25 February 2021
EMA/CHMP/186236/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SARCLISA

International non-proprietary name: isatuximab

Procedure No. EMEA/H/C/004977/II/0003

Note

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

Table of contents

List of abbreviations

ADA	anti-drug antibodies
ADCC	antibody dependent cell mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
ASCT	autologous stem cell transplantation
AUC	area under the concentration-time curve
CD38	cluster of differentiation 38
CDC	complement dependent cytotoxicity
CI	confidence interval
CL	clearance
Cmax	maximum plasma concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CRenal	complete renal response
CT4W	trough concentration at the end of 4 weeks
DOR	duration of response
D-Rd	daratumumab with lenalidomide and dexamethasone
D-Vd	daratumumab with bortezomib and dexamethasone
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire
E-R	exposure-response
EU	European Union
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
GHS	global health status
IAT	indirect antiglobulin test, also known as indirect Coombs test
IFE	immunofixation electrophoresis
IgG1	immunoglobulin G1
IKd	isatuximab in combination with carfilzomib and dexamethasone
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IPd	isatuximab in combination with pomalidomide and dexamethasone
IR	infusion reaction
IRC	Independent Response Committee
ISS	international staging system
ITT	intent-to-treat
IV	intravenous

Kd	carfilzomib and dexamethasone
KdD	daratumumab with carfilzomib and dexamethasone
LC-HRMS	liquid chromatography high resolution mass spectrometry
LC-MS/MS	tandem mass spectometry
LLOQ	lower limit of quantification
MDRD	modification of diet in renal disease
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
NDMM	newly diagnosed multiple myeloma
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
Pd	pomalidomide and dexamethasone
PD	pharmacodynamic
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	preferred term
QoL	quality of life
QW/Q2W	once weekly for the first cycle and every 2 weeks thereafter
RDI	relative dose intensity
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
sCR	stringent complete response
SOC	system organ class
SPEP	serum M-protein electrophoresis
SPM	second primary malignancy
TEAE	treatment-emergent adverse event
TTP	time to progression
US	United States
V1	volume of distribution of central compartment
V2	volume of distribution of peripheral compartment
Vd	bortezomib and dexamethasone
VGPR	very good partial response

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 25 August 2020 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 and IIIB

An Extension of indication for Sarclisa to add combination with carfilzomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. As a consequence the sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 have been updated. The PL is updated accordingly. The MAH took the opportunity to introduce minor changes in the SmPC sections 4.9, 6.3 and 6.6 and update the details of local representatives. Revised RMP version 1 has been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0156/2018 and P/0193/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0156/2018 and PIP P/0193/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 22 July 2017 (EMEA/H/SA/2998/1/FU/3/2017/PA/II, EMEA/H/SA/2998/1/FU/2/2017/PA/III). The Protocol assistance pertained to orphan similarity considerations and the adequacy of the isatuximab dose and schedule proposed for use in combination with carfilzomib and dexamethasone in EFC15246, as well as on the proposed phase III study design to support registration and labelling.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	25 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur Assessment Report	6 November 2020
PRAC Rapporteur Assessment Report	13 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 December 2020
Request for supplementary information (RSI)	10 December 2020
CHMP Rapporteur Assessment Report	26 January 2021
PRAC Rapporteur Assessment Report	26 January 2021
PRAC members comments	3 February 2021
Updated PRAC Rapporteur Assessment Report	5 February 2021
PRAC Outcome	11 February 2021
CHMP members comments	15 February 2021
Updated CHMP Rapporteur Assessment Report	19 February 2021
Opinion	25 February 2021
The CHMP adopted a report on similarity of Sarclisa with name of the authorised orphan medicinal product(s) on	25 February 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

SARCLISA is indicated:

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

This EoI is to include the combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Epidemiology

Multiple myeloma (MM) accounts for 10% of all haematological malignancies. The incidence in Europe is

4.5-6/100.000/year with a median age at diagnosis between 65 and 70 years.

Aetiology and pathogenesis

The cause of a myeloma cell's failure to differentiate is unknown. However, translocations between chromosome 14q32 and its neighbours (involving the immunoglobulin heavy chain region) and deregulation of the c-myc oncogene appear to play a role in the initial stages of the disease; additionally, mutations in N-Ras and K-Ras are seen in up to 15% of patients at the time of diagnosis. Conversely, mutations in p53 are rarely seen at diagnosis but instead are noted in extramedullary relapses, along with phenotypic and cytological changes. With the exception of chromosome 13q deletions, which are consistently associated with a poor prognosis, the role of other changes in the pathogenesis and severity of the disease have yet to be defined.

Clinical presentation, diagnosis and stage

The clinical features of MM are varied and can arise from the effects of the tumour itself, or the toxicity of the tumour products, or the host's own immune response.

The most common symptoms include persistent skeletal pain (especially pain in the back or thorax), pathological fractures and vertebral collapse, anaemia, renal impairment, hypercalcaemia and recurrent or persistent bacterial infections. Approximately 20% of patients are asymptomatic at the time of diagnosis.

The most common criteria used in diagnosis of symptomatic MM are the presence of $\geqslant$10% clonal BM plasma cells or biopsy proven bony or extramedullary plasmacytoma; paraprotein (M protein) in the serum and/or urine; and evidence of related organ or tissue impairment due to plasma cell disorder.

Prognostic factors that have been identified to predict the heterogeneity in survival are: serum ß2-microglobulin, albumin, C-reactive protein and lactate dehydrogenase. In addition, the genetic abnormalities t(4;14), deletion(17p), t(14;16) and chromosome 1 abnormalities are mostly associated with a poorer outcome. The International Staging System (ISS) relies on the combination of the level of serum ß2-microglobulin and albumin in 3 different stages with ISS 3 being associated with the poorest outcome. The ISS was revised by the International Myeloma Working Group (IMWG) in 2015[1] to include cytogenetics by fluorescence in situ hybridisation (FISH) and lactate dehydrogenase (LDH). This revised ISS (R-ISS) is now widely accepted. At the time of diagnosis, patients are typically categorised according to R-ISS, their age, comorbidity and their suitability for intensive treatment.

In general, the disease is characterised by a chronic phase lasting several years, and an aggressive terminal phase. Almost all patients with multiple myeloma (MM) who survive initial treatment will eventually relapse and require further therapy. Progress has been made over the last 15 years in the treatment of multiple myeloma, such that survival of patients with newly diagnosed multiple myeloma has increased from approximately 3 years from the years 1985 to 1998 (Kyle 2003) to 6 to 10 years (Moreau 2015).

First line treatment options contain at least one of the novel therapies, i.e. proteasome inhibitors and/or immunomodulatory drugs, followed by autologous stem cell transplantation (ASCT), if indicated. Depth of response after autologous transplantation appears to correlate with the duration of disease control until disease progression with the need for salvage therapy. Although second and later remissions can be achieved with further therapy, myeloma typically reappears more aggressively after each relapse, leading to decreased duration of response and culminating in treatment-refractory disease with short survival times.

Management

[1] Lancet Oncol. 2014 Nov;15(12):e538-48. doi: 10.1016/S1470-2045(14)70442-5. Epub 2014 Oct 26.

The treatment landscape for patients with RRMM is rapidly changing following the recent approval of several second generation medicinal products and products belonging to novel classes of agents and the use of multidrug combinations of two, three and sometimes even 4 different products. Current treatment regiments for MM include glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell transplantation (ASCT), proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (IMiDs, such as thalidomide, lenalidomide and pomalidomide) and the monoclonal antibody (mAbs) directed at cell surface markers (daratumumab, elotuzumab and isatuximab).

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse). In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT and had a PFS of more than 24 months.

The most commonly used regimens in the relapsed/refractory setting are proteasome inhibitor- or lenalidomide-containing regimens. Recently approved treatment regiments for MM who have received at least one prior therapy include the combinations of carfilzomib/lenalidimide/dexamethasone (approval in 2016) and carfilzomib/dexamethasone (approval in 2016), elotuzumab/lenalidomide/dexamethasone (approval in 2016), daratumumab/lenalidomide/dexamathasome (approval in 2017), daratumumab/bortezomib/dexamethasone (approval in 2017), pomalidomide/bortezomib/dexamethasone (approval in 2019).

2.1.2. About the product

Isatuximab (SAR650984, hu38SB19) is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 receptor. CD38 is a transmembrane glycoprotein that is highly expressed on plasma cells. It is both an enzyme, able to catalyze the formation of nucleotide metabolites involved in calcium signalling, and a receptor, which induces cell signalling through interaction with other receptors at the surface of the cell. The CD38 receptor is involved in the homeostasis of the hematopoietic compartment as a modulator of cell survival and differentiation.

The CD38 antigen is expressed in several haematological malignancies of B lymphocyte, T lymphocyte, and myeloid origin. Moreover, CD38 was identified as a negative prognostic marker in chronic lymphocytic leukemia (CLL). Thus, mAbs directed at CD38 are potentially effective as treatment of various hematological malignancies, MM, Non-Hodgkin lymphoma (NHLs), acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML).

In vitro, isatuximab acts through IgG Fc-dependent mechanisms including: antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Furthermore, isatuximab can also trigger tumor cell death by induction of apoptosis via an Fc-independent mechanism. In vitro, isatuximab blocks the enzymatic activity of CD38 which catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR), a calcium mobilising agent. Isatuximab inhibits the cADPR production from extracellular nicotinamide adenine dinucleotide (NAD) in MM cells. In vitro, isatuximab can activate NK cells in the absence of CD38 positive target tumour cells. In vivo, a decrease in absolute counts of total CD16+ and CD56+ NK cells, CD19+ B-cells, CD4+ T-cells and TREG (CD3+, CD4+, CD25+, CD127-) was observed in peripheral blood of patients treated with isatuximab monotherapy. In MM patients, isatuximab monotherapy induced clonal expansion of the T-cell receptor repertoire indicating an adaptive immune response.

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

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

Data to support the current application for the use of isatuximab

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

comes from one pivotal phase III study (EFC15246) and 3 additional studies to support the combination with dexamethasone or carfilzomib. The design of the pivotal study, comparator arm, isatuximab dose, randomisation, and endpoints were discussed and agreed in scientific advice (EMEA/H/SA/2998/1/FU/3/2017/PA/II, EMEA/H/SA/2998/1/FU/2/2017/PA/III).

2.1.4. General comments on compliance with GCP

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

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

No ERA studies were submitted (please see Discussion on Non-clinical aspects).

2.2.2. Discussion on non-clinical aspects

The MAH has submitted a claim of exclusion from submission of environmental risk assessment studies according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline corr. 2) as isatuximab is a monoclonal antibody consisting of linked naturally occurring amino acids and its use is unlikely to alter the concentration or distribution of the substance in the environment. Therefore, the mAb is not expected to pose a risk to the environment. This is agreed and no environmental risk assessment would be required.

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 type	Study code/Report location	Dose regimen	Number of patients treated[a]
PK and PD in clinical studies supporting the IKd combination			
Efficacy and safety	[EFC15246]	**IKd arm:**	**IKd:** 177
Phase 3 - IKd combination	5.3.5.1	Isatuximab: 10 mg/kg weekly for the first cycle, then Q2W	
		Carfilzomib: Cycle 1: 20 mg/m^2 Day 1-2, then 56 mg/m^2 Days 8-9 and 15-16; all further cycles: 56 mg/m^2 Days 1-2, 8-9, 15-16	
		Dexamethasone: 20 mg Days 1-2, 8-9, 15-16, and 22-23	
		Kd arm:	**Kd:** 122
		Carfilzomib: Cycle 1: 20 mg/m^2 Day 1-2, then 56 mg/m^2 Days 8-9 and 15-16; all further cycles: 56 mg/m^2 Days 1-2, 8-9, 15-16	
		Dexamethasone: 20 mg Days 1-2, 8-9, 15-16, and 22-23	

2.3.2. Pharmacokinetics

The PK of isatuximab have been characterised in the clinical development program to date across multiple studies in MM patients with diverse demographic characteristics. In the original submission, isatuximab was approved for the treatment in combination with pomalidomide and dexamethasone (Ipd). Isatuximab was administered by IV infusion over the dose range of 0.0001 to 20 mg/kg as Q2W, QW, QW/Q2W, or Q2W/Q4W loading/maintenance regimens. The PK of isatuximab are characterised by parallel linear (time-dependent) and nonlinear Michaelis-Menten (concentration-dependent) elimination pathways.

In the current submission, the applicant is seeking approval of isatuximab in combination with carfilzomib (Kyprolis) and dexamethasone , so called IKd combination, for the treatment of patients with MM who have received at least one prior therapy, based on the pivotal Phase 3 study EFC15246. PK has been studied in the Phase III study (EFC15246) in addition to the studies submitted in the initial MAA.

The proposed dosing regimen is the same as for isatuximab in combination with pomalidomide and dexamethasone (IPd): 10 mg/kg administered intravenously (IV) once weekly (QW) for the first cycle (28 days; 4 once-weekly administrations), and every 2 weeks (Q2W) thereafter (QW/Q2W). The proposed drug product is a concentrate for solution for infusion at a concentration of 20 mg/mL.

Pop-PK model isatuximab (POH0630)

The objectives of this analysis were to provide individual PK and exposure parameter estimates of isatuximab for the 172 patients who received 10 mg QW/Q2W and were included in the interim analysis of Study EFC15246, and for further PK/PD analyses and to investigate the PK sources of variability.

Methods

The final population PK (PPK) model developed in POH0503 (from studies TED10893, TCD14079, TED14154 and EFC14335 in a total of 476 patients) was used to perform an empirical Bayesian estimation and to derive empirical Bayes estimates (EBE: conditional modes of the distribution) in patients from EFC15246.

Individual PK parameters were generated for patients from Phase 3 study EFC15246 with a Bayesian method using a previously developed population PK model POH0503 (included in the original submission) as prior information and the concentration-time data for each patient. Briefly, this was a 2 compartment PK model with parallel nonlinear Michaelis-Menten (concentration-dependent) elimination and linear time-dependent elimination (sigmoidal Emax function, where Emax is maximum effect) from the central compartment. In the model, linear CL at steady state was significantly related to β2 microglobulin, body weight, and Ig MM type (IgG versus non-IgG) whereas central volume of distribution was found to be related to body weight, gender, material (isatuximab P1F1 versus isatuximab P2F2) and race (Asian versus non-Asian).

The analysis was performed using the SAEM algorithm for nonlinear mixed-effects models implemented in MONOLIX software (Version 2019R1).

Graphical and statistical analyses were then performed in order to identify potentially influential covariates on posterior individual Ctrough values at the end of 4 weeks (CT4W), the best PK predictor for efficacy. The continuous covariates at baseline tested were age, body surface area, body weight, body mass index (BMI), serum albumin, serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, estimated glomerular filtration rate (eGFR), lactate dehydrogenase (LDH), β2-microglobulin, percent of plasma cells in bone marrow, serum M-protein, lymphocytes, and number of prior lines of treatment. Gender, race, MM International Staging System (ISS), serum albumin by group, performance status (ECOG), the nature of multiple myeloma disease including the main Ig MM type, renal and hepatic impairment grades, and obesity were explored as categorical covariates at baseline.

Model validation

Figure 1 illustrates the agreement between individual observed plasma concentrations vs individual predicted plasma concentrations whereas the lack of trend in **Figure 2** and **Figure 3** (IWRES vs time and predictions, respectively) show that the structural model and especially the time-dependency, as implemented in POH0503, was able to describe what happened in EFC15246 on an individual basis. In addition, all individual fittings indicate that different kind of profiles could be described by the POH0503 model.

Figure 1. *Observations vs individual predictions from pop-PK model.*

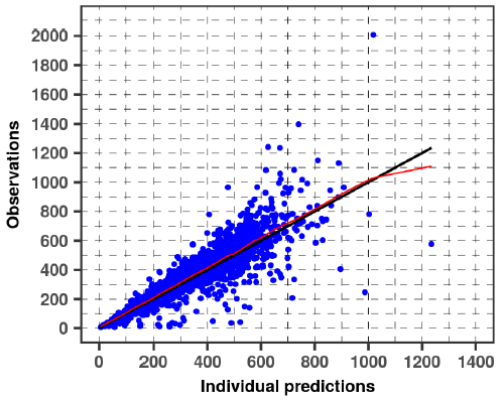


Figure 2. *IWRES vs time from pop-PK model.*

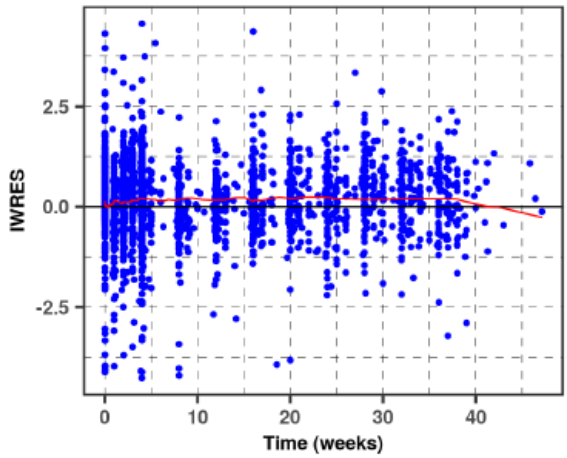
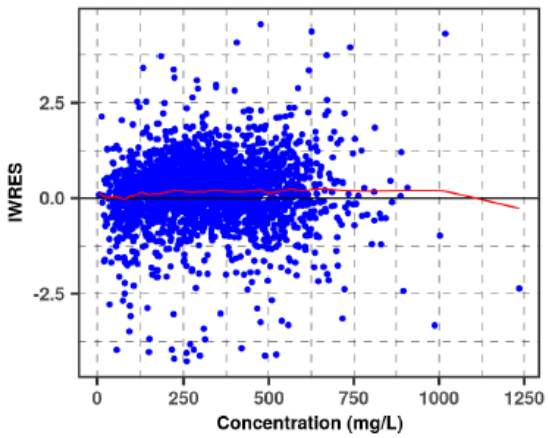


Figure 3. *IWRES vs observations from pop-PK model.*



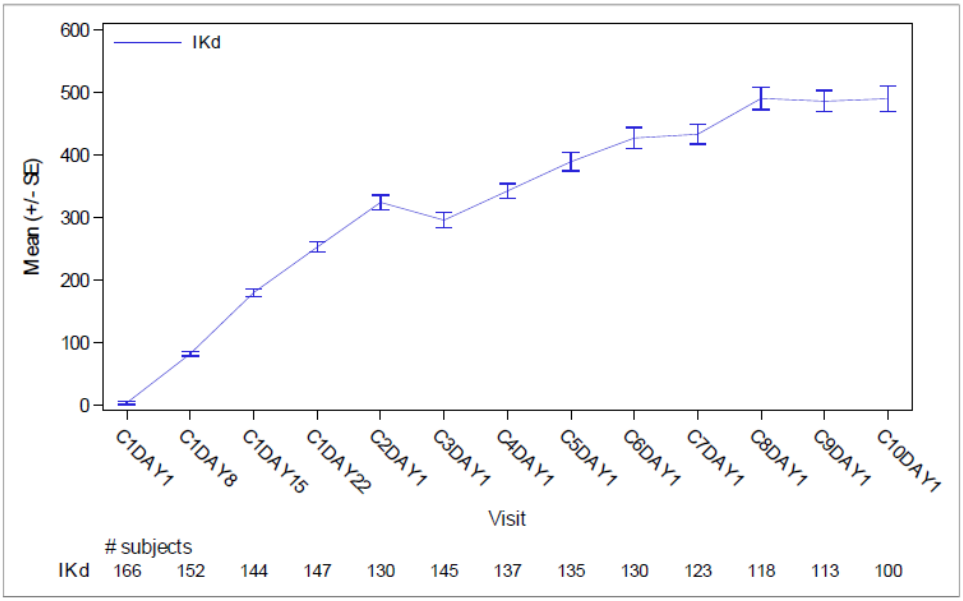
Results

PK in the target population

In study EFC15246, isatuximab PK were evaluated in 172 patients; however, only 166 predose concentrations were included in the descriptive statistics of Ctrough because 5 predose samples were in fact collected in the 30 minutes following the start of infusion and one patient had no predose sample.

A plot of the Ctrough profile throughout the course of the treatment are presented in Figure 4.

