NC (NC to NC)	NC (51.35 to NC)	SoE: HR = 0.643 (95% CI 0.456 – 0.907; p = 0.011) SoE: Support from other endpoints in the trial (e.g. MRD negativity with OR: 1.84, 95% CI: 1.35-2.51) Unc: OS: HR: 1.036 (95% CI 0.62 – 1.74) Immature data (12.7% vs 14.8% of events met)	GMMG-HD7
Unfavourable Effects						
≥ Grade 3 IND-TEAEs	Grade ≥3 TEAEs during induction phase	%	63.6	61.3	Derived from a phase 3 RCT	GMMG-HD7
IND-TEAEs leading to death	TEAEs leading to death in induction phase	%	1.2	2.1	Overall percentage of TEAEs leading to death (including intensification phase, post treatment, death during maintenance period were not included in this report) 2.1% for IVRd and 2.4% for VRd arm	
IND- TEAEs leading to discontinuations	TEAEs leading to discontinuation in induction phase	%	3.0	4.3		
Severe neutropenia	≥ Grade 3 neutropenia During induction phase	%	16.1	4.0		
IR	Grade 3-4 During induction phase	%	12.7	-	Only grade 2 and above IR were collected.	

ASCT - autologous stem cell transplant; IND - induction; NC - not calculated; NDMM - newly diagnosed multiple myeloma; OS - overall survival; PFS - Progression free survival; HR-hazard ratio, CI- confidence interval; IVRd – isatuximab, bortezomib, lenalidomide, and dexamethasone; VRd - bortezomib, lenalidomide, and dexamethasone; SOC: standard of care; TEAE - treatment emergent adverse event; IR- infusion reactions

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Survival for patients with NDMM is still less than that of the general population, and there is an unmet medical need for new treatments with increased and more durable responses, and reduced toxicity. Addition of isatuximab to the SOC first-line triplet induction regimen VRd showed a longer progression-

free survival in patients treated with IVRd when compared to VRd during induction, both regardless of the maintenance they later received (IR or R), and followed by the SOC maintenance alone (R). These latter results are considered to have most clinical relevance, since isatuximab is not currently approved in maintenance therapy, and lenalidomide maintenance accurately reflects current clinical practice. This benefit is supported by a statistically significant improvement in MRD negativity rate chosen as primary endpoint by the study sponsor.

OS data are currently immature and the Kaplan-Meier curves appear to be mostly overlapping. Although an OS detriment is unlikely, the MAH will submit the final OS analysis to provide further re-assurance on this.

The safety profile of isatuximab in addition to VRd induction therapy in patients with newly diagnosed multiple myeloma, was consistent with the known safety profile of isatuximab combination therapy.

Addition of isatuximab to VRd did not increase overall incidence of Grade 3 or higher AEs, SAEs, discontinuation due to AE or death due to AE during induction period. Furthermore, the safety profile of intensification treatment was generally similar for patients who received or did not receive isatuximab during induction treatment. No new safety signals were identified.

3.7.2. Balance of benefits and risks

The benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone for the induction treatment of NDMM patients who are eligible for ASCT has been established from the submitted results of study GMMG-HD7. No new safety concerns were identified for isatuximab. The observed toxicity generally reflects the known safety profile of isatuximab. The safety profile is acceptable in the context of the observed clinical activity, i.e., a benefit in PFS.

3.8. Conclusions

The overall B/R of isatuximab in combination with bortezomib, lenalidomide and dexamethasone for the first line induction treatment of NDMM who are transplant eligible is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an	Type II	I, II and IIIB

	approved one		
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Extension of indication to include, in combination with bortezomib, lenalidomide and dexamethasone, the induction treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT) for Sarclisa, based on the results from study IIT15403 (GMMG-HD7); this is a randomised phase III study designed to assess the efficacy and safety of Sarclisa for the induction and maintenance treatment of NDMM. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial and formatting changes to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

Additional risk minimisation measures

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

The educational program is aimed at:

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

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

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

1. HCPS AND BLOOD BANKS EDUCATIONAL MATERIAL

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

1.1 Healthcare professionals and Blood Banks brochure

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

Relevant information of the safety concern “Interference for blood typing (minor antigen) (positive indirect Coombs’ test)”:

- Isatuximab bound to red blood cells (RBCs) may mask the detection of antibodies to minor antigens in the patient’s serum
- The determination of a patient’s ABO and Rh blood type are not impacted

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

- All patients should be blood typed and screened prior to start treatment with isatuximab. Phenotyping may be considered prior to starting isatuximab treatment as per local practice.
- There is currently no available information with regards to how long the interference with the indirect Coombs test may persist after the last infusion of isatuximab. Based on the half-life of isatuximab, isatuximab mediated positive indirect Coombs test may persist for at least 6 months after the last isatuximab infusion therefore the HCP should advise the patient to carry the patient card until at least 6 months after the treatment has ended.
- The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt isatuximab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.
- In case of urgent need for transfusion, non-cross matched ABO/Rh compatible RBC units can be administered as per local bank practices.
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the risk of interference with indirect antiglobulin tests.
- Emphasize the need to consult the SmPC.
- Instruct the HCP regarding the need to give the patient card to the patients and to advise them to consult the Package Leaflet (PL).

1.2 Patient Card

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

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sarclisa is not similar to Darzalex, Farydak, Kyprolis, Ninlaro, Carvykti, Talvey and Abecma, within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Sarclisa-H-C-004977-II-0035'.