***Figure 4**. Plot of mean Ctrough of isatuximab (+/- SE) by sample time (day) – Pharmacokinetic population.*



Note: isatuximab concentrations below the limit of quantification (equal to 5 µg/mL) are set to 0 µg/mL.
PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/pk_ctrough_p_f.sas
OUT=REPORT/OUTPUT/pk_ctrough_p_f_i.rtf (15JUN2020 11:10)

Relative to Cycle 1 Day 8 (1st administration), accumulation based on the observed trough concentration (Ctrough) was 4.25- and 4.18-fold for Cycle 2 Day 1 (5th administration, N=130) and Cycle 4 Day 1 (9th administration, N=137), respectively. Relative to Cycle 1 Day 1 (1st administration), accumulation based on the concentration at the end of infusion (Ceoi) was 1.96-fold for Cycle 2 Day 1 (5th administration, N=130). Further PK parameters for isatuximab in the combination with carfilzomib/dexamethasome were predicted in pop-PK analysis below.

Pop-PK analysis isatuximab (Report POH0630)

In the IKd population, isatuximab exhibited a low linear mean clearance at steady state ([CL], 0.00426 L/h [55.0%]) (i.e. 0.102 L/day) and low volume of distribution of the central compartment ([V1], 3.07 L [30.7%]) and peripheral compartment ([V2], 3.41 L [56.7%]). The median decrease in linear CL was approximately 40%. The approximate median time to reach half of this decrease was 5.5 weeks, with a slower kinetics of decrease in patients secreting clonal IgG compared to patients secreting other types of Ig. The mean (percent coefficient of variation [CV%]) half-life associated with the linear elimination at steady-state was 53.6 (42.1%) days. The mean (CV%) Cmax and AUC2weeks at steady state (Cycle 6) were 655 µg/mL (30.8%) and 159 000 µg•h/mL (37.1%), respectively, in the IKd Phase 3 study EFC15246 (N=172; see **Table 1**).

***Table 1.** Simulated mean (%CV) post-hoc isatuximab exposure by study at Cycle 1 and at steady-state by study at 10 mg/kg QW/Q2W in MM patients (popPK reports POH0503, POH0630)*

Study (N) Assay	Cycle 1[a]					Steady state[b]		
	C_{max} (µg/mL)	AUC_{1week} (µg•h/mL)	CT1W (µg/mL)	AUC4W (µg•h/mL)	CT4W (µg/mL)	C_{max} (µg/mL)	AUC_{2weeks} (µg•h/mL)	C_{trough} (µg/mL)
Single agent (±dexamethasone)								
TED10893 Phase 1 (N=73)	166	13 600	45.5	95 100	156	331	72 800	162
ELISA assay DOH0716	(26.8)	(40.8)	(64.4)	(47.8)	(62.6)	(51.3)	(71.4)	(88.2)
Phase 2 Stage 1 (N=95)	148	12 600	43.2	88 000	143	308	70 200	159
ELISA assay DOH0716	(20.4)	(25.8)	(44.0)	(33.1)	(48.6)	(41.6)	(58.6)	(73.7)
Phase 2 Stage 2 (N=90)	178	14 900	53.7	106 000	174	384	88 100	205
ELISA assay DOH0716	(22.8)	(31.4)	(49.8)	(39.0)	(55.4)	(42.4)	(58.3)	(70.1)
TED14154 (N=26)	151	12 600	45.6	90 200	152	343	80 900	191
ELISA assay DOH0716	(31.7)	(33.8)	(49.5)	(39.2)	(51.1)	(43.1)	(55.0)	(64.7)
TCD14906 (N=24)[c]	323	27 100	86.9	-	-	-	-	-
Gyrolab Assay DOH1586	(29)	(34)	(48)					
Combination with pomalidomide/dexamethasone (IPd)								
TCD14079 Part A (N=44)	163	12 900	45.7	94 100	161	366	85 300	201
ELISA assay DOH0716	(30.7)	(30.2)	(46.4)	(35.3)	(46.8)	(33.6)	(44.9)	(54.6)
EFC14335 (N=148)	192	15 100	50.1	102 000	158	351	72 600	157
ELISA assay DOH1417	(35.0)	(30.4)	(46.3)	(31.5)	(42.5)	(36.0)	(51.7)	(68.1)
Combination with carfilzomib/dexamethasone (IKd)								
EFC15246 (N=172)	259	21 400	85.2	161 000	290	655	159 000	394
Gyrolab Assay DOH1586	(37.6)	(27.6)	(35.9)	(28.5)	(34.6)	(30.8)	(37.1)	(42.3)

AUC: area under the plasma concentration curve; AUC_{1week} and AUC_{2weeks}: area under the plasma concentration time curve over the dosing interval of 1 or 2 weeks, respectively; AUC4W: cumulative AUC over the first 4 weeks; C_{max}: maximum plasma concentration; CT1W: C_{trough} at 1 week; CT4W: C_{trough} at 4 weeks; ELISA: enzyme-linked immunosorbent assay; IKd: isatuximab in combination with carfilzomib and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone

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

b Represents Cycle 6 (Q2W maintenance regimen, predose [Week 20], C_{max} and AUC_{2weeks} after the first dose of the cycle).

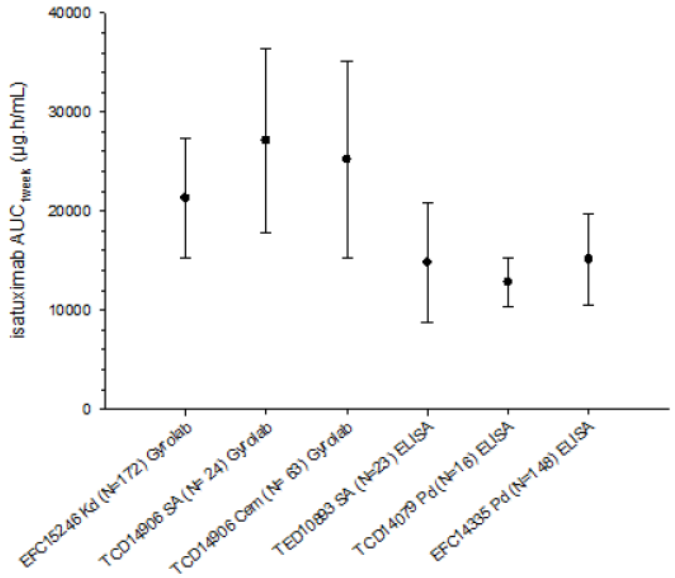
c A non-compartmental analysis was used in TCD14906. N=22 for CT1W.

Comparison with IPd (isatuximab in combination with pomalidomide and dexamethasone)

The mean Cmax (259 µg/mL) and AUC1week (21 400 µg•h/mL) after the first administration in subjects treated with IKd were approximately 1.35- and 1.42-fold higher, respectively, than those in the approved indication (EFC14335; N=148). The difference increased to approximately to 1.87- to 2.19-fold for the Cmax and AUC2weeks, respectively, at steady state (Cycle 6) (**Table 1**).

The potential reasons (ie, bioanalytical methods, patient characteristics, and response over time) for this difference between IKd and IPd populations were explored as described hereafter (see discussion).

Figure 5. *Comparison of AUC1week (mean±SD) after the first administration at 10 mg/kg across clinial studies.*



Besides the assay method differences, the differences in patient populations were also considered because study EFC15246 had patients with less advanced disease status with slightly higher serum

albumin levels at baseline, slightly lower serum M-Protein levels at baseline, β2 microglobulin levels at baseline, and LDH level at baseline, a lower percent of plasma cells in bone marrow, and fewer patients at ISS Stage III, ECOG Performance Status 2, and aged ≥75 years at baseline, compared to EFC14335. To assess the contribution of patient characteristics at baseline on PK differences between the two Phase 3 studies EFC14335 and EFC15246, matched analyses were conducted for exposure parameters after the first isatuximab administration, when no impact of the treatment is expected, as well as at 4 weeks. Different case control analyses were performed adjusting for covariates included in the population PK model using nearest neighbor matching from EFC14335 based on Mahanalobis distance. 'Matched EFC15246 patients' were patients from study EFC15246 who matched with EFC14335 patients' characteristics for the following baseline covariates: Ig MM type, body weight, β2 microglobulin, serum albumin, and ISS stage. As it was a match with replacement, a patient from study EFC15246 could have been counted several times in the matched study EFC15246 population if it happened that he/she was the nearest one from several patients from study EFC14335.

Absorption

As shown in **Table 2**, the mean AUC1week for the IKd study EFC15246 was closer to the corresponding mean value for the IPd study EFC14335 after the matching, but not enough to fully explain the difference observed between the two studies by differences in patients characteristics. The matched analysis also showed a bigger difference in isatuximab exposure after repeated administration, as demonstrated by the 85% higher CT4W in study EFC15246 compared to study EFC14335. This increase in the exposure difference over time is attributed to a higher proportion of responders, especially VGPR+ patients, in study EFC15246 than in study EFC14335 (ORR: 86.6% versus 60.4%; VGPR+: 72.6% versus 31.8%), acknowledging that the relative difference (expressed as mean, median, or geometric mean ratio) in exposure (CT4W and AUC2weeks) between responders and non-responders appeared to be of the same magnitude for both IKd and IPd populations (**Table 3**). Consistent between the two studies, isatuximab CL decreases (and exposure increases) over time in patients who respond to isatuximab treatment; this was interpreted in the original submission dossier as an impact of the status improvement on the PK of isatuximab trough by mechanisms such as reduction in inflammation and IgG M-protein, leading to a greater proportion of isatuximab going through salvage pathways and subsequently resulting in lower clearance.

Table 2. *Matched analysis of exposure (mean predicted post-hoc AUC1week and CT4W) – EFC 15426 (IKd combination) versus EFC14335 (IPd combination)*

PK Parameter	Analysis			Matched analysis		
	EFC15246 (N=170)	EFC14335 (N=145)	EFC15246/ ECF14335	Matched EFC15246 (N=145)	EFC14335 (N=145)	EFC15246/ ECF14335
AUC_{1week} (µg•h/mL)	21 300	14 886	1.43	20 631	14 886	1.39
CT4W (µg/L)	280	139	2.01	257	139	1.85

AUC_{1week}: AUC over the first week; CT4W: C_{trough} at 4 weeks

Table 3. *Comparison of simulated post-hoc CT4W and AUC2weeks at cycle 6 between responders and non-responders – EFC 15426 (IKd combination) versus EFC14335 (IPd combination) (corrected Table 11 2.7.2 [Section 3])*

Study	Parameter	CT4W (µg/mL)			AUC_{2weeks} at Cycle 6 (µg•h/mL)		
		Responder (VGPR+)	Non-responder	Ratio	Responder (VGPR+)	Non-responder	Ratio
EFC14335	Mean	188	144	1.31	94 832	61 950	1.53
	Median	183	139	1.32	88 937	56 258	1.58
	Geo mean	177	128	1.38	88 221	54 582	1.62
EFC15246	Mean	306	244	1.25	176 548	106 942	1.65
	Median	305	245	1.24	182 446	91 278	2.00
	Geo mean	292	205	1.42	170 066	89 325	1.90

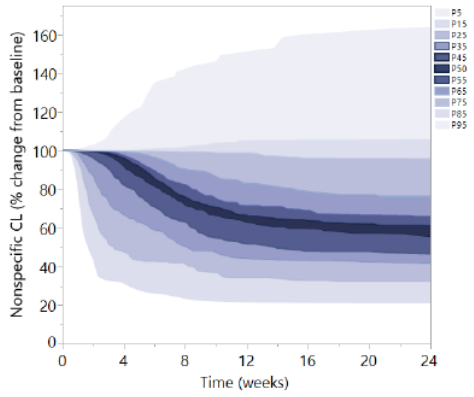
Ratio is a ratio of the responder to non-responder values.
$AUC_{2\ Weeks}$ after the first dose of the Cycle 6; CT4W: C_{trough} at 4 weeks; Geo mean: geometric mean; VGPR+: very good partial response or better

Distribution/Elimination

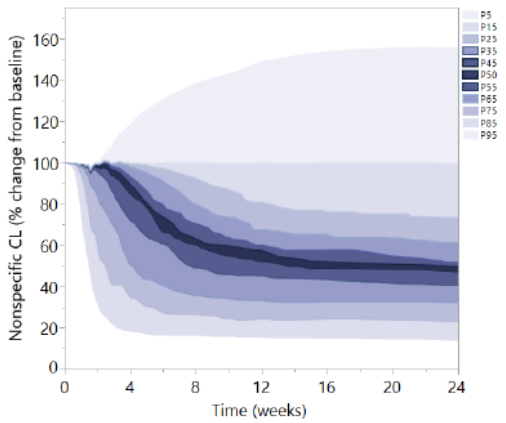
Similar to the IPd population in the original submission, isatuximab exhibited a low linear clearance and low volume of distribution in the IKd population in the pivotal Phase 3 study EFC15246 in the current submission. However, compared to those estimated in patients from the IPd study EFC14335, the linear clearance at steady state was lower (0.00426 L/h [0.102 L/day] versus 0.00822 L/h) and was associated with a longer terminal half-life (53.6 days versus 33.1 days), while the volumes of distribution of the central (V1) and peripheral (V2) compartments were comparable (V1: 3.07 versus 3.95 L; V2: 3.41 L versus 3.31 L) in the IKd study EFC15246. Additionally, while the distribution of CL estimates over the course of IKd treatment presented the same pattern for the time dependency in CL, the decrease in CL appeared to be slightly delayed and less pronounced than for the IPd treatment in Study EFC14335 (**Figure 6**). The difference in PK parameters between IKd and IPd populations translated into differences in isatuximab exposure as shown above.

Figure 6*. Distribution of individual estimates (5th ot 95th percentile) relative %change of linear CL from baseline.*

a) IKd Phase 3 study EFC15246 (POH0630)



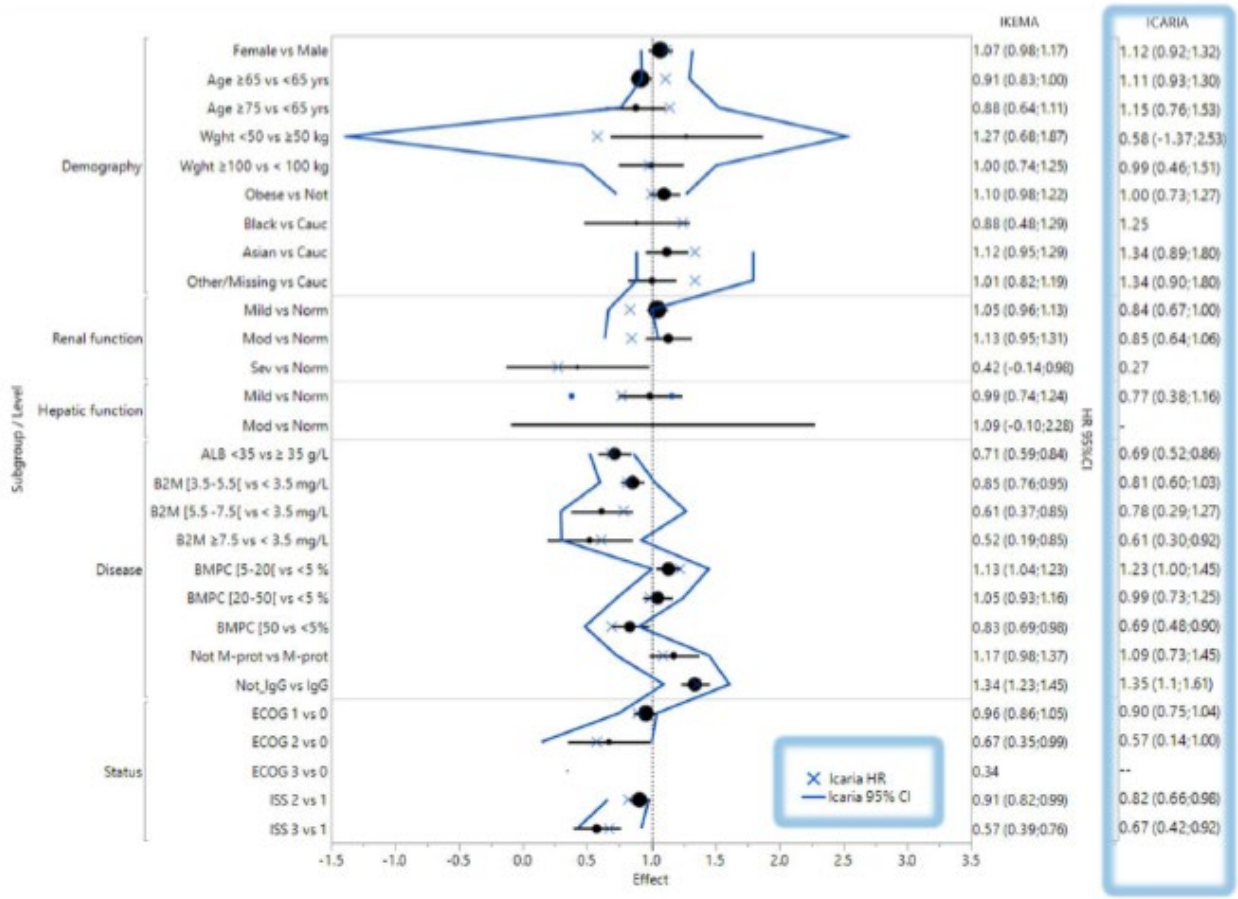
b) IPd Phase 3 study EFC14335 (POH0503, original submission)



Special populations

Forest plot of CTW4 vs covariates in EFC15246 and EFC14335 is presented in **Figure 7** and shows that most important covariates were the same in both studies. Taking into account sample sizes and intrinsic effect of all covariates; Ig MM Type was considered as the most influential one with a 1.34 fold higher predicted CTW4 in Non IgG patients vs IgG ones. β2 microglobulin, albumin and then derived ISS showed also some pronounced effects in CTW4, as in POH0503. It should be also noted that low body weighted patients (<50 kg) showed higher CTW4 in EFC15246 (Ikema) than normal weighted patients whereas exposure in same patients was lower in EFC14335 (Icaria) than in the reference group.

Figure 7. *Forest plot of predicted Ctrough week 4 (mean and 95% CI) - – EFC 15426 (IKEMA) versus EFC14335 (ICARIA)*



Pharmacokinetic interaction studies

Effects of carfilzomib on the pharmacokinetics of isatuximab

The PK of isatuximab were assessed in EFC15246 using the new bioanalytical method with the Gyrolab platform (DOH1586). Since this assay method was also used for the isatuximab single-agent arm of the combination study TCD14906, the isatuximab PK data from study EFC15246 were compared with those from study TCD14906 in order to characterise how carfilzomib may affect isatuximab PK.

Table 4. *Descriptive statistics for isatuximab AUC_{1week} at cycle 1 day 1 for isatuximab alone (TCD14906) or in combination with carfilzomib/dexamethasone (EFC15246).*

Treatment	Study, isatuximab dose regimen	N	Mean	SD	Geometric mean	CV (%)
				(µg.h/mL)		
Isatuximab alone	TCD14906, 10 mg/kg QW/Q2W	24	27 100	9 280	25 400	34
Isatuximab/carfilzomib	EFC15246, 10 mg/kg QW/Q2W	172	21 300	5990	20 500	28

AUC: area under the plasma concentration-time curve; CV: coefficient of variation; QW: weekly administration; Q2W: every 2 weeks administration; QW/Q2W: 4 weekly administrations followed by every 2 weeks administration; SD: standard deviation
AUC_{1week}: Predicted AUC_{1week} in study EFC15246 and AUC_{1week} estimated by NCA for study TCD14906.

In addition, these results are confirmed by an investigator-sponsored study (Martin T, et al.) in which isatuximab was given in combination with carfilzomib/dexamethasone. After the first administration following 10 mg/kg QW/Q2W isatuximab in combination with carfilzomib/dexamethasone, isatuximab exposure (AUC1week, 15 100 µg•h/mL; CV, 26%) was comparable to that observed with isatuximab administered as a single agent (mean AUC1week range: 14 400-17 000 µg•h/mL), suggesting no effect of carfilzomib at a dose of 20-27 mg/m2 on the PK of isatuximab.

Effect of isatuximab on the pharmacokinetics of carfilzomib

The effect of isatuximab on carfilzomib and cemiplimab has been evaluated based on the comparison of PK data from 2 combination studies (EFC15246 and TCD14906, respectively) and data published in literature.

In study EFC15246 within the IKd arm, blood samples were collected from 30 patients at Cycle 1 Day 15 to evaluate the PK of carfilzomib administered at 56 mg/m² in combination with isatuximab 10 mg/kg. The exposure of carfilzomib in Cycle 1 day 15 was calculated using non-compartmental analysis. After the administration of carfilzomib at 56 mg/m2 in combination with isatuximab at 10 mg/kg, the carfilzomib PK parameters are in range with those of carfilzomib single-agent therapy published in literature, indicating no effect of isatuximab on carfilzomib PK.

Table 5*. Comparison of carfilzomib PK parameters from EFC15246 with published data, after IV administration of 56mg/m2 carfilzomib on cycle 1 day 15 – geometric mean (CV%) [mean].*

Data source	Treatment	N	Statistical descriptor	C_{max} (ng/mL)	t_{max}[a] (h)	AUC (ng•h/mL)	$t_{1/2z}$[a] (h)
EFC15246	IKd	16	Geometric mean (CV%) [mean]	1420 (65) [2090]	0.54 (0.35-0.75)	581 (65) [784]	0.819 (39) [0.870]
Literature (patients with normal renal function [10])	Carfilzomib single agent	10	Geometric mean (CV%)	1389 (26.8)	0.47 (0.25-0.73)	563 (41.8)	0.34 (0.11-0.50)
Literature (11)	Carfilzomib single agent	12	Geometric mean (CV%)	2079 (43.9)	-	917 (24.4)	0.875 (30.4)
FDA label (12)	-	-	Mean (CV%)	2079 (44)	-	948 (34)	-

AUC: area under the plasma concentration-time curve from 0 to infinity; C_{max}: maximum plasma concentration; CV: coefficient of variation; FDA: United States Food and Drug Administration; IKd: isatuximab in combination with carfilzomib and dexamethasone; t_{max}: time to reach the maximal concentration; $t_{1/2z}$: terminal half life
a Median (range)

2.3.3. Pharmacodynamics

Mechanism of action

The mechanism of action is described in the initial submission.

Primary and secondary pharmacology

The primary pharmacodynamic (PD) assessments were described in the initial submission.

Pharmacodynamic assessments were performed in the pivotal study, EFC15246, and in single agent studies TED10893 Phase 2 Stage 2, TED14154 Part B, and TED14095, and in combination studies TCD14906 and TCD14079 Part B. Data are reported for serum M-protein (all studies) and FCGR3A genotypes (all studies except for study TCD14906, in which this analysis was not part of the study objectives).

M-protein is an immunoglobulin (entire or light chain) secreted in excess by an abnormal clonal proliferation of plasma cells in patients with MM. M-protein level is a key component in the assessment of clinical response.

To engage effector functions, isatuximab binds to NK cells through Fc gamma receptors (FCGR). Several polymorphisms identified in these genes result in either high or low affinity receptor expression, impacting the effector functions.

An association analysis of F158V bi-allelic polymorphism of FCGR3A with efficacy parameters in study EFC15246 is presented in this submission. These data are discussed in the efficacy section under ancillary analysis. The F158V single nucleotide polymorphism of FCGR3A was analysed in studies EFC15246, TED10893 Phase 2 Stage 2, TED14154 Part B, TED14095, and TCD14079 Part B.

Immunogenicity

Immunogenicity was evaluated throughout the clinical development program. This section provides an update to the integrated summary of immunogenicity that was included in the original IPd submission.

In the pivotal IKd Phase 3 study EFC15246, ADA samples were collected in all patients in the isatuximab arm at baseline, on Day 1 of each subsequent 28-day cycle up to Cycle 10 (or the last cycle if a patient discontinued study treatment before Cycle 10), or up the PFS cut-off date, whichever came first, unless previously positive. If patients were ADA positive or inconclusive at Cycle 10 (or the last cycle of treatment) or at the PFS cut-off date, one additional sample for ADA evaluation was collected 3 months later; no further ADA was sampled, even if this 3-month sample was positive.

ADA response for the supplemental studies was assessed at baseline, during treatment, and then at 30 days and 60 or 90 days after the last isatuximab treatment. Studies TED10893 Phase 2 Stage 2, TED14095, and TCD14079 were amended to assess ADA response in a similar manner to what was implemented in EFC15246 (ie, baseline, during treatment up to Cycle 10 or the last cycle if a patient discontinued study treatment before Cycle 10).

In the results, there was no confirmed positive ADA response in the pivotal Phase 3 study EFC15246 for the IKd combination; hence, no neutralising ADA assessment was done. Among the 9 completed studies, a total of 21 patients exhibited a positive response in the ADA assay in at least one patient sample (**Table 6**).

***Table 6**. ADA incidence in the target combination (EFC15246); single agent studies TED 10893 (phase 1 stages 1 and 2, and phase 2 stages 1 and 2), TED14154 (Part A and B), and TED14095; and combination studies TCD14079(Part A and B), TCD14906, EFC14335, TCD11863, TCD13983*

	IKd (N=168)	IPd (N=241)	Isa (+/- Dex) (N=466)	All (N=1018)
ADA-positive patient at baseline (pre-existing ADA)	0	0	1 (0.2)	2 (0.2)
Patients with treatment boosted ADA	0	0	0	0
Post-baseline peak titer				
Number	0	0	0	0
Median	NC	NC	NC	NC
Min ; Max	NC ; NC	NC ; NC	NC ; NC	NC ; NC
Q1 ; Q3	NC ; NC	NC ; NC	NC ; NC	NC ; NC
ADA-negative patient at baseline	166 (98.8)	230 (95.4)	453 (97.2)	988 (97.1)
Patients with treatment induced ADA	0	1 (0.4)	14 (3.0)	19 (1.9)
Post-baseline peak titer				
Number	0	1	14	19
Median	NC	80.0	10.0	10.0
Min ; Max	NC ; NC	80 ; 80	10 ; 80	10 ; 320
Q1 ; Q3	NC ; NC	80.0 ; 80.0	10.0 ; 10.0	10.0 ; 40.0
Patients with transient ADA response	0	1 (0.4)	12 (2.6)	16 (1.6)
Patients with persistent ADA response	0	0	2 (0.4)	2 (0.2)
Patients with indeterminate ADA response	0	0	0	1 (<0.1)
ADA negative patients	168 (100)	240 (99.6)	452 (97.0)	999 (98.1)
ADA prevalence	0	1 (0.4)	15 (3.2)	21 (2.1)
ADA incidence	0	1 (0.4)	14 (3.0)	19 (1.9)

IKd: Isatuximab in combination with carfilzomib and low-dose dexamethasone; IPd: Isatuximab in combination with pomalidomide and dexamethasone; Isa: isatuximab; Dex: dexamethasone.
Note: ADA prevalence is the proportion of ADA positive patients including pre-existing ADA positive, ADA incidence is the proportion of patients of ADA positive patients excluding pre-existing ADA positive.
NC: not calculated.
PGM=PRODOPS/SAR650984/OVERALL/POOL MM SUB 2/REPORT/PGM/ae pk ada a t.sas
OUT=REPORT/OUTPUT/ae_pk_ada_p2_a_t_i.rtf (21JUL2020 8:12)

2.3.1. PK/PD modelling

The relationships between PK and efficacy and between PK and safety were assessed using data from the pivotal IKd study, EFC15246, for justification of the proposed dose for the target indication. Exposure-Response (E-R) analyses were performed with population PK model-predicted exposure parameters of isatuximab as prognostic factors for efficacy outcomes (rate of very good partial response or better [VGPR+], rate of minimum residual disease negativity [MRD-], and progression-free survival [PFS]). With regard to the E-R safety analyses, the endpoints of interest were infusion reactions (IRs), thrombocytopenia, neutropenia, infections, respiratory events, cardiac events, and cardiac failure.

Exposure-response (E-R) analyses for efficacy (report POH0804)

Similar to the previous exposure-response (E-R) analyses for efficacy with either single agent or combination therapy (presented in the original submission), isatuximab trough concentration at the end of 4 weeks (CT4W) was determined to be the best PK exposure predictor of response (VGPR+, MRD-, and PFS) in the Phase 3 study EFC15246 with the isatuximab dose regimen of 10 mg/kg once weekly for the first cycle and every 2 weeks thereafter (QW/Q2W) in combination with Kd.

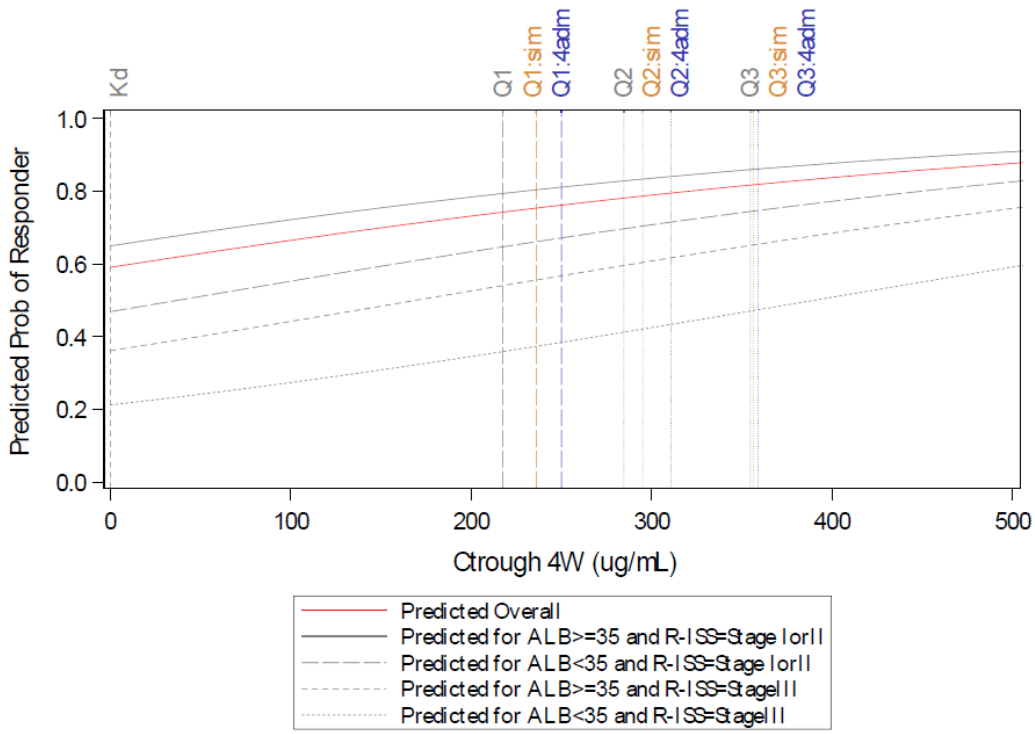
Overall, when the E-R curves are divided at the median CT4W, both IKd subpopulations (CT4W below and above median) showed a treatment benefit versus Kd (higher VGPR+ rate, higher MRD- rate, PFS HR<1).

Among the different PK exposure parameters tested, CT4W was found to be the best predictor ($p<0.0001$) of VGPR+ after adjusting for baseline LDH level. The probability of a VGPR+ response was found to increase with a linear increase of CT4W (linear form of logit function CT4W link). Besides CT4W, the final logistic regression model included plasmacytoma (yes/no), the Revised-ISS (R-ISS) group (R-ISS Stage I or II versus III), and the baseline serum albumin level (<35 or ≥35 g/L).

Based on the final model, the overall model-predicted VGPR+ rate was 82.66% when the CT4W was above or equal to the median, and was 65.45% when the CT4W was below median. Moreover, when focusing on the lowest part of the E-R curve, the model-predicted VGPR+ response rate was 56.20% for the 1st exposure quartile (Q1) comparable to the response rate for the Kd arm (56.83%).

Figure 8 illustrates the E-R relationship model expected probability of VGPR+ by R-ISS Stage and albumin level group (<35 or ≥35 g/L) according to each quartile of CT4W in the absence of plasmacytoma, acknowledging that the vast majority of the patients in the study had no plasmacytoma (≥85%).

Figure 8. *Model-predicted probability of VGPR for patients without plasmacytoma by R-ISS stage and albumin groups (10mg/kg QW/Q2W, POH0804).*



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OUT=REPORT/OUTPUT/pk_0804_vgpr_finallinear_f_x.rtf (10JUL2020 14:19)
In the figure above, Q represents the predicted proportion of responders for each quartile of CT4W group for overall population. Q:sim represents the predicted proportion of responders for each quartile of CT4W group assuming all patients received 4 weekly administrations. Q:4adm represents the predicted proportion of responders for each quartile of CT4W for patients who completed 4 weekly administrations.

Among the 43 patients in the lowest quartile of the E-R curve (Q1), 86.0% were IgG MM patients (a lower proportion of patients were IgG MM type in the upper quartiles). It has been shown that the typical IgG MM patient has a higher linear CL at steady state which translates into a 44% lower CT4W compared to the CT4W in the typical non-IgG MM patient (POH0503); however, IgG MM type was not the only reason for the lower exposure in the first quartile. A total of 24 patients (55.8%) in Q1 received 4 isatuximab administrations, while 19 patients (44.2%) received <4 isatuximab administrations; of those 19 patients, 16 encountered isatuximab dose delay and/or dose omissions due to the occurrence of certain AEs during the first four weeks of the treatment period.

For MRD negativity, analyzed as a subgroup of IKd VGPR+ patients, the PK/PD relationship was described by a sigmoid Emax model. In addition to CT4W, for a given CT4W value the probability to respond to isatuximab treatment as MRD- was greater for those without prior PI therapy compared to those who had previously received a PI. From the final model, 90% of maximal effect (EC90) was reached in the upper part of the second quartile (Q2) for CT4W. When CT4W was above or equal to the median, the model-predicted MRD- rate was 37.59%, and was 25.21% when CT4W was below the median. Moreover, when focusing on the lowest part of the E-R curve, the model predicted a lower MRD- response rate (16.77% in Q1), but still above the predicted MRD negativity rate for Kd arm (10.65%).

For PFS, from the Kaplan-Meier plots, PFS appeared to improve with increasing isatuximab exposure (**Figure 9**). Patients in the highest quartiles seemed to have a better PFS than patients in the lower quartiles. However, this analysis does not account for the potential effect of confounding variables; therefore, model-based analyses were conducted. The PK/PD relationship was described by a Weibull parametric hazard model. The E-R analysis revealed that PFS increased as CT4W increased. In addition to CT4W, PFS increases with decreases in the β2 microglobulin level and with decreases in the percent of plasma cells in bone marrow; PFS decreases in patients with both prior PI and IMiD treatment. The estimation of the PFS HR versus Kd at the median CT4W of subgroups (median or quartiles) showed that patients with ≤median CT4W benefit from isatuximab treatment (HR 0.52), even those in the lowest quartile of exposure (HR 0.63) (**Figure 10**). However, similar to the outcome of E-R analyses for the other efficacy endpoints, this observation in Q1 is heavily confounded by the poorer myeloma prognostic factors and high incidence of carfilzomib and isatuximab dose modifications in this quartile. Finally, since the patient characteristics of the IKd subgroups populations were unbalanced with the Kd population, a matched analysis was done for the IKd subgroup defined by low or high exposure (≤ median or >median) of the PK predictor with their corresponding matched subgroups of the Kd population. From this matched analysis, patients with isatuximab in the two lowest and two highest exposure quartiles (ie, ≤ or > median CT4W, respectively) showed treatment benefit in terms of PFS compared to the matched Kd, which resulted in a HR of 0.522 and 0.475, respectively.

***Figure 9**. Kaplan Meier estimates of PFS by CT4W quartiles (POH0804)*

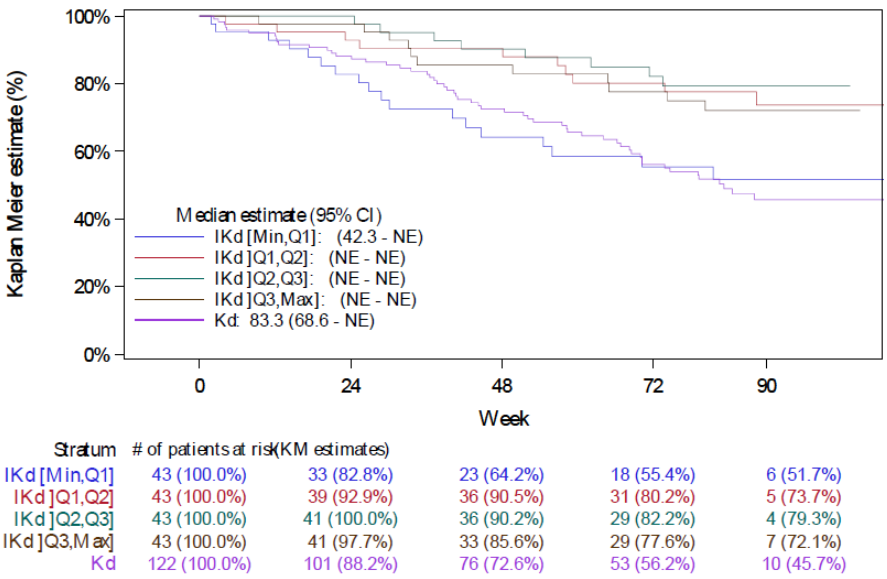
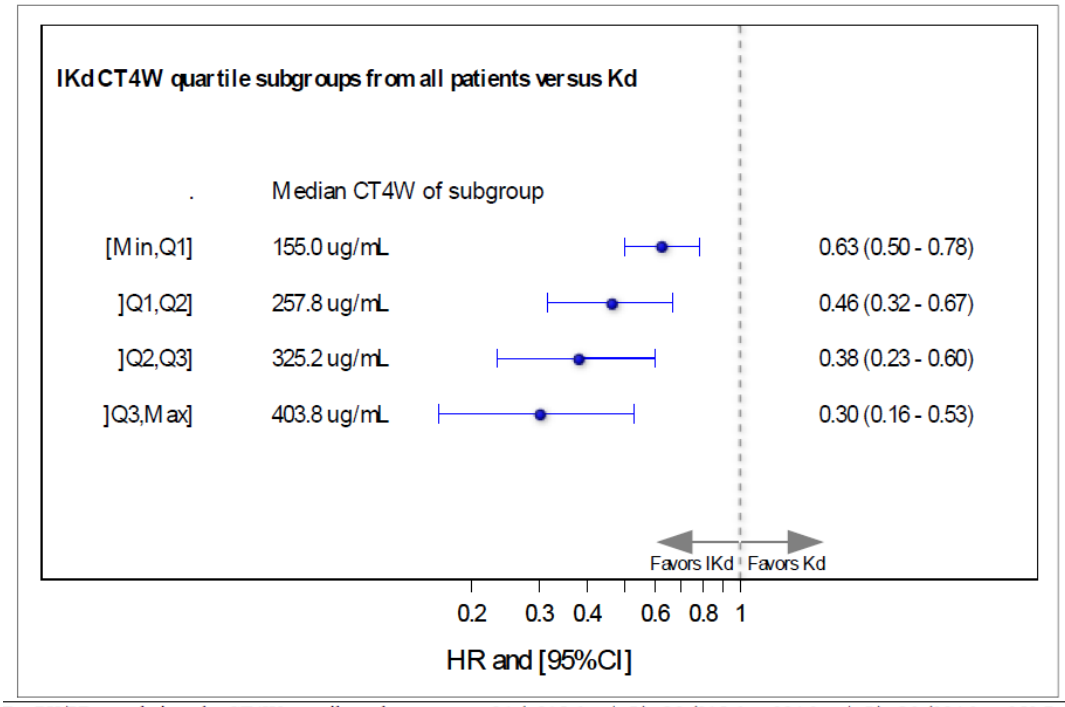


***Figure** 10. Forest plot of HR associated with CT4W of PFS at the median of CT4W when comparing the quartiles subgroups to the Kd arm for PK/PD population (POH0804).*



For PK/PD population, the CT4W quartiles subgroups are: Q1 (<215.6 ug/mL), Q2 (215.6 -< 284.3 ug/mL), Q3 (284.3 -< 353.7 ug/mL), Q4 (353.7 - 554.9 ug/mL).

Exposure-response (E-R) analyses for safety

While Grade ≥3 TEAEs were reported more frequently in the IKd arm than in the Kd arm (76.8% versus 67.2%), the addition of isatuximab to Kd did not add substantial safety concerns. In the IKd arm, there was a higher incidence of respiratory infections all grades (83.1% versus 73.8%) and of Grade ≥3 neutropenia by laboratory analysis (19.2% versus 7.4%; driven by a difference in Grade 3 neutropenia: 17.5% versus 6.6%) compared to the Kd arm. Isatuximab IRs occurred in 45.8% of patients; 1 patient experienced a Grade 3 IR, but otherwise the IRs were Grade 1-2, and all had an onset at the first infusion (ie, mainly during the first 2 days of treatment).

2.3.2. Discussion on clinical pharmacology

This application concerns a new indication of treatment for the MM patients with isatuximab in the combination with carfilzomib and dexamethasone (IKd), but the dose regimen of isatuximab was the same as in combination with pomalidomide and dexamethasone (IPd), i.e. 10 mg/kg administered intravenously (IV) once weekly (QW) for the first cycle (28 days; 4 once-weekly administrations), and every 2 weeks (Q2W) thereafter (QW/Q2W). ADME of isatuximab was mainly referred to the original dossier. The exposure of isatuximab in the combination with carfilzomib and dexamethasone has been studied in the target patient population in Study EFC15246 (Phase III) and compared to the exposure of isatuximab in study EFC14335 (IPd).

Bioanalytical methods

A new bioanalytical (Gyros) method has been used to analyse isatuximab in study EFC15236. The method was validated in line with the bioanalytical method validation guideline (EMEA/CHMP/EWP/192217/2009), however the intra-assay precision exceeded the acceptance margin of within 20% of the nominal value at each concentration level (25% at the LLOQ and ULOQ), however, on average over the 6 runs, the intra-

assay variability was acceptable. In the cross-validation, a systematically higher Gyros concentrations than ELISA concentrations (mean relative difference of +25.4%) were observed. This is likely due to much lower dilution and higher calibration curve (5.00 - 500 µg/mL) with the Gyros method than ELISA (0.5 – 20 ng/ml). The systematically higher Gyros concentrations may in part explain the observed higher exposure of isotuximab in study EFC15246 than in previous studies e.g. study EFC14335.

The bioanalytical methods for antibody isatuximab antibodies have been validated in the original dossier, the provided adendum was also in line with the guideline and also the bioanalytical method for carfilzomib was adequately validated. The methods are considered robust.

Pharmacokinetics

Pharmacokinetics of carfilzomib was evaluated for one dose interval at cycle 1 day 15 using non-compartmental analyses while pharmacokinetics of isatuximab were evaluated by popPK analysis since mainly Ctrough and few post-dose samples were collected for isatuximab in study EFC15246. Therefore, the existing popPK model POH0503, used in the assessment for the original dossier, was updated with the sparse sampling data from study EFC15246. Based on the model validation presented here, the population PK model analysis (POH0630) from POH0503, used in posterior Bayesian estimation methodology, was considered suitable to describe individual PK profiles of EFC15246 patients.

Drug interaction between isatuximab and carfilzomib was evaluated by cross-study comparison with monotherapy studies. Since no interaction is expected between an antibody and a small molecule other than interleukine levels mediated effect of some antibodies, such across study comparion is considered acceptable. Indeed, cross-study comparison indicated that there is no clinically relevant pharmacokinetic interaction between isatuximab and carfilzomib. Isatuximab exposure when administered in combination with carfilzomib/dexamethasone (EFC15246) was comparable to that after single agent therapy (TCD14906), with the geometric mean ratio (EFC15246/TCD14906) for AUC1week being 0.81. Of note, this comparison used isatuximab PK data generated for each study by the same bioanalytical method (using the Gyrolab platform).

In general, study EFC15246 showed a higher exposure of isatuximab than reported previously reported for study EFC14335. As indicated above there was no pharmacokinetic interaction between isatuximab and carfilzomib. The 30-40% higher exposure after the first dose observed in IKd study EFC15246 compared to the IPd study EFC14335 is considered to be mainly due to the difference in the assay methods, where the cross-validation found a 25% difference in the sample concentrations. Differences in baseline characteristics of the patients may have contributed to a lesser extent. Following multiple dosing, isatuximab exposure was 2-fold higher in IKd study EFC15246 compared to the IPd study EFC14335. With additional responder analyses, it was shown that subjects with a response had a lower clearance of isatuximab both in IKd study EFC15246 compared to the IPd study EFC14335. Since the response rate was higher in the IKd population compared to the IPd population, exposure was higher in the IKd population and the difference is amplified over time. It has been shown for several antibodies that patients with a good response/longer OS have a lower clearance of the antibody (Bajaj et al. 2017, Wang et al. 2017, Turner et al. 2018), hence differences in response rate between the IKd population compared to the IPd population is likely to result in some difference in pharmacokinetics of isatuximab.

The PK data of isatuximab in study EFC15246 have been adequately presented in the SmPC of Sarclisa.

Exposure-response analyses

In line with the original dossier, isatuximab Ctrough at 4 weeks (CT4W) was used for studying the exposure and efficacy/safety relationship.

The model predicted a higher probability of VGPR+ response in R-ISS Stage I or II patients when compared to R-ISS Stage III for the same isatuximab exposure. In addition, within the same R-ISS group (the R-ISS Stage I or II group or the R-ISS Stage III group), the model predicted a higher probability of VGPR+ response in patients with a serum albumin level ≥35 g/L compared to those with a low albumin level (<35 g/L). Also, the predicted probability of being a responder without plasmacytoma was higher than with plasmacytoma for a given CT4W value. This is not unexpected, as this is an additional response criterion in IMWG to meet versus non-plasmacytoma; additionally, extramedullary plasmacytoma is more resistant to treatment.

The model also suggested that the probability of responding to treatment would have been higher if patients completed the 4 weekly administrations; 149 of 172 patients in the IKd arm received 4 administrations at Cycle 1, with most of the patients being in the three highest quartiles of exposure (55.8%, 90.7%, 100%, and 100% of patients received 4 weekly administrations in CT4W exposure quartiles Q1, Q2, Q3, and Q4, respectively). Indeed, the predicted probability of being a responder was 56.4% for the Kd arm, 66.0% in Q1 in the IKd arm, 68.0% in Q1 assuming all patients completed the 4 weekly administrations of IKd (Q1 Sim), and 69.4% for patients in Q1 who completed the 4 weekly administrations in the IKd arm (Q1:4 adm).

Of note, the interactions between R-ISS and serum albumin, R-ISS and CT4W, and serum albumin and CT4W were not statistically significant. Also, the interaction between IgG MM types and CT4W was not significant; this indicates that VGPR+ will be similar between the IgG and non-IgG populations for the same CT4W value.

There appeared to be a positive exposure – efficacy (PFS) relationship, but it was only seen between Q1 and other quartiles. Overall, when divided by median CT4W, both IKd subpopulations (CT4W below and above median) had a treatment benefit versus Kd (higher VGPR+ rate, higher MRD- rate, PFS HR<1). The treatment effect on VGPR+, MRD-, and PFS appeared to be less in the lower part of the E-R curve (Q1 versus the other quartiles of CT4W); However, this finding in Q1 was confounded by differences in patient characteristics and dose modifications for isatuximab and carfilzomib. Forty-four percent (44%) of the patients in Q1 were identified as patients with missed doses of isatuximab in the first 4 weeks, leading to lower exposure. These patients had more aggressive myeloma characteristics, which make patients less responsive to treatment, and also puts them at greater risk of adverse events (AEs), particularly respiratory infections, leading to isatuximab and carfilzomib dose reduction/delay.

Of note, half of the patients (8/16) with dose delay or omissions had these modifications due to occurrence of a respiratory infection at Cycle 1. Consistently, among these patients, most (14/16) also had carfilzomib dose reductions/omissions at Cycle 1. This higher incidence of isatuximab and carfilzomib dose modifications, those mainly due to respiratory events, is likely linked to the more aggressive myeloma characteristics in patients in this quartile (as mentioned above): there was a higher proportion of patients in Q1 had a lower baseline albumin, higher baseline β2 microglobulin, more bone marrow plasma cells, and higher lactate dehydrogenase compared to other quartiles. In Q1, there were also more patients with plasmacytoma and at R-ISS Stage III, and a larger portion of these patients received more prior chemotherapy lines (>1), which consisted mainly of prior proteasome inhibitor (PI) and immunomodulatory imide drug (IMiD) therapies (which by themselves decrease the likelihood of tumor response), compared to the other quartiles. All of these parameters are associated with higher disease burden or poor prognosis characteristics in multiple myeloma. This suggests that the lower part of the slope in the E-R curve was confounded by the patients' baseline disease characteristics and by high incidence in dose modifications both for isatuximab and carfilzomib.

This phenomenon of lower monoclonal antibody exposure in subjects with risk factors for survival compared to subjects with better disease severity/health status has been observed for other monoclonal antibodies in treatment of cancer (Azzopradi et al. 2011, Han et al. 2014, Cosson et al. 2014, Feng et al.

2013,Bajaj et al. 2017, Wang et al. 2017, Turner et al. 2018). Also here, the low exposure-PFS relationship was shown to be heavily confounded by the poorer myeloma prognostic factors and high incidence of carfilzomib and isatuximab dose modifications in this quartile. When accounting for β2 microglobulin level, in the percent of plasma cells in bone marrow, and pre-treatment regimen, the estimation of the PFS HR versus Kd at the median CT4W of subgroups (median or quartiles) showed that patients in the lowest quartile of exposure HR was 0.63.. These analyses, along with the observed clinical data, provide a justification for the 10 mg/kg QW/Q2W of isatuximab in combination therapy with Kd.

The exploratory E-R analyses conducted using quartile of exposure metrics did not show an apparent relationship between an increase of isatuximab exposure and an increase in the incidence of the safety endpoints of interest (including IRs, thrombocytopenia, neutropenia, infections, respiratory events, cardiac disorders, and cardiac failure), based on the PK/PD population for the different subgroups and on Ig MM type (IgG versus non-IgG MM patients).

The lack of exposure-safety relationship, was also the case in the original application for IPd treatment in study EFC14335.

Immunogenicity

Anti-isatuximab antibodies have not been identified in the patient's samples in study EFC15246, which indicates a very low immunogenicity of isatuximab (in line with the results in the original dossier).

2.3.3. Conclusions on clinical pharmacology

Overall, the exposure of isatuximab has been studied in the target patient population and the data supports the proposed dose regimen in the patients.

2.4. Clinical efficacy

Data to support the current application comes from one pivotal phase III study EFC15246 evaluating isatuximab in combination with carfilzomib and dexamethasone (Kd) in 302 patients with relapsed and/or refractory multiple myeloma (RRMM). Furthermore, the addition of dexamethasone to isatuximab or carfilzomib to isatuximab was studied in a company sponsored study TED10893 Phase 2 Stage 2 and investigator-sponsored study TCD12795, respectively (see **Table** 7).

***Table** 7 Summary of completed company-sponsored studies included in the summary of clinical efficacy*

Study	Study design and indication	Isatuximab dose/schedule	# of patients (isatuximab)	Dossier Inclusion	Status at cut-off date
Pivotal study: Isatuximab + carfilzomib/dexamethasone (IKd) combination study in multiple myeloma					
EFC15246	Phase 3 randomized, open-label, multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib and dexamethasone versus carfilzomib with dexamethasone in patients with RRMM previously treated with 1 to 3 prior lines	10 mg/kg QW/Q2W	179	New for dossier	Completed CSR for 65% of PFS events (cutoff 07-Feb-2020)
Other combination study					
TCD14079	Phase 1b study of isatuximab in combination with pomalidomide and dexamethasone in patients with RRMM	Part B: 10 mg/kg QW/Q2W	47	New for dossier[a]	Completed Part B interim CSR (cutoff 26-Feb-2019)
Single-agent isatuxmab (±dexamethasone) study					
TED10893	Phase 1/2 dose escalation and expansion safety, PK, and efficacy study of multiple intravenous administrations of isatuximab in patients with selected CD38+ hematological malignancies (NHL, CLL)	Phase 2 Stage 2: 20 mg/kg QW/Q2W (±dexamethasone)[b]	93	Original submission	Completed P2S2 interim CSR (cutoff: 15-Nov-2017)
			71	New for dossier[c]	Completed P2S2 final analysis (DBL 22-Aug-2019)
			Total: 390		

MM = multiple myeloma; RRMM = relapsed or refractory multiple myeloma; CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin lymphoma; IKd = isatuximab/carfilzomib/dexamethasone; QW/Q2W = weekly for the first cycle, and then bi-weekly after the first cycle; PK = pharmacokinetics; PFS = progression-free survival.

a The CSR presented only the safety results.

b Total 164 patients: 109 Isatuximab alone, 55 Isatuximab+dexamethasone.

c Included in the integrated safety database and SCS/ISS only (CSR not approved at the dossier cutoff date).

2.4.1. Dose response study(ies)

No dose-response studies have been performed for the combination of isatuximab with Kd (see above).

2.4.2. Main study(ies)

Title of Study

Study EFC15246 (IKEMA) - a randomised, open-label, multicenter study of isatuximab combined with carfilzomib and dexamethasone (IKd) versus carfilzomib and dexamethasone (Kd) in patients with relapsed and/or refractory multiple myeloma (RRMM)

Methods

Study participants

Patients were included in the study according to the following criteria (baseline studies for determining eligibility were to be obtained within 21 days prior to randomisation):

Inclusion criteria

I 01. Multiple myeloma.

I 02. Measurable disease: Serum M protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis (SPEP) and/or urine M protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis (UPEP).

I 03. Patient with RRMM with at least 1 prior line and no more than 3 prior lines.

I 04. Patient gave voluntary written informed consent before performance of any study related procedures not part of normal medical care.

Exclusion criteria

E 01. Less than 18 years (or country's legal age of majority if the legal age was >18 years).

E 02. Primary refractory MM, defined as patients who never achieved at least a MR with any treatment during the disease course.

E 03. Patient with serum FLC measurable disease only.

E 04. Patient with prior anti-CD38 mAb treatment with progression on or within 60 days after end of anti-CD38 mAb treatment or failure to achieve at least MR to treatment (ie, refractory to anti-CD38).

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

E 06. Patient who received any other investigational drugs or prohibited therapy for this study within 28 days prior to randomisation

E 07. Prior treatment with carfilzomib.

E 08. Known history of allergy to captisol (a cyclodextrin derivative used to solubilise carfilzomib), prior hypersensitivity to sucrose, histidine (as base and hydrochloride salt), polysorbate 80, or any of the components (active substance or excipient) of study treatment that were not amenable to premedication with steroids, or H2 blockers, that prohibited further treatment with these agents.

E 09. Patients with contraindication to dexamethasone.

E 10. Prior allogenic hematopoietic stem cell transplant with active graft versus host disease (any grade and/or were under immunosuppressive treatment within 2 months before randomisation).

E 11. Known amyloidosis or concomitant plasma cell leukemia

E 12. Pleural effusions requiring thoracentesis or ascites requiring paracentesis or any major procedures within 14 days before randomisation: eg, plasmapheresis, curative radiotherapy, major surgery (kyphoplasty was not considered a major procedure).

E 13. Eastern Cooperative Oncology Group (ECOG) performance status (PS) >2

E 14. Platelets <50,000 cells/μ L if <50% of bone marrow nucleated cells were plasma cells and <30,000 cells/μ L if ≥50% of bone marrow nucleated cells were plasma cells. Platelet transfusion was not allowed within 3 days before the screening hematological test.

E 15. Absolute neutrophil count (ANC) <1000 μ/L (1 x 109/L). The use of granulocyte colony stimulating factor (GCSF) was not allowed to reach this level.

E 16. Creatinine clearance <15 mL/min/1.73 m2

E 17. Total bilirubin >1.5 x upper limit of normal (ULN), except for known Gilbert syndrome.

E 18. Corrected serum calcium >14 mg/dL (>3.5 mmol/L).

E 19. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN.

E 20. Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy of Grade >1 (based on NCI-CTCAE v4.03).

E 21. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer or low risk prostate cancer or any in situ malignancy after curative therapy were allowed, as well as any other cancer for which therapy was completed ≥5 years prior to randomisation and from which the patient was disease-free for ≥5 years.

E 22. Any of the following within 6 months prior to randomisation: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association class III or IV congestive heart failure (CHF), Grade ≥3 arrhythmias, stroke, or transient ischemic attack.

E 23. Left ventricular ejection fraction <40%.

E 24. Known acquired immune deficiency syndrome (AIDS) related illness or human immunodeficiency virus (HIV) disease requiring antiretroviral treatment, or to have active hepatitis A, B (defined as a known positive hepatitis B surface antigen [HBsAg] result), or C (defined as known quantitative hepatitis C virus [HCV] ribonucleic acid [RNA] results greater than the lower limits of detection of the assay or positive HCV antigen) infection.

E 25. Any of the following within 3 months prior to randomisation: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.

E 26. Any severe acute or chronic medical condition which could have impaired the ability of the patient to participate in the study or interfered with interpretation of the study results (eg, systemic infection unless anti-infective therapy was employed), or patient unable to comply with the study procedures.

E 27. Female patients who were pregnant or lactating.

E 28. Women of childbearing potential (WOCBP) not protected by highly-effective method of birth control and/or who were unwilling or unable to be tested for pregnancy

E 29. Male participant with a female partner of childbearing potential not protected by highly-effective method of birth control.

Treatments

Study treatment is defined as isatuximab/carfilzomib/dexamethasone in IKd experimental arm and carfilzomib/dexamethasone in Kd control arm.

Patients randomised to the IKd arm received the following treatments:

- Isatuximab 10 mg/kg was administered IV on Days 1, 8, 15, and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles. The first infusion was initiated at 175 mg/hour and in the absence of IRs after 1 hour of infusion, the infusion rate was increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions were initiated at 175 mg/hour and in the absence of IR after 1 hour of infusion, the rate was increased by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

- Carfilzomib (after appropriate hydration) was administered IV over 30 minutes at a dose of 20 mg/m^2 on Days 1 and 2 and 56 mg/m^2 on Days 8, 9, 15, and 16 of Cycle 1 and Days 1, 2, 8, 9, 15, and 16 of subsequent cycles if the patient did not experience any Grade >2 toxicity except in case of non-complicated hematological toxicity related to treatment or resolved tumor lysis syndrome [TLS]).

- Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 in a 28-day cycle, between 15 to 30 minutes (but no longer than 60 minutes) prior to isatuximab or at least 30 minutes prior to carfilzomib on the days when there was no isatuximab administration.

Dexamethasone was administered intravenously (IV) on the days of isatuximab and/or carfilzomib administration and orally (PO) on the other days.

Patients randomised to the Kd arm received the following treatments:

- Carfilzomib was administered as described for the IKd arm

- Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23, at least 30 mins prior to carfilzomib on the days of carfilzomib administration. Dexamethasone was administered IV on the days of carfilzomib administration and PO on the other days.

Both isatuximab and carfilzomib can induce infusion associated reactions (IARs) and premedication was required prior to their administration. Premedications and guidelines and medications administered for patients who developed IRs were provided in the protocol.

The recommended premedication agents are listed below in the order in which they were to be given.

- Acetaminophen (paracetamol) 650 mg to 1000 mg PO 15 to 30 minutes (but no longer than 60 minutes prior to isatuximab infusion).

- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25 mg to 50 mg IV (or equivalent).
- Dexamethasone 20 mg IV (which is also part of study treatment, and was to be administered prior to isatuximab or carfilzomib administration).

Oral hydration (30 mL/kg/day) for carfilzomib started at least 48 hours before Cycle 1 Day 1, and was continued for infusions within Cycle 1 and in Cycle 2 and beyond at the Investigator's discretion.

A cycle duration is 28 days. Patients could continue study treatment until disease progression, unacceptable AEs, patient wish to discontinue further study treatment, or any other reasons. There is no limitation in the number of cycles to be administered in the absence of major toxicity, disease progression or any other discontinuation criteria.

No dose reductions are allowed for isatuximab infusion, but dose interruptions, omissions, and delays were permitted for subsequent treatment cycles based on individual patient tolerance. For carfilzomib and dexamethasone also dose reductions were allowed.

Objectives

The primary objective was *to demonstrate the benefit of isatuximab in combination with carfilzomib and dexamethasone in the prolongation of PFS using IMWG criteria as compared to carfilzomib and dexamethasone in patients with relapsed and/or refractory MM previously treated with 1 to 3 lines of therapy.*

The key secondary efficacy objectives were:

- To evaluate ORR.
- To evaluate rate of very good partial response (VGPR) or better.
- To evaluate rate of VGPR or better (IMWG criteria) with minimal residual disease (MRD) negativity in both arms.
- To evaluate complete response (CR) rate in both arms (IMWG criteria).
- To evaluate OS in both arms.

Other secondary objectives were:

- To evaluate safety in both arms.
- To evaluate duration of response (DOR) in both arms.
- To evaluate time to progression (TTP) in both arms.
- To evaluate the second progression-free survival (PFS2) in both arms.
- To evaluate time to first response in both arms.
- To evaluate time to best response in both arms.
- To determine the PK profile of isatuximab and carfilzomib when combined together.
- To evaluate immunogenicity of isatuximab in isatuximab arm.
- To evaluate generic and disease- and treatment-specific health-related quality of life (HRQL), and changes in HRQL, health state utility, and health status in both arms.

Exploratory objectives were:

- To explore PK and pharmacodynamic (PDy) relationship.
- To explore the relationship between immune genetic determinants and efficacy endpoints.
- To explore relationship between cytogenetic abnormalities (CAs) not part of Revised International Staging System (R-ISS) including, but not limited to, del (1p) and gain (1q) and efficacy endpoints.
- To explore the impact of M-protein measurement without isatuximab interference on best overall response assessment.

Outcomes/endpoints

Primary endpoint:

PFS, defined as the time from the date of randomisation to the date of first documentation of progressive disease (PD) or the date of death from any cause, whichever came first. Progressive disease was to be determined by the IRC according to IMWG criteria using central laboratory results and central review of radiologic imaging and, if any, local bone marrow assessment. Response and progression based on serum and/or urine M protein were to be confirmed by 2 consecutive assessments. Progression based on plasmacytomas/bone lesions did not require confirmation. The date of the PD was defined as the earliest date that indicated PD (provided that progression was subsequently confirmed when required).

If PD and death were not observed before the analysis cut-off date or the date of initiation of further anti-myeloma treatment, PFS was censored at the date of the last valid disease assessment not showing PD (censoring for further anti-myeloma treatment) or the analysis cut-off date, whichever came first. A patient without an event (death or PD) and without any valid post-baseline disease assessments was censored at the day of randomisation (Day 1).

The sensitivity analyses included:

- PFS analysis based on IRC ignoring further anti-myeloma treatment
- PFS analysis based on investigator's disease assessment and including symptomatic deterioration
- PFS analysis based on investigator's disease assessment and ignoring symptomatic deterioration
- PFS analysis based on IRC including initiation of further anti-myeloma treatment considered as event
- Analysis based on scheduled assessment dates instead of actual assessment dates and late PFS events censored (analysis done if lack of adherence to the protocol-defined schedule of disease assessments between the treatment arms was detected)
- Unstratified PFS analysis
- PFS analysis using stratification factors as per eCRF

Key secondary efficacy endpoints

• ORR: Defined as the proportion of patients with stringent complete response (sCR), CR, VGPR, and PR as best overall response (BOR), as assessed by the IRC using the IMWG criteria. Bone marrow biopsy could have been done for sCR assessment as per Investigator decision.

• Rate of VGPR or better: Defined as the proportion of patients with sCR, CR, and VGPR as BOR.

• MRD negativity rate in patients with VGPR or better: Defined as the proportion of patients for whom MRD was negative at any timepoint after first dose of study treatment. MRD status was assessed centrally by NGS-based test in bone marrow samples from patients who achieved VGPR or better. The threshold for negativity was 10^{-5}.

• CR rate: Defined as the proportion of patients with sCR and CR as BOR. Patients with demonstrated isatuximab interference will be considered in the BOR category corresponding to the M protein assessment obtained without interference, when the antibody-capture interference assay will be available.

• OS: Defined as the time from the date of randomisation to death from any cause.

Other secondary efficacy endpoints

• DOR: Defined as the time from the date of the first IRC determined response (PR or better) to the date of first documented PD determined by IRC or death, whichever occurred first. DOR was censored at the date of the last valid disease assessment not showing PD performed prior to initiation of a new anti-myeloma treatment (if any) or the analysis cut-off date, whichever occurred first.

• TTP: Defined as time from randomisation to the date of first documentation of PD (as determined by the IRC). If progression was not observed before the analysis cut-off date or the date of initiation of further anti-myeloma treatment, TTP was censored at the date of the last valid disease assessment not showing disease progression prior to the initiation of any further anti-myeloma treatment (if any) or the analysis cut-off date, whichever came first.

• PFS2: Defined as time from the date of randomisation to the date of first documentation of PD (as reported by the Investigator) after initiation of further anti-myeloma treatment or death from any cause, whichever happens first. For patients alive without progression after initiation of further anti-myeloma treatment before the analysis cut-off date, PFS2 was censored at the date of the last FU visit without disease progression after initiation of further anti-myeloma treatment or the analysis cut-off date, whichever came first.

• Time to first response (TT1R): TT1R was defined as the time from randomisation to the date of first IRC determined response (PR or better) that was subsequently confirmed. In the absence of response, patients were censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever came first.

• Time to best response (TTBR): Defined as the time from randomisation to the date of first occurrence of IRC determined best overall response (PR or better) that was subsequently confirmed. In the absence of response, patients were censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever came first.

• Renal response: A complete renal response (CR renal) was defined as an improvement in estimated glomerular filtration rate (eGFR) from <50 mL/min/1.73m^2 at baseline to ≥60 mL/min/1.73m^2 in at least 1 assessment during the on-treatment period.

- A partial renal response (PR renal) was defined as an improvement in eGFR from <15 mL/min/1.73m^2 at baseline to at least 1 assessment in the range [30 to 60[mL/min/1.73m^2 during the on-treatment-period.

- A minor renal response (MR renal)was defined as an improvement in eGFR from <15 mL/min/1.73m^2 at baseline to at least 1 assessment in the range [15 to 30[mL/min/1.73m^2 during the on-treatment-period

or from [15 to 30 mL/min/1.73m^2 at baseline to at least 1 assessment in the range [30 to 60[mL/min/1.73m^2 during the on-treatment-period.

- A durable CR renal was defined as a response that lasted ≥60 days.

The following analyses were added after database lock:

• Analyses for PFS and overall response in patients with isolated gain(1q21) abnormalities at baseline to determine whether the addition of isatuximab was beneficial in this group of patients.

• Analyses of baseline characteristics and patient disposition in the following subgroup of patients: America geographical region, FCGR3A, and MRD negative and MRD positive patients.

• Progression free survival analysis within the IKd arm depending on premature carfilzomib discontinuation (yes versus no).

• Analysis of adjusted potential CR rate considering interference tested by mass spectrometry.

• A sensitivity analysis has been added upon United States Food and Drug Administration request to evaluate the impact of late progressions and deaths. In this sensitivity analysis, progressions or deaths occurring more than 8 weeks after the last disease assessment (corresponding to two consecutive missed assessments) were censored at the earliest of the date of last valid disease assessment without evidence of progression before initiation of new anti-myeloma treatment and the cut-off date.

Sample size

The sample size calculation was based on the primary efficacy endpoint (ie, PFS). It was assumed that Kd arm would have a median PFS of 19 months and the IKd arm would have a 41% risk reduction in HR compared with the Kd arm. A planned interim analysis for PFS was done when 65% of the PFS events had been observed. An O'Brien and Fleming α-spending function was used to obtain the nominal significance levels for the interim and final analyses of PFS.

Based on the above assumptions, a total of 159 PFS events were needed to achieve a 90% power for the study. Three hundred patients (180 patients in the IKd arm and 120 patients in the Kd arm) were expected to be adequate to achieve the targeted number of events for PFS.

Randomisation

Eligible patients were randomly assigned to a treatment group (IKd arm or Kd arm) in a 3:2 ratio using interactive response technology (IRT). Patient were stratified according to

- number of prior lines (1 versus >1), and
- R-ISS (I or II versus III versus not classified [inconclusive FISH unless stage can be determined on LDH, albumin, and β2 microglobulin only]).

Blinding (masking)

This was an open-label study but assessment of outcomes (response, progression) was based on the review of the data collected for disease evaluation (radiological assessment, bone marrow assessments and central laboratory disease assessments) by IRC blinded to study treatment arms.

Statistical methods

The interim efficacy analysis was the comparison of PFS based on the IRC assessment in the IKd arm versus the Kd arm using a log-rank test procedure stratified by the stratification factors as entered in the IRT (ie, R-ISS and number of previous lines of therapy).

An O'Brien and Fleming α-spending function was used to obtain the nominal significance levels for the interim and final analyses of survival on PFS. The 1-sided nominal significance level to declare overwhelming efficacy when 103 PFS events (65% information fraction) were observed was 0.005 (corresponding to an HR of 0.6) and to declare superiority of IKd at the final analysis (159 events) was 0.023 (corresponding to a HR of 0.725). The stopping boundaries on PFS endpoint at the interim analysis were calculated using the actual number of events. The interim analysis was performed by an independent statistician under the supervision of the DMC. The DMC also reviewed secondary efficacy endpoints and safety data available at the time of the interim analysis.

Analysis populations

- Randomised population: The randomised population includes all patients who signed an ICF and were allocated a randomisation number by the IRT, regardless of whether the patient was treated.
- Intent-to-treat (ITT) population: The ITT population is the randomised population. This was the primary population for all efficacy analyses.

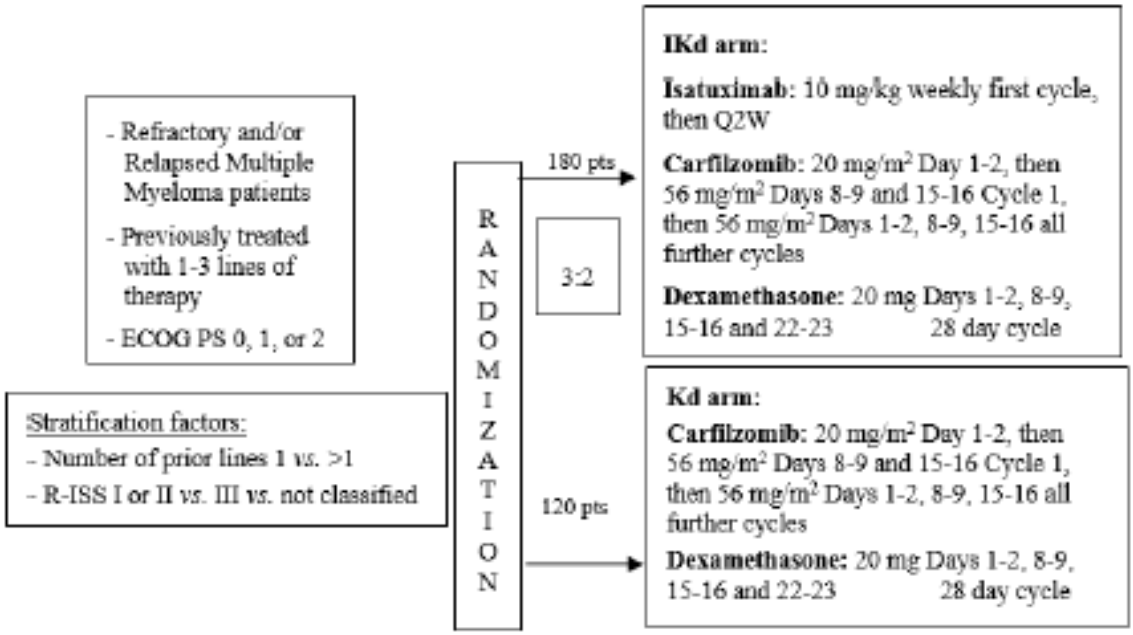
All efficacy analyses using the stratification factors were performed based on the stratification factor as per the IRT.

- Safety population: The safety population includes patients in the ITT population who received at least 1 dose or a partial dose of the study treatments. This population was the primary population for the analysis of all safety parameters. All analyses using this population were based on the treatment actually received.
- PK population: The PK population was defined independently for isatuximab and carfilzomib and included all participants from the IKd safety population with at least one available concentration post-baseline (whatever the cycle and even if dosing is incomplete) with adequate documentation of dosing and sampling dates and times.
- Immunogenicity population: The immunogenicity population included all participants from the IKd safety population with at least one ADA result (negative, positive or inconclusive) post-baseline.

Results

Participant flow

Figure 11 Study EFC15246



Recruitment

A total of 341 patients were screened and 302 were randomised into the study between 25 October 2017 and 21 March 2019. Patients were randomised at 69 sites in 16 countries. The countries with the largest enrolment were France (39 patients), Australia (37 patients), Czech Republic (34 patients), Brazil (33 patients), and Republic of Korea (27 patients).

Three patients out of 302 randomised patients (2 in the IKd arm and 1 in the Kd arm) did not receive treatment.

As of the interim analysis cutoff date (07 February 2020), 168 patients have discontinued study treatment (84 [46.9%] in the IKd arm and 84 [68.3%] in the Kd arm). Most subjects discontinued due to progressive disease (see Table 8).

***Table** 8 Disposition - Randomised population - EFC15246*

	Kd (N=123)	IKd (N=179)
Randomized and not treated	1 (0.8)	2 (1.1)
Randomized and treated	122 (99.2)	177 (98.9)
Patients still on treatment	38 (30.9)	93 (52.0)
Patients with definitive treatment discontinuation	84 (68.3)	84 (46.9)
Reason for definitive treatment discontinuation		
Adverse event	17 (13.8)	15 (8.4)
Progressive disease	49 (39.8)	52 (29.1)
Poor compliance to protocol	0	0
Withdrawal by subject	14 (11.4)	11 (6.1)
Other	4 (3.3)	6 (3.4)
Reason for treatment withdrawal by subject		
Adverse event	5 (4.1)	3 (1.7)
Study procedure	1 (0.8)	1 (0.6)
Other	8 (6.5)	7 (3.9)
Status at the cutoff date[a]		
Alive	98 (79.7)	148 (82.7)
Death	25 (20.3)	31 (17.3)
Time from last contact to the cutoff date[b]		
≤ 2 weeks	19 (15.4)	8 (4.5)
> 2 weeks and ≤ 1 month	1 (0.8)	0
> 1 month and ≤ 2 months	0	0
> 2 months	3 (2.4)	7 (3.9)

a Cut-off date for overall survival (07FEB2020).

b For patients censored for overall survival before the Cut-off date.

Note: Definitive treatment discontinuation is defined as the discontinuation of all the study drugs. When all study drugs are not discontinued at the same time, the reason for definitive discontinuation is the reason for discontinuation of the last study drug stopped

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

1 month = 4 weeks

PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/dis_dispo_r_t.sas
OUT=REPORT/OUTPUT/dis_dispo_r_t_i.rtf (15JUN2020 10:50)

Conduct of the study

Protocol Amendments

There were 6 global amendments and 1 country-specific (UK) amendment. One global amendment and the country-specific amendment were implemented prior to patient enrollment.

The timing, rationale, and key details of major changes to the protocol statistical section which were implemented after the first patient was randomised and before the cut-off date of the planned interim analysis are provided in Table 9. Importantly, the censoring rules for the primary endpoint PFS were amended based on Health Authority feedback (amendment 7). The PFS definition was modified such that the date of initiation of further anti-myeloma treatment was considered when determining the cut-off date for PFS. PFS2 was also updated according to the change.

Of note, in amendment 4 (global July 2018) it was clarified that in absence of radiological and M protein progression, if clinical and biological data together provided clear evidence of clinical progression based on IRC judgement, the IRC could consider clinical progression as a PFS event.

***Table** 9 Protocol amendment statistical changes*

Protocol amendment number	Date approved	Rationale	Description of statistical changes
7	13 November 2019	Health authorities (FDA) feedback	Change in censoring rules for the primary PFS analysis to consider the initiation of further anti-myeloma therapy. Update of PFS2 definition related to this change.
	13 November 2019	Update of statistical sections in order to reflect the changes made in the SAP amendment 1 of July 2019	Please refer to Table 8.
3	08 February 2018	Error in number of PFS events	Modification of the number of events required for the final PFS analysis: 159 instead of 158 events
	08 February 2018	Recent data strongly suggests MRD negativity is a prognostic factor for PFS and OS not only in patients with CR. Patients who were MRD-negative despite a persistent M-protein component showed similar PFS and OS to patients who were MRD-negative with CR	To add MRD assessment in patients with VGPR
	08 February 2018	The order of key secondary endpoints was revised after the addition of MRD assessment in patients with VGPR	Modification of the order of key secondary endpoints: MRD negativity rate in patients with VGPR or better will be tested prior to CR rate
	08 February 2018	Updates related to the statistical section of the protocol made in the initial version of the SAP were included in the statistical section of the protocol	Clarifications of infusion/dose delay and dose reduction Confidence interval of primary and key secondary endpoints: replace 95% by (1-2α) % Quality of life: replace 95% confidence intervals by SEM in the graph of mean of EQ-5D-5L VAS and the mean of index utility score over time. Corrections of typos

CR=complete response; EQ-5D-5L VAS=Euro QoL Group Self-Report Questionnaire with 5 Dimensions and 5 Levels per Dimension Visual Analog Scale; IR=infusion reaction; MRD=minimal residual disease; FDA=Food and Drug Administration; OS=overall survival; PD=progressive disease; PFS=progression-free survival; SAP=statistical analysis plan; PK=pharmacokinetic; SEM=standard error of mean; VGPR=very good partial response

Protocol deviations

Inclusion criteria violations of having received more than 3 previous treatment were reported in both arms: n=1 (0.6%) in the IKd arm and n=2 (1.6%) in the Kd arm. Three other inclusion criteria violations were reported only in the IKd arm: one patient was refractory to prior anti-CD38 treatment, one patient had received anti-myeloma treatment within 7 days of randomisation, and one patient did not have an LVEF measurement taken until after study treatment initiation.

The most frequent critical or major deviations related to randomisation procedures were wrong stratum of randomisation (7.3% in the IKd arm and 16.3% in the Kd arm) with stratification error in R-ISS stage (4.5%, 10.6%) and number of prior lines (2.8%, 5.7%), and IMP given without IRT procedure at resupply visit (2.2%, 2.4%). According to the study report the stratification errors did not lead to an imbalance in incidence of patients with each stratification factor between IKd and Kd.

Baseline data

Efficacy analyses were performed using the ITT analysis set. A summary of demographics and subject characteristics and disease characteristics at study entry in the ITT is shown in Table 10, Table 11, 12, 13 and 14.

***Table** 10 Demographic characteristics*

	Kd (N=123)	IKd (N=179)	All (N=302)
Age (years)			
Number	123	179	302
Mean (SD)	62.9 (10.0)	63.3 (9.8)	63.1 (9.9)
Median	63.0	65.0	64.0
Min ; Max	33 ; 90	37 ; 86	33 ; 90
Age group (years) [n(%)]			
Number	123	179	302
<65	66 (53.7)	88 (49.2)	154 (51.0)
≥65 to <75	47 (38.2)	74 (41.3)	121 (40.1)
≥75	10 (8.1)	17 (9.5)	27 (8.9)
Gender [n(%)]			
Number	123	179	302
Female	55 (44.7)	78 (43.6)	133 (44.0)
Male	68 (55.3)	101 (56.4)	169 (56.0)
Race [n(%)]			
Number	123	179	302
White	83 (67.5)	131 (73.2)	214 (70.9)
Black or African American	4 (3.3)	5 (2.8)	9 (3.0)
Asian	24 (19.5)	26 (14.5)	50 (16.6)
Multiple	0	3 (1.7)	3 (1.0)
White/Black or African American	0	1 (0.6)	1 (0.3)
White/Asian	0	1 (0.6)	1 (0.3)
White/Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.3)
Missing/Not reported	12 (9.8)	14 (7.8)	26 (8.6)
Ethnicity [n(%)]			
Number	123	179	302
Hispanic or Latino	14 (11.4)	12 (6.7)	26 (8.6)
Not Hispanic or Latino	94 (76.4)	144 (80.4)	238 (78.8)
Unknown	8 (6.5)	9 (5.0)	17 (5.6)
Not Reported	7 (5.7)	14 (7.8)	21 (7.0)
Geographical region* [n(%)]			
Number	123	179	302
Europe	60 (48.8)	85 (47.5)	145 (48.0)
America	20 (16.3)	24 (13.4)	44 (14.6)
Asia	21 (17.1)	25 (14.0)	46 (15.2)
Other Countries	22 (17.9)	45 (25.1)	67 (22.2)

***Table** 11 Disease characteristics*

	Kd (N=123)	IKd (N=179)	All (N=302)
Initial diagnosis [n(%)]			
Number	123	179	302
Multiple Myeloma	123 (100)	179 (100)	302 (100)
Time from initial diagnosis of MM to randomization (years)			
Number	123	179	302
Mean (SD)	4.25 (3.15)	4.10 (3.02)	4.16 (3.07)
Median	3.33	3.23	3.32
Min ; Max	0.2 ; 21.3	0.4 ; 17.9	0.2 ; 21.3

	Kd (N=123)	IKd (N=179)	All (N=302)
MM subtype at study entry* [n(%)]			
Number	123	179	302
Ig G	85 (69.1)	126 (70.4)	211 (69.9)
Ig A	30 (24.4)	38 (21.2)	68 (22.5)
Ig M	0	0	0
Ig D	1 (0.8)	4 (2.2)	5 (1.7)
Ig E	0	0	0
Kappa light chain only (urines)	4 (3.3)	5 (2.8)	9 (3.0)
Lambda light chain only (urines)	3 (2.4)	6 (3.4)	9 (3.0)
Biclonal status at study entry* [n(%)]			
Number	123	179	302
Yes	5 (4.1)	4 (2.2)	9 (3.0)
No	118 (95.9)	175 (97.8)	293 (97.0)
Beta 2-microglobulin (mg/L)			
Number	123	179	302
Mean (SD)	3.77 (2.67)	4.14 (4.65)	3.99 (3.96)
Median	3.02	3.19	3.11
Min ; Max	1.1 ; 17.6	1.6 ; 55.0	1.1 ; 55.0
Beta 2-microglobulin (mg/L) [n(%)]			
Number	123	179	302
< 3.5	79 (64.2)	103 (57.5)	182 (60.3)
≥ 3.5 and <5.5	24 (19.5)	50 (27.9)	74 (24.5)
≥ 5.5	20 (16.3)	26 (14.5)	46 (15.2)
Albumin (g/L)			
Number	121	176	297
Mean (SD)	39.68 (5.83)	39.02 (5.18)	39.29 (5.46)
Median	40.00	39.00	40.00
Min ; Max	13.0 ; 54.0	25.0 ; 51.8	13.0 ; 54.0
Albumin (g/L) [n(%)]			
Number	121	176	297
< 35	20 (16.5)	39 (22.2)	59 (19.9)
≥ 35	101 (83.5)	137 (77.8)	238 (80.1)
Serum LDH (IU/L)			
Number	122	176	298
Mean (SD)	238.28 (95.62)	254.63 (135.44)	247.94 (120.82)
Median	204.00	206.50	205.70
Min ; Max	81.0 ; 513.0	98.0 ; 949.0	81.0 ; 949.0
Serum LDH (IU/L)[n(%)]			
Number	122	176	298
≤ ULN	105 (86.1)	132 (75.0)	237 (79.5)
> ULN	17 (13.9)	44 (25.0)	61 (20.5)

***Table** 12 Disease characteristics (continued)*

	Kd (N=123)	IKd (N=179)	All (N=302)
ISS stage at study entry [n(%)]			
Number	123	179	302
Stage I	71 (57.7)	89 (49.7)	160 (53.0)
Stage II	31 (25.2)	63 (35.2)	94 (31.1)
Stage III	20 (16.3)	26 (14.5)	46 (15.2)
Unknown	1 (0.8)	1 (0.6)	2 (0.7)
R-ISS stage at study entry [n(%)]			
Number	123	179	302
Stage I	33 (26.8)	45 (25.1)	78 (25.8)
Stage II	70 (56.9)	110 (61.5)	180 (59.6)
Stage III	8 (6.5)	16 (8.9)	24 (7.9)
Not classified[c]	12 (9.8)	8 (4.5)	20 (6.6)
Fish done but risk not classified	9 (75.0)	5 (62.5)	14 (70.0)
Fish assessment missing	1 (8.3)	2 (25.0)	3 (15.0)
At least one biological assessment missing	2 (16.7)	2 (25.0)	4 (20.0)
Refractory status			
Number	123	179	302
Relapsed and refractory[b]	94 (76.4)	122 (68.2)	216 (71.5)
Primary refractory	0	0	0
Relapsed	29 (23.6)	57 (31.8)	86 (28.5)

[a]: as per eCRF

[b]: excluding primary refractory

[c]: a patient can have more than one reason to have a R-ISS stage not classified.

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

PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/dem_dischar_ent_t.sas OUT=REPORT/OUTPUT/dem_dischar_ent_r_t_i.rtf (15JUN2020 10:49)

***Table** 13 Other disease characteristics*

	Kd (N=123)	IKd (N=179)	All (N=302)
Bone marrow plasma cells (%) at baseline[a]			
Number	120	176	296
Mean (SD)	24.29 (22.10)	29.16 (27.26)	27.18 (25.37)
Median	18.50	20.00	19.80
Min ; Max	0.0 ; 98.0	0.0 ; 100.0	0.0 ; 100.0
Bone marrow plasma cells (%) at baseline by category[a] [n(%)]			
Number	123	179	302
0%	2 (1.6)	1 (0.6)	3 (1.0)
>0% to <5%	18 (14.6)	35 (19.6)	53 (17.5)

	Kd (N=123)	IKd (N=179)	All (N=302)
≥5% to <20%	41 (33.3)	51 (28.5)	92 (30.5)
≥20% to <50%	41 (33.3)	52 (29.1)	93 (30.8)
≥50%	18 (14.6)	37 (20.7)	55 (18.2)
Missing	3 (2.4)	3 (1.7)	6 (2.0)
Patients with soft tissue plasmacytoma as per eCRF [n(%)]			
Number	123	178	301
No	110 (89.4)	167 (93.8)	277 (92.0)
Yes	13 (10.6)	11 (6.2)	24 (8.0)
Patients with bone lesions as per eCRF [n(%)]			
Number	123	178	301
No	33 (26.8)	55 (30.9)	88 (29.2)
Yes	90 (73.2)	123 (69.1)	213 (70.8)
Number of bone lesions as per eCRF [n(%)]			
Number	123	178	301
No lesion	33 (26.8)	55 (30.9)	88 (29.2)
1 to 4	36 (29.3)	39 (21.9)	75 (24.9)
5 to 10	20 (16.3)	32 (18.0)	52 (17.3)
More than 10	34 (27.6)	52 (29.2)	86 (28.6)
Patients with soft tissue plasmacytoma as per IRC [n(%)]			
Number	123	178	301
No	116 (94.3)	166 (93.3)	282 (93.7)
Yes	7 (5.7)	12 (6.7)	19 (6.3)
Patients with bone lesions as per IRC [n(%)]			
Number	119	167	286
No	27 (22.7)	41 (24.6)	68 (23.8)
Yes	92 (77.3)	126 (75.4)	218 (76.2)
Number of bone lesions as per IRC [n(%)]			
Number	119	167	286
No lesion	27 (22.7)	41 (24.6)	68 (23.8)
1 to 4	21 (17.6)	27 (16.2)	48 (16.8)
5 to 10	15 (12.6)	12 (7.2)	27 (9.4)
More than 10	56 (47.1)	87 (52.1)	143 (50.0)

*: Based on last assessment up to first dose of study treatment recorded in eCRF

PGM=PRODOPS/SAR650984/EFC15246/DMC 2020 01/REPORT/PGM/dem bone t.sas
OUT=REPORT/OUTPUT/dem_bone_r_t_i.rtf (15JUN2020 10:49)

Overall 61 (20.2%) patients overall had renal impairment (eGFR <60 mL/min/1.73m^2 at baseline), 43 (24.0%) patients in the IKd arm and 18 (14.6%) patients in the Kd arm.

Cytogenetic risk, as determined by central laboratory based on FISH, was assigned to 87.2% of patients in the IKd arm, and in 88.6% of patients in the Kd arm. High-risk cytogenetic status was defined as the presence of del(17p) in at least 50% of analysed plasma cells and/or translocation t(4;14) and /or translocation t(14;16) in at least 30% of analysed plasma cells. Overall, 24.2% of patients had high risk cytogenetic abnormalities with a incidence in the IKd and Kd arms of 23.5% and 25.2%, respectively. Gain (1q21) was present (i,e. at least 3 copies in at least 30% of analyzed plasma cells) in 127 subjects , 49 (16.2%) also had one of the other high risk cytogenetic abnormalities (CA) and 78 (25.8%) had isolated gain (1q21) (47 (26.3%) patients in the IKd arm and 31 (25.2%) patients in the Kd arm).

The median number of prior lines was 2.0 (range 1 to 4) in both arms (see

Table 14). The main anti-myeloma therapies which were most frequently used were corticosteroids (100% patients), proteasome inhibitors (overall 89.7%, Kd 86%; IKd 93%, mostly bortezomib),

alkylating agents (overall 89.4%; Kd 82%; IKd 94%, mostly cyclophosphamide and/or melphalan), and immunomodulators (overall 78.1%; Kd: 81% vs IKd 76%, mostly lenalidomide and/or thalidomide). A total of 32.8% of patients were refractory to lenalidomide (31.8% in IKd arm, and 34.1% in Kd), 30.1% were refractory to bortezomib (29.1% in IKd arm, and 31.7% in Kd) and 14.9% of patients were refractory to both (14.5% in IKd, and 15.4% in Kd).There were 61.3% of patients who had undergone prior ASCT (64.8% in IKd arm, 56.1% in Kd arm).

Almost no subject had received prior Abs, only 1 subject (in the IKd) arm had received prior CD38 directed therapy and 5 subjects (1 Kd arm and 4 in IKd) had received prior elotuzumab.

***Table** 14 Prior anti-myeloma treatments*

	Kd (N=123)	IKd (N=179)	All (N=302)
Number of prior regimens			
Number	123	179	302
Mean (SD)	3.1 (1.6)	3.3 (1.8)	3.2 (1.7)
Median	3.0	3.0	3.0
Min ; Max	1 ; 8	1 ; 11	1 ; 11
Number of prior regimens [n(%)]			
Number	123	179	302
1	19 (15.4)	29 (16.2)	48 (15.9)
2	29 (23.6)	32 (17.9)	61 (20.2)
3	29 (23.6)	44 (24.6)	73 (24.2)
4	22 (17.9)	38 (21.2)	60 (19.9)
5	14 (11.4)	16 (8.9)	30 (9.9)
6	6 (4.9)	13 (7.3)	19 (6.3)
> 6	4 (3.3)	7 (3.9)	11 (3.6)
Number of prior lines			
Number	123	179	302
Mean (SD)	1.8 (0.9)	1.8 (0.8)	1.8 (0.8)
Median	2.0	2.0	2.0
Min ; Max	1 ; 4	1 ; 4	1 ; 4
Number of prior lines [n(%)]			
Number	123	179	302
1	55 (44.7)	79 (44.1)	134 (44.4)
2	36 (29.3)	64 (35.8)	100 (33.1)
3	30 (24.4)	33 (18.4)	63 (20.9)
> 3	2 (1.6)	3 (1.7)	5 (1.7)

Numbers analysed

All randomised patients (179 in the IKd arm and 123 in the Kd arm) were included in the efficacy (ITT) population (see Table 156). Three randomised patients did not receive study drug and were excluded from the safety population. The safety population included 177 patients in the IKd arm and 122 patients in the Kd arm. All treated patients received the study treatment allocated by the IRT.

***Table** 15 Analysis populations*

	Kd	IKd
Randomized population	123 (100)	179 (100)
Efficacy population: Intent-To-Treat (ITT)	123 (100)	179 (100)
Safety population	122	177
ADA population	0	168
PK population (Isatuximab)	0	172
PK population (Carfilzomib)	0	28

Note: For the randomized and ITT populations, patients are tabulated according to their randomized treatment
For other populations, patients are tabulated according to the treatment actually received (as treated)
No patients are randomized in a group and taking another study treatment.
PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/dis_population_r_t2.sas
OUT=REPORT/OUTPUT/dis_population_r_t2_i.rtf (15JUN2020 10:49)

At the cut-off date, 131 patients (93 [52.0%] in the IKd arm and 38 [30.9%] in the Kd arm) were still on treatment. The overall median duration of exposure was 72.9 weeks (range 1 to 114). The median number of cycles was 18.0 (range 1 to 28). Exposure (median duration of exposure and median number of Cycles) was higher in IKd arm (see Table 24 in safety section).

The median relative dose intensity (defined as the ratio of the actual dose intensity to the planned dose intensity in percent) was:

- Isatuximab: 94.27% in the IKd arm;
- Carfilzomib: 91.31% (range 18.2 to 108.7) and was similar in both arms (91% Kd vs 91% IKd);
- Dexamethasone: 87.1% (range 24.5 to 101.6) and was similar in both arms (88% Kd vs 85% IKd).

Outcomes and estimation

The PFS analysis cutoff date for this interim analysis was 07 February 2020, at which time a total of 103 PFS events (per IRC) were reported as defined in the protocol. This was also the cutoff date for all other efficacy analyses.

Primary endpoint

At the cutoff date, 48 (26.8%) and 55 (44.7%) patients had an PFS event in the IKd and Kd arms, respectively, with a median follow-up of 20.73 months. The HR for the primary analysis was 0.531 (99% CI: 0.318 to 0.889), corresponding to a reduction of 46.9% in risk for disease progression or death with IKd compared to Kd. The median PFS was not reached in the Ikd arm and was 19.15 months (95% CI: 15.770 and upper limit not reached) in the Kd arm (see Figure 12). The 1-sided stratified log rank test resulting from the comparison of PFS between the 2 arms was statistically significant with a p-value of 0.0007, which met the prespecified efficacy boundary of 0.005.

At the time of the cut-off date, a total of 131 (73.2%) and 68 (55.3%) patients in the IKd and Kd arms, respectively, had not had a PFS event and were censored with the main reason for censoring ongoing follow-up (83.2% and 72.1% of the censored subjects in the IKd and Kd arms respectively).

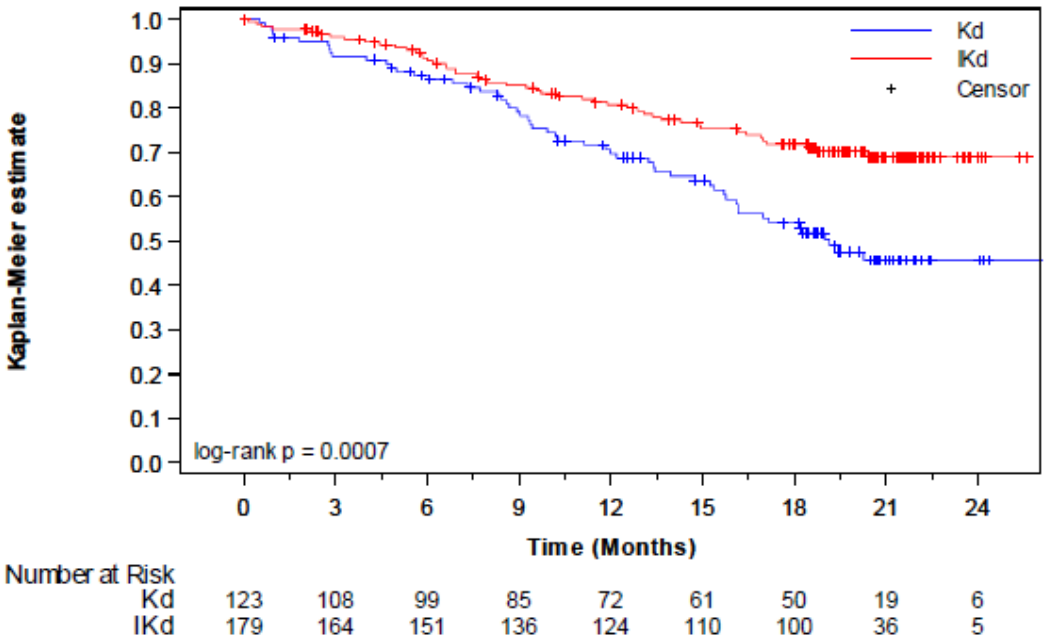


Figure 12 *Primary analysis based on disease assessment by the IRC*

PFS sensitivity analyses

Several sensitivity analyses were performed resulting in HRs ranging from 0.510 to 0.595 (see **Table** 16, median PFS was not reached in the IKd arm and ranged from 16.1 to 20.3 months in the Kd arm. They all showed statistically significance differences favoring of IKd over Kd (range p-values 0.0003 to 0.0024).

Table *16 Summary of main sensitivity analyses*

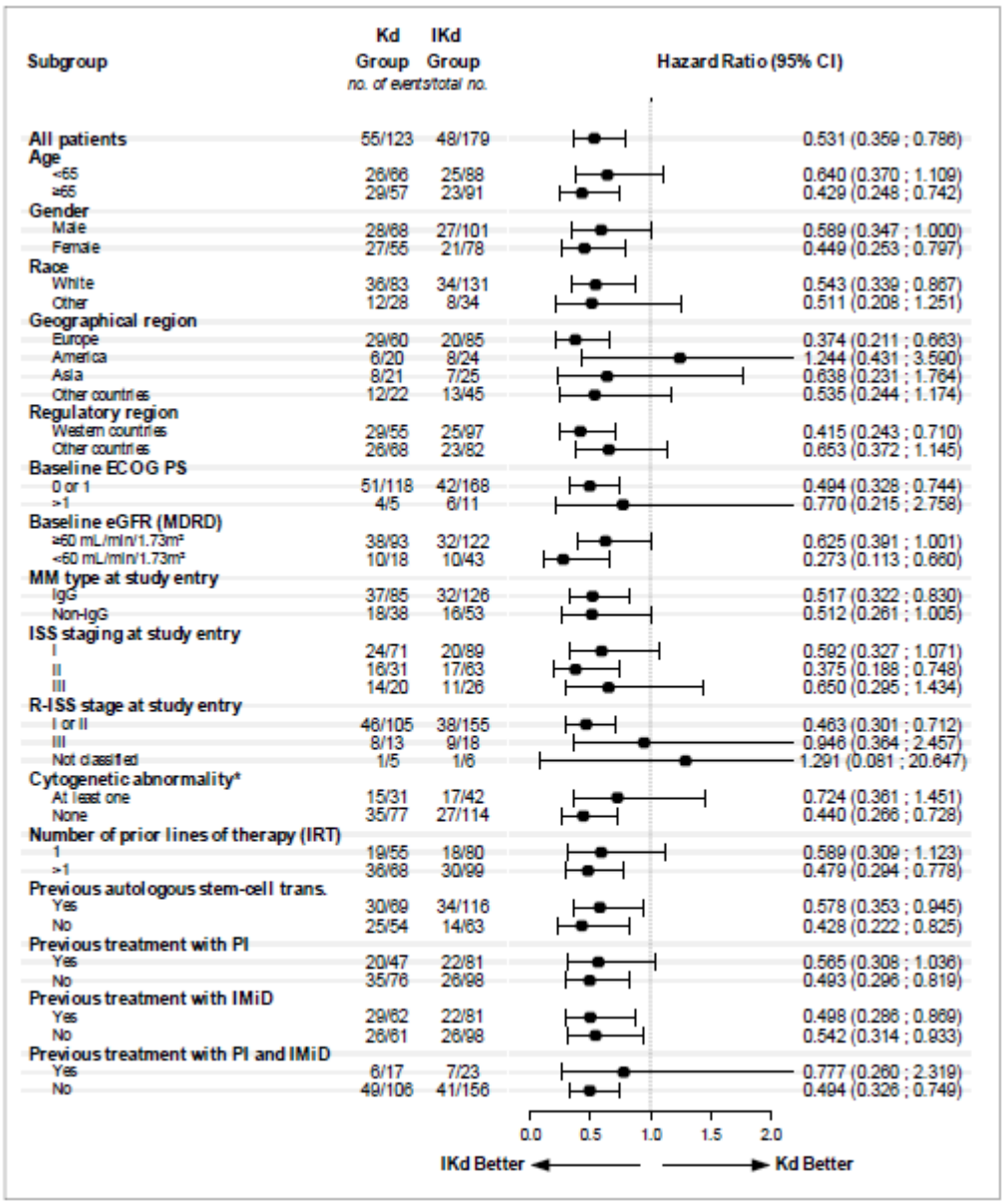
		Kd		IKd			
	Total Number of Events	N(%) of Events	Median (Months) (95% CI)	N(%) of Events	Median (Months) (95% CI)	Hazard Ratio (95% CI) vs Kd	P-value[a]
Main analysis: PFS as per IRC, stratified by stratification factors as entered in the IRT	103	55 (44.7)	19.15 (15.770 to NC)	48 (26.8)	NC (NC to NC)	0.531 (0.318 to 0.889)	0.0007
PFS as per IRC without censoring for further anti-myeloma treatment	118	61 (49.6)	18.99 (15.376 to NC)	57 (31.8)	NC (NC to NC)	0.572 (0.354 to 0.925)	0.0012
PFS as per investigator including symptomatic deterioration as an event	127	65 (52.8)	16.99 (13.667 to NC)	62 (34.6)	NC (NC to NC)	0.577 (0.363 to 0.916)	0.0010
PFS as per investigator ignoring symptomatic deterioration	119	60 (48.8)	18.20 (15.244 to NC)	59 (33.0)	NC (NC to NC)	0.595 (0.369 to 0.960)	0.0024
PFS as per IRC including initiation of further anti-myeloma treatment as an event	138	71 (57.7)	16.10 (12.715 to 19.154)	67 (37.4)	NC (NC to NC)	0.574 (0.368 to 0.895)	0.0006
PFS as per IRC, stratified by stratification factors as entered in the eCRF	103	55 (44.7)	19.15 (15.770 to NC)	48 (26.8)	NC (NC to NC)	0.510 (0.305 to 0.851)	0.0003
PFS as per IRC with censoring of progression or death occurring more than 8 weeks after the last valid disease assessment	96	50 (40.7)	20.27 (15.770 to NC)	46 (25.7)	NC (NC to NC)	0.548 (0.322 to 0.934)	0.0016

CI: Confidence interval; IRC=Independent Response Committee; NC=not calculated; PFS=progression-free survival
Cutoff date = 07 February 2020
a One-sided significance level is 0.005.
Source: Table 24 and Tables 16.2.6.1.1.8, 16.2.6.1.1.12, 16.2.6.1.1.16, 16.2.6.1.1.22, 16.2.6.1.1.30, 16.2.6.1.1.35, 16.2.6.1.7.8

PFS Subgroup analysis

Subgroup analyses for prespecified patient subgroups were conducted when at least 10 patients were included in each treatment arm within a subgroup (see Figure 13).

In the America geographical region (PFS subgroup analysis), the HR was 1.244 (95% CI 0.431 to 3.590). Further analyses have been performed to understand these results (see section on Ancillary analyses below).



CI: Confidence interval, PFS: Progression-free survival, IRC: Independent Response Committee, America includes : United States, Canada and Brazil

MM: Multiple Myeloma, Ig: Immunoglobulin, ISS: International staging system, R-ISS: Revised International staging system, IRT: Interactive Response Technology

Figure 13 *PFS - Summary of subgroup analyses in Study EFC15246 (forest plot)*

Key secondary endpoints

Overall response rate

The ORR (≥PR based on IRC assessment) in the IKd and Kd arms was 86.6% and 82.9%, respectively. The difference between the 2 arms was not statistically significant (p-value was 0.1930). As a concequence subsequent endpoints were not to be tested for statistical significance.

The ORR based on the Investigator assessment was 85.5% and 83.7% in the IKd and Kd arms, respectively.

The median time to first response was 1.08 months (95% CI: 1.051 to 1.117) and 1.12 months (95% CI: 1.051 to 1.183) in the IKd and Kd arms, respectively. The median time to best response was: 4.60 months in the IKd arm (95% CI: 3.811 to 5.257) and 3.78 months in the Kd arm (95% CI: 2.858 to 4.172).

Rate of VGPR or better

VGPR or better response was achieved in 72.6% versus 56.1% in the IKd and Kd arms, respectively (nominal p=0.0011).

MRD negativity rate in patients with VGPR or better

The incidence of patients with at least one evaluable MRD sample among with patients with VGPR or better as per Ivestigator was similar in the IKd and Kd arms (78% versus 74%). MRD negativity rate (10^{-5} sensitivity level by central lab NGS) in the ITT population in patients with VGPR or better was 29.6% [95% CI: 0.2303 to0.3688] in the IKd arm and 13.0% [95% CI: 0.0762 to 0.2026] in the Kd arm (see Table 18).

Table 17 *- MRD negativity rate*

	Kd (N=123)	IKd (N=179)
MRD negativity rate[e]	16 (13.0)	53 (29.6)
95% CI[c]	0.0762 to 0.2026	0.2303 to 0.3688
Stratified Cochran-Mantel-Haenszel test p-value[d] vs Kd		0.0004
Complete response (sCR or CR)	34 (27.6)	71 (39.7)
95% CI[c]	0.1996 to 0.3643	0.3244 to 0.4723
MRD negativity[a] and complete response (sCR or CR)	13 (10.6)	36 (20.1)
95% CI[c]	0.0575 to 0.1740	0.1450 to 0.2674

CI: Confidence interval, IRC: Independent Response Committee, IRT: Interactive Response Technology, sCR: stringent Complete Response, CR : Complete Response, VGPR : Very Good Partial Response, PR : Partial Response, MR : Minimal response

a Two consecutive negative M-protein and negative immunofixation with missing bone marrow.

b All criteria for a complete response were met except that immunofixation remained positive.

c Estimated using Clopper-Pearson method.

d Stratified on randomization factors according to IRT. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a control of the overall type-I error rate. One-sided significance level is 0.025. Biochemical CR and Near-CR were assessed only for patients with confirmed VGPR as BOR. Criteria for confirmation was not applied to Near-CR subcategory.

e For analysis purpose, subjects in the ITT population but without MRD assessment will be considered as having positive MRD.

PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/eff_bestresp_i_t.sas
OUT=REPORT/OUTPUT/eff_bestresp_irc_i_t_i.rtf (08JUL2020 17:41)

CR rate

CR rate was 39.7% vs 27.6% in the IKd and Kd arm, respectively.

Isatuximab may co-migrate with M-protein on serum protein electrophoresis (SPEP) and immunofixation electrophoresis assays that are used for monitoring the MM disease and determining response to treatment. This interference can mislead the interpretation of the response assessment based on International Myeloma Working Group (IMWG) criteria. To evaluate whether isatuximab had interfered with M-protein quantification, 27 patients in the IKd arm, who either had immunofixation-positive near-

CR in whom criteria for CR were met except for residual immunofixation positivity (historic near-CR category) as their best response as per investigator, or had SPEP ≤0.5 g/dL with IgG kappa or kappa subtypes (potential CR), were identified. Serum samples from these patients were tested by mass spectrometry after separation of isatuximab signal from the myeloma M-protein signal. In 17 out of the 27 tested patients, there was no residual myeloma M-protein detectable at the sensitivity level of the immunofixation test (0.025 g/dL), at least at one time point. Among these 17 patients, 2 patients had best response CR as per IRC and 15 were VGPR as per IRC (including 11 identified near CR and 4 VGPR).

Among these 15 patients, a local BMA showing less than 5% plasma cells infiltration is available for 11 patients, meaning that 11 additional patients could have CR as best response leading to an adjusted potential CR rate of 45.8% (71 + 11 patients) in the IKd arm.

In addition, among these 11 additional patients, 7 reached MRD negativity, leading to an adjusted potential MRD negativity CR rate of 24.0% (36 + 7 patients) in the IKd arm.

This suggests that the CR rate in the IKd arm was likely underestimated due to the interference of isatuximab with M protein measurements and in particular the immunofixation test.

***Table** 18 Summary of overall response rate as per IRC*

	Kd (N=123)	IKd (N=179)
Best Overall Response [n(%)]		
Stringent complete response	0	0
Complete response	34 (27.6)	71 (39.7)
Very good partial response	35 (28.5)	59 (33.0)
Biochemical CR but with missing bone marrow[a]	7 (5.7)	6 (3.4)
Near-CR[b]	13 (10.6)	36 (20.1)
Partial response	33 (26.8)	25 (14.0)
Minimal response	5 (4.1)	4 (2.2)
Stable disease	6 (4.9)	13 (7.3)
Non Progressive disease	1 (0.8)	1 (0.6)
Progressive disease	3 (2.4)	2 (1.1)
Unconfirmed progressive disease	1 (0.8)	0
Not evaluable/Not assessed	5 (4.1)	4 (2.2)
Overall Response		
Responders (sCR, CR, VGPR or PR)	102 (82.9)	155 (86.6)
95% CI[c]	0.7509 to 0.8911	0.8071 to 0.9122
Stratified Cochran-Mantel-Haenszel test p-value[d] vs Kd		0.1930
VGPR or better	69 (56.1)	130 (72.6)
95% CI[c]	0.4687 to 0.6503	0.6547 to 0.7901
Stratified Cochran-Mantel-Haenszel test p-value[d] vs Kd		0.0011

	Kd (N=123)	IKd (N=179)
MRD negativity rate[e]	16 (13.0)	53 (29.6)
95% CI[c]	0.0762 to 0.2026	0.2303 to 0.3688
Stratified Cochran-Mantel-Haenszel test p-value[d] vs Kd		0.0004
Complete response (sCR or CR)	34 (27.6)	71 (39.7)
95% CI[c]	0.1996 to 0.3643	0.3244 to 0.4723
MRD negativity[e] and complete response (sCR or CR)	13 (10.6)	36 (20.1)
95% CI[c]	0.0575 to 0.1740	0.1450 to 0.2674

CI: Confidence interval, IRC: Independent Response Committee, IRT: Interactive Response Technology, sCR: stringent Complete Response, CR : Complete Response, VGPR : Very Good Partial Response, PR : Partial Response, MR : Minimal response

a Two consecutive negative M-protein and negative immunofixation with missing bone marrow.

b All criteria for a complete response were met except that immunofixation remained positive.

c Estimated using Clopper-Pearson method.

d Stratified on randomization factors according to IRT. The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a control of the overall type-I error rate. One-sided significance level is 0.025. Biochemical CR and Near-CR were assessed only for patients with confirmed VGPR as BOR. Criteria for confirmation was not applied to Near-CR subcategory.

e For analysis purpose, subjects in the ITT population but without MRD assessment will be considered as having positive MRD.

PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/eff_bestresp_i_t.sas
OUT=REPORT/OUTPUT/eff_bestresp_irc_i_t_i.rtf (08JUL2020 17:41)

OS

Overall survival was not planned to be tested at the time of the interim analysis as it was not mature and is planned per protocol to be analyzed 3 years after primary PFS positive analysis. At the cutoff date, with a median follow-up of 20.73 months, 31 (17.3%) and 25 (20.3 %) patients had a death event in the IKd and Kd arms, respectively.

Other secondary endpoints:

Duration of response:

Among 155 and 102 patients in the IKd and Kd arms, respectively, who were responders based on IRC assessment (PR or better), the median duration of response was not reached in either arm (at the analysis cut-off date) the HR was 0.425 (95% CI 0.269 to 0.672 favoring IKd over Kd).

Time to progression

The median TTP based on IRC assessment was not reached in the IKd arm and was 20.27 months (95% CI: 16.986 and upper limit not estimable) in the Kd arm. A low HR was observed for TTP (0.495 [95% CI 0.324 to 0.757]) which was consistent with the primary PFS analysis.

Time to next treatment

Overall, time to next treatment in the IKd arm was delayed compared with the Kd arm (stratified HR 0.566, 95% CI: 0.380 to 0.841. The median time to next treatment was not reached in either treatment arm. Among patients who received further anti-myeloma treatment (26.3% and 43.1% of patients in the IKd and Kd arms, respectively), the most frequent subsequent therapy given was an IMiD (83.0% and 79.2% in the IKd and Kd arms, respectively) and corticosteroids (80.9% and 83.0%, in the IKd and Kd treatment arms respectively). Monoclonal antibodies were given less frequently in the IKd arm than the Kd arm (23.4% versus 54.7%) and was most often daratumumab (21.3% and 47.2%, respectively).

PFS2

At the cutoff date, 26.3% of patients in the IKd arm and 43.1% of patients in the Kd arm initiated a further anti-myeloma therapy. Median PFS2 had not been reached at the cutoff date in either treatment arm, the percentage of patients with PFS2 events was lower in the IKd arm than in the Kd arm (21.8% versus 28.5%) a positive treatment effect (stratified HR 0.77, 95% CI: (0.486 to 1.228)) on PFS2 was observed in favor of the IKd arm.

Among patients who had a PFS2 events, the most frequent event in the IKd and Kd arms were disease progression (48.7% and 65.7%, respectively) and death without any further anti-myeloma therapy before the cut-off (33.3% and 28.6%, respectively). A total of 140 (78.2%) and 88 (71.5%) patients in the IKd and Kd arms, respectively, did not have a PFS2 event and were censored.

Renal response

Renal function impairment (defined as eGFR <60 mL/min/1.73m^2) was present at baseline in 43 of 163 (26.4%) patients in the IKd arm and 18 of 111 (16.2%) patients in the Kd arm in the ITT population with an evaluable eGFR value at baseline. In patients with renal impairment the ORR was 93% vs. 61%, with VGPR or better rates of 79.1% vs. 44%, CR rates of 41.9% vs. 22% and MRD negativity (30.2% vs. 11.1%) in the IKd arm vs the Kd arm respectively.

Ancillary analyses

Exploratory and post-hoc subgroup analyses

Patient-reported outcomes:

Analyses of PROs were performed on the ITT population with patient-reported outcome assessments evaluable for C30, MY20, and EQ 5D-5L. Statistical significance for within or between arm differences was not assessed, only descriptive summaries were provided. Clinically important changes from baseline were defined as increases or decreases of 10 points for C30 and MY20 summary scores, subscales and symptom items, 0.074 points for EQ-5D-5L health state utility values (HSUV) and 7 points for EQ-5D-5L VAS.

Health related quality of life was largely maintained during the treatment period in the IKd and Kd arms as measured by the EORTC QLQ-C30 global health status/quality of life (GHS QoL) score. Increases in C30 GHS/QoL scores of greater than 10 points were observed toward the end of the treatment period for those on Kd arm at Cycle 19 to Cycle 24.

Isolated changes in MY20 summary scores of at least 10 points have been recorded, mostly observed towards the end of the treatment period, for both treatment arms, no clear or consistent patterns were observed on the MY20 body image, future perspective, disease symptoms, and side effects of treatment scales/items.

No clear or consistent patterns were observed on the on the EQ 5D 5L HSUV and EQ 5D-5L VAS.

Effect on ECOG status: Changes in ECOG performance status during study treatment (best score and worst score) were generally similar in the IKd and Kd arms.

Cytogenetic abnormalities: An additional analysis was performed to characterise the PFS treatment effect within the individual cytogenetic abnormalities. Improvements in PFS were seen in patients with t(4,14) and gain (1q21) chromosomal abnormalities (HRs 0.549 and 0.569, respectively), and for del(17p) chromosomal abnormality the HR was higher (HR 0.837).

Among the patients with isolated gain (1q21), the PFS HR was 0.462 (95% CI: 0.219 to 0.972).

FCGR3A polymorphism was analyzed in blood samples from 285 patients, among which 114 patients received Kd therapy and 171 patients received IKd therapy.

For the goup with *genotypes 158F/F,* PFS was in favor of the IKd group over the Kd group with a HR of 0.722; (median PFS IKd not reached). The ORR in the Ikd and Kd arm was 86.6% in 58 patients vs 91.2% in 31 patients, the VGPR+ rate was 71.6% (N=48) versus 67.6% (N=23) and the MRD negativity rate was 32.8% (N=22) versus 23.5% (N=8).

For the group with *genotype 158F/V* PFS was in favor of the IKd group over the Kd group with a HR of 0.353 (median PFS IKD 18.20 months, 95% CI: 15.244 and upper bound not reached). The ORR in the Ikd and Kd arm was 91.0% in 71 patients vs 79.4% in 54 patients, VGPR+ rate was 79.5% (N=62) versus 51.5% (N=35), and the MRD negativity rate was 30.8% (N=24) versus 10.3% (N=7).

For the group with *genotype 158V/V***,** PFS was similar between the IKd and Kd arm (HR 0.968; median PFS not reached). The ORRs in the Ikd and Kd arm 84.6% in 22 patients versus 91.7% in 11 patients, VGPR+ rate was 65.4% (N=17) versus 58.3% (N=7), and the MRD negativity rate was 26.9% (N=7) versus 8.3% (N=1).

Baseline characteristics in the FCGR3A 158V/V subgroup were not all well balanced between the IKd and Kd treatment arms, with more patients with worse prognostic factors in the IKd arm (eg, more patients with high risk cytogenetics, R-ISS Stage III, 3 prior lines of therapy, and ECOG Performance Status 2 or 3). These considerations may explain the similarity in PFS between treatment groups observed at the time of the interim analysis in the FCGR3A 158V/V subgroup.

In was concluded that within the IKd arm no consistent trends associated with improvements in the different efficacy endpoints and FCGR3A polymorphism were observed. The interpretation is impacted by the low number of patients in some genotypic subgroups, and the imbalance in baseline disease characteristics between treatment arms within a genotype.

Geographical area: In the population from the America geographical region (14.6% of the ITT, 24 subjects in IKd and 20 subjects in Kd arm), the HR of the PFS subgroup analysis was 1.244 (95% CI 0.431 to 3.590). Further analyses have been performed to understand these results. It was noted that study treatment discontinuation at subjects request was high (30%) and inconsistent with ITT population. Baseline characteristics were not well balanced between the IKd and Kd treatment arms for the America

geographic region (amongst other things IKd arm enrolled more subjects with R-ISS stage III, with at least one cytogenetic abnormality, with 3 or more prior lines, with bone marrow involvement ≥50% and with eGFR <60 ml/min/1.73 m²). These differences suggest patients in the IKd arm had worse prognosis than patients in the Kd arm and may explain the difference in PFS HR observed at the time of the interim analysis in the America subgroup.

Prior therapies: Post-hoc analyses were performed in patients with and without prior lenalidomide exposure and in patients refractory or not to lenalidomide and in patients with and without prior bortezomib exposure and in patients refractory or not to bortezomib. In these sugroups all analysis favored IKd over Kd, with HR ranged between 0.383 and 0.692 for subgroups with at least 10 patients in each treatment arm.

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 19**. Summary of Efficacy for trial EFC15246***

Title: IKEMA			
Study identifier	EFC15246		
Design	Randomised, open label, multicentre study assessing the clinical benefit of isatuximab combined with carfilzomib (Kyprolis) and dexamethasone versus carfilzomib with dexamethasone in patients with relapsed and/or refra refractory multiple myeloma previously treated with 1 to 3 prior lines		
	Duration of main phase:		25 October 2017 (first patient enrolled) to 7 Febreuary 2020 (interim analysis, study ongoing)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority<Exploratory: specify>		
Treatments groups	IKd		Isatuximab (10 mg/kg QW/Q2W), carfilzomib (20/56 mg/m^2.), dexamethasone (20 mg), until disease progression or unacceptable toxicity (n=179)
	Kd		carfilzomib (20/56 mg/m^2.), dexamethasone (20 mg), until disease progression or unacceptable toxicity (n=123)
Endpoints and definitions	Primary endpoint	PFS	time from the date of randomisation to the date of first documentation of PD by IRC or the date of death from any cause. PFS was censored at the date of the last valid disease assessment not showing PD and at start of further anti-myeloma treatment
		PFS*	PFS per IRC without censoring for further anti-myeloma treatment (recommended)
	Secondary endpoint	ORR	the proportion of patients with sCR, CR, VGPR, and PR as assessed by the IRC
	Secondary endpoint	Rate of VGPR or better	Defined as the proportion of patients with sCR, CR, and VGPR
	Secondary endpoint	MRD negativity in VGPR+	MRD negativity rate in patients with VGPR or better

	Secondary endpoint	CR rate	Defined as the proportion of patients with sCR and CR	
Database lock	7 Febreuary 2020			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	IKd	Kd	
	Number of subjects	179	123	
	Median PFS (months)	Not calculated	19.15	
	95% CI	(NC to NC)	(15.77 to NC)	
	Median PFS* (months) 95% CI	Not calculated (NC to NC)	18.99 15.38 to NC	
	ORR (%)	86.6	82.9	
	95% CI	0.807 to 0.912	0.751 to 0.891	
	VGPR+ (%) 95% CI	72.6 0.655 to 0.790	56.1 0.469 to 0.650	
	MRD in VGPR+ (%) 95% CI	29.6 0.2303 to 0.3688	13.0 0.0762 to 0.2026	
	CR (%) 95% CI	39.7 0.324 to 0.472	27.6 0.200 to 0.364	
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	IKd vs Kd	
		HR	0.531	
		95% CI	0.318-0.889	
		P-value	P=0.0007	
	PFS*	Comparison groups	IKd vs Kd	
		HR	0.572	
		95% CI	0.354-0.925	
		P-value	P=0.0012	
	Secondary Endpoint ORR	Comparison groups	IKd vs Kd	
		Odds ratio	1.324	
		95% CI	0.697-2.571	
		P-value	P=0.19	
	Secondary Endpoint VGPR+	Comparison groups	IKd vs Kd	
		Odds ratio	2.185	
		95% CI	1.318-3.626	
		P-value	P=0.0011	
	Secondary Endpoint VGPR+ and MRD negative	Comparison groups	IKd vs Kd	
		Odds ratio	2.812	
		95% CI	1.512-5.231	
		P-value	P=0.001	
	Secondary Endpoint CR	Comparison groups	IKd vs Kd	
		Odds ratio	1.792	
		95% CI	1.074-2.989	

		P-value	P=0.0004

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

Table 20 summarises key demographics, disease disease characteristics, and efficacy outcomes observed with the IKd regimen in study EFC15246 and with treatments consisting of the different components of the IKd regimen (Kd, Isa+K, Isa+d, Isa mono) as presented by MAH to support the efficacy of isatuximab (see supportive studies below). Although the MAH notes that cross-trial comparison is to be interpreted with caution, these data were interpreted to indicate that the IKd regimen has the best efficacy outcomes of the different regimens, and that each of the components (isatuximab, carfilzomib, and dexamethasone) is an active anti-myeloma agent contributing to the antitumor activity of the IKd regimen.

***Table** 20 Comparison of baseline and efficacy parameters across studies*

Parameters	EFC15246		TCD12795	TED10893 P2S2	
	Isa Kd	Kd	Isa K	Isa-dex	Isa
	N=179	N=123	N=33	N=55	N=109
Baseline					
Age (yrs), median (range)	65 (37-86)	63 (33-90)	61 (38-78)	66 (42-85)	68 (37-84)
ISS Stage III	29.1%	20.3%	NA	36.4%	41.3%
Prior lines, median (range)	2 (1-4)	2 (1-4)	3 (2-8)	4 (2-10)	4 (2-10)
Prior IMID	76%	81.3%	100%	100%	99.1%
Prior PI	92.7%	85.4%	100%	100%	100%
Efficacy					
ORR	86.6%	82.9%	70%	43.6%	23.9%
At least VGPR	72.6%	56.1%	36%	20%	9.2%
PFS (months)	NR (HR 0.53)	19.15	10.1	10.5	4.86
OS (months)	NR	NR	NR	17.25	18.92

Abbreviations: HR=hazard ratio; IMID=immunomodulatory imide drugs; ISA=isatuximab; Isa-dex=isatuximab in combination with dexamethasone; OS=overall survival; PFS=progression-free survial; NR=not recorded; ORR=overall response rate; PI=proteasome inhibitors; VGPR=very good partial response.

Clinical studies in special populations

There were no specific clinical studies for special populations.

Supportive study(ies)

The Applicant submitted results from TCD14079 Part B, TED10893 Phase 2 Stage 2 and the investigator-sponsored trial (IST) (Phase 1b IST TCD12795) to support the current application.

Study TCD14079 Part B

The efficacy data from study TCD14079 Part B (isatuximab-pomalidomide and dexamethasone) are included in this submission to again confirm the efficacy of the isatuximab fixed-volume infusion (data not available at initial submission, CSR date 28 April 2020).

The primary objective of this study was to evaluate the safety of isatuximab administered as a fixed infusion volume in combination with Pd as assessed by occurrence of grade ≥3 infusion associated reactions (IAR). The secondary objectives were to evaluate the infusion duration, the safety profile of the combination with isatuximab administration with fixed volume, the immunogenicity of isatuximab in combination with Pd and the efficacy of the combination of isatuximab with Pd (measured as ORR (CR + VGPR + PR) and clinical benefit rate (CR + VGPR + PR + MR) and the duration of response in RRMM patients.

Isatuximab was dosed at 10 mg/kg (QW/Q2W), pomalidomide dose was 4 mg (daily D1-D21) and dexamethasone was dosed at 40 mg. Isatuximab was administered using a fixed infusion volume of 250 mL. The starting infusion rates for the first second, and subsequent infusions are in line with that described in the SmPC, as well as the possibilities to increase infusion rates for the first and second infusion. For enrollment, the MM subjects had to have received at least two previous therapies including lenalidomide and proteasome inhibitor and have demonstrated disease progression on last therapy or after completion of the last therapy.

From 30 March 2018 to 27 December 2018, 47 patients were enrolled in Part B of the TCD14079 study from 11 sites based in the US. At the time of the final cut-off (October 2019), 22 patients (46.8%) were still on treatment. The reasons for study treatment discontinuation at the time of the analysis were: disease progression (15 patients, 31.9%), adverse events (AEs; 5 patients, 10.6%), and other reasons (5 patients, 10.6%). One patient (2.1%) prematurely discontinued pomalidomide treatment due to an adverse event, and no patient prematurely discontinued dexamethasone treatment.

The median age was 65 years (range 45 to 85 years), with the largest proportion of patients being aged <65 years (23 patients, 48.9%). All the patients had an ECOG PS of 0 or 1, except 2 patients (4.3%) who had an ECOG PS of 2. The median number of prior treatment lines was 3 (min-max: 1-8) with 1 patient (2.1%) having received 1 prior line of treatment and 17 patients (36.2%) having received 2 prior lines of treatment. All patients had received an IMiD, a PI and corticosteroid in prior lines of treatment. The majority (39 patients, 83.0%) of patients received an alkylating agent. Seven (14.9%) and 9 (19.1%) patients, respectively, had received daratumumab (anti-CD38 monoclonal antibody) and elotuzumab (anti-SLAM7 monoclonal antibody), prior to study entry. At study entry, 23 (48.9%), 12 (25.5%), and 7 (14.9%) patients had ISS Stage I, II, and III, respectively. most patients (33 patients, 70.2%) had measurable serum M-protein. There were 10 patients (21.3%) with high risk cytogenetic characteristics and 17 patients (36.2%) entered the study with moderate renal impairment, 1 patient had severe renal impairment.

Responses and disease progression were assessed by investigator. The ORR, determined in the all treated population (n=47), was 53.2% (95% CI: 38.1% to 67.9%), including 2 patients (4.3%) with CR (see **Table** 21). The median DoR (for patients who achieved a response of PR or better), median PFS and median OS could not be calculated because a high rate of censoring (21 of 25 pt with ≥ PR were censored for DoR, 27 of 47 patients (57.4%) patients were censored for PFS, 35 (74.5%) patients were censored for OS. The PFS probability was 0.741 at 4 months, 0.650 at 6 months, 0.604 at 8 months and 0.557 at 12 months. The OS probability was 0.893 at 4 months, 0.845 at 6 months, 0.764 at 8 months and 0.706 for 12 and 16 months. According to the MAH these efficacy results are consistent with the prior observations of this combination in Part A and in the ICARIA study (EFC15246).

Among the 7 patients who had previous exposure to daratumumab treatment, there was 1 response of PR which lasted 0.85 months. One patient with prior exposure to daratumumab (014079B-840-017-204) was non-evaluable for response due to sudden death 7 days after the first study.

***Table** 21 Study TCD14079 part B: Best overall response, overall response rate and clinical benefit rate - All-treated*

	Isatuximab (dose level and schedule) + pomalidomide/dexamethasone 10 mg/kg QW/Q2W (N=47)
Overall Response Rate (≥PR)	25 (53.2%)
95% CI[a]	(38.1% to 67.9%)
- Complete response (CR)	2 (4.3%)
- Very Good Partial Response (VGPR)	11 (23.4%)
- Partial response (PR)	12 (25.5%)
Minimal response (MR)	9 (19.1%)
Stable disease (SD)	11 (23.4%)
Not evaluable	2 (4.3%)
Clinical benefit rate (≥MR)	34 (72.3%)
95% CI[a]	(57.4% to 84.4%)

a estimated by Clopper-Pearson Exact method.

CI: Confidence interval, CR : Complete Response, VGPR : Very Good Partial Response, PR : Partial Response, MR : Minimal response, SD : stable disease

PGM=PRODOPS/SAR650984/TCD14079B/CSR/REPORT/PGM/eff_oresp_s_t.sas
OUT=REPORT/OUTPUT/eff_oresp_s_t_i.rtf (24FEB2020 - 12:05)

Study TED10893 Phase 2 Stage 2

The efficacy data from TED10893 Phase 2 Stage 2 are provided as they confirm the relevance of addition of dexamethasone to isatuximab.

This study was an open-label, randomised, multicentre study designed to evaluate the activity and safety of isatuximab with or without dexamethasone in patients with relapsed or RRMM. The primary objective was to evaluate the activity in terms of overall response rate (ORR) of isatuximab at the selected dose/schedule (20 mg QW/Q2W), as single agent (ISA arm) and in combination with dexamethasone (ISAdex arm) in patients with RRMM. Secondary objectives were to evaluate safety, efficacy (measured as DOR, Clinical benefit rate (CBR), PFS, and OS), the PK profile and immunogenicity of isatuximab in each arm.

A total of 165 patients were enrolled in the study, and randomised (110 ISA arm; 55 ISAdex arm), 1 patient was randomised and not treated. As of data cutoff date (21 January 2019), 96 (88.1%) patients in the ISA arm and 40 (72.7%) of patients in the ISAdex arm had definitively discontinued study treatment. The main reasons for treatment discontinuation were disease progression (64.2% ISA arm; 60.0% ISAdex arm), and adverse events (11.9% ISA arm; 9.1% ISAdex arm). Three (5.5%) patients in the ISAdex arm prematurely discontinued dexamethasone due to an AE. 12 patients in the ISA arm and 2 patients in the ISAdex arm discontinued because of a reason classified as "other"(unconfirmed disease progression, withdrawal of consent, investigator decision).

The median age was 68.0 years (range 37 to 84 years) and 66.0 years (range 42 to 85 years) in the ISA and ISAdex arms, respectively. The vast majority of patients had an ECOG PS of 0, or 1. Few patients (6.4% and 10.9%) had ECOG status 2 (Isa and Isadex). The median number of therapy lines was 4.0 (range 2 to 10 lines) in both the ISA arm and in the ISAdex arm. Forty-three (39.4%) patients in the ISA arm and 21 (38.1%) patients in the ISAdex arm received ≥5 prior lines of therapy. All patients except 1 in the ISA arm received a PI and an ImiD agent, 4 (3.7%) patients in the ISA arm and 3 (5.5%) patients in the ISAdex arm received elotuzumab. 90.8% of patients in ISA arm and 89.1% of patients in ISAdex arm were refractory to their last regimen of anticancer treatment (IMiD, PI, IMiD and PI, IMiD or PI, and alkylating agent). A total of 72.0% patients were double refractory to IMiD and PI.

A total of 26 (23.9%) patients in the ISA arm and 24 (43.6%) patients in the ISAdex arm achieved a response (see **Table** 22). The difference between the ISA arm and the ISAdex arm was considered significant, with a p-value of 0.0083 obtained by a 1-sided Fisher test. In responding patients the median DOR was 8 months (1-21 months min/max) in the ISA arm, and 12.2 months (2-19 months min/max) in the ISAdex arm. The clinical benefit rate (response MR or better) was 43.1% in the ISA arm and 54.5% in the ISAdex arm.

Median PFS was 4.86 months in the ISA arm, and 10.15 months in the ISAdex arm. The unstratified hazard ratio was 0.677 versus the ISA arm (95% CI 0.44-1.043), with a p-value of 0.0743. Median OS was 18.92 months for patients in the ISA arm and 17.25 months for patients in the ISAdex arm The unstratified hazard ratio was 0.799 (95% CI 0.484-0.1321), with a p-value versus ISA arm of 0.3808.

***Table** 22 Study TED108984-P2S2: Best overall response, overall response rate and clinical benefit rate based on IAC*

	Isa (N=109)	IsaDex (N=55)	All (N=164)
Best overall response [n(%)]			
Very good partial response(VGPR)	10 (9.2)	11 (20.0)	21 (12.8)
Partial response(PR)	16 (14.7)	13 (23.6)	29 (17.7)
Minimal response(MR)	21 (19.3)	6 (10.9)	27 (16.5)
Stable disease(SD)	35 (32.1)	14 (25.5)	49 (29.9)
Progressive disease(PD)	9 (8.3)	5 (9.1)	14 (8.5)
Unconfirmed progressive disease(PDu)	8 (7.3)	2 (3.6)	10 (6.1)
Not evaluable(NE)	10 (9.2)	4 (7.3)	14 (8.5)
Overall response			
Responders (sCR, CR, VGPR or PR)	26 (23.9)	24 (43.6)	50 (30.5)
95% CI[a]	0.1621 to 0.3297	0.3030 to 0.5768	
p-value[b] vs Isa		0.0083	
Odds ratio (95% CI) vs Isa		0.4046 (0.1918 to 0.8586)	
VGPR or better	10 (9.2)	11 (20.0)	21 (12.8)
95% CI[a]	0.0449 to 0.1623	0.1043 to 0.3297	
p-value[b] vs Isa		0.0460	
Clinical benefit			
Responders (MR or better)	47 (43.1)	30 (54.5)	77 (47.0)
95% CI[a]	0.3367 to 0.5295	0.4055 to 0.6803	

CI: Confidence interval
a Estimated by Clopper-Pearson exact method.
b p-values are from 1-sided Fisher test.
Cutoff date: 21JAN2019
PGM=PRODOPS/SAR650984/TED10893_P2S2/CSR/REPORT/PGM/eff_oresp_s_t.sas
OUT=REPORT/OUTPUT/eff_oresp_ac_s_t_x.rtf (21OCT2019 17:03)

Study TCD12795

This was an investigator initiated study (Martin et al,manuscript in preparation), the study database is not available to the MAH. However a summary of the efficacy data of this IST have been briefly summarised in support of the relevance of addition of carfilzomib to isatuximab.

In this US study, 33 patients received IKd with 3 isatuximab dose regimens, including 24 patients at the 10 mg/kg QW/Q2W dose used in the pivotal EFC15246 study. All patients received carfilzomib 20 mg/m^2 IV Cycle 1 Day 1 ,2, then 27 mg/m^2 IV on Days 8, 9, 15, 16, and then for all subsequent doses. After Cycle 8, patients were allowed to decrease carfilzomib frequency to D1, 2, 15, 16 per cycle while maintaining biweekly isatuximab, per investigator and patient choice. Dexamethasone was not considered part of the treatment regimen, but was given to prevent infusion reactions. At the time of data cut-off, 4 patients remained on-treatment and 28 patients had discontinued study treatment due to disease progression.

The median age was 61 years (range 38 to 78). The majority were male (73%) and 30% were age>65 years. There were 6 patients (18%) with high risk cytogenetic characteristics. The median number of prior treatment lines was 3 (range 2 to 8). All patients were previously exposed to IMIDs and to proteasome inhibitors.

Overall, the median number of cycles for study treatment was 10 (range 2 to 34). The median duration of follow-up was 26.7 months (range 13.3 to 61). The ORR for the entire study population (N=33) was 70% (95% CI: 51% to 84%) with 4 patients achieving sCR/CR (12%), 8 patients VGPR (24%), and 11 patients PR (33%). The median DOR was 10 months (≥PR; range 1.9-29.4), and over one-third of responders achieving a remission duration of >18 months. Responses were consistently observed in all subgroups investigated. The median PFS was 10.1 months (95% CI: 6.4 to 16.4). The median OS has not been reached, and the 2-year OS was 76% (95% CI:, 63 to 92%).

2.4.3. Discussion on clinical efficacy

Data to support the current application for the use of isatuximab in combination with carfilzomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy, come from one pivotal phase III study (EFC15246) and 3 additional studies to support the combination with dexamethasone or carfilzomib. The design of the pivotal study, comparator arm, isatuximab dose, randomisation, and endpoints were discussed and agreed in scientific advice.

Design and conduct of clinical studies

The pivotal study is a randomised, open-label, multicentre study comparing the combination of isatuximab with carfilzomib and dexamethasone (IKd) versus carfilzomib and dexamethasone (Kd) in patients with relapsed and/or refractory multiple myeloma (RRMM). Three hundred patients were to be randomly assigned to a treatment group (IKd arm or Kd arm) in a 3:2 ratio stratified according to number of prior lines (1 versus >1), and R-ISS (I or II versus III versus not classified).

The target population consisted of MM patients with measurable disease with at least 1 but no more than 3 prior lines of therapy. Patients who had primary refractory disease, were refractory to prior anti-CD38 mAb, with measureable disease only by free light chain (FLC), or had prior carfilzomib treatment were excluded from the study. The target population is relatively fit given the requirement for ECOG PS $\leq$ 2 and criteria on organ dysfunction.

Patients were to receive isatuximab (10 mg/kg QW for 1st cycle of 28 days, followed by Q2W in subsequent cycles) in combination with carfilzomib (20/56 mg/m^2) and dexamethasone (20 mg) (IKd regimen), or carfilzomib and dexamethasone alone in the control arm of the study (Kd regimen). The choice for an add-on study, with carfilzomib and dexamethasone (Kd) as backbone was agreed in scientific advice. It was agreed that the objective of this study was not comparing the IKd regimen with other triplet regiments but to show the added benefit of adding isatuximab to this (highly active) doublet therapy. At the time of the scientific advice the Kd regimen was recently approved for RRMM subjects with 1 prior line of therapy, and it is still one of the treatment options for MM in 2nd line and beyond.

The rationale for the dose and absence of dose-response studies for the combination was agreed upon in scientific advice. The exposure-response analysis is supportive for the 10 mg/kg dose (see discussion on Clinical Pharmacology).

As is often seen in the treatment of MM, patients could continue study treatment until disease progression, unacceptable AEs or patient decision to stop study treatment.

The primary endpoint is PFS. ORR, rate of VGPR or better (VGPR+), VGPR+ with MRD negativity, and OS were key secondary endpoints. As is needed for an open label study, PFS and response rate were determined by an IRC blinded to the randomisation and using central laboratory results and central review of radiologic imaging, and, if any, local bone marrow assessment. PFS and response were to be determined according to IMWG criteria, however progression on bone marrow was not a criterion for disease progression as patients without any measurable serum M-protein and/or urine M-protein were not eligible for study EFC15246. This is in line with the algorithm on this topic in the IMWG criteria[2]. Efficacy analysis was on the ITT set (which is also the randomised population).

The choice for PFS as the main outcome variable in this setting is generally accepted as there are different efficacious subsequent treatment options that patients could receive in subsequent therapies, which will likely modify the expected survival and because of a rather expected long PFS (expected to be >18 months in the control arm). As noted in scientific advice, the results on OS and PFS2 must be indicative of no detrimental effect.

Regarding the definition of PFS and the choice for handling of intercurrent events, it was noted that the start of subsequent therapy and clinical deterioration were considered the most important events that influence the interpretation of PFS. Clinical deterioration was mostly ignored for assessing PFS (treatment policy strategy) and subsequent therapy was mostly censored (hypothetical strategy). This led to multiple 'sensitivity' analyses for PFS which relate in fact to a number of estimands in the sense of EMA/CHMP/ICH/436221/2017. Of the various estimands 3 are of particular interest: PFS as if subsequent therapy would not have occurred (this is the primary analysis); PFS based on the first PFS event regardless whether subsequent therapy was started (treatment policy; the analysis recommended in the Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man - methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials CHMP/27994/2008 Rev. 1); and PFS counting subsequent therapy as an event (composite strategy, as investigators can see a progression coming upfront in this disease and therefore start a new therapy) is considered the main efficacy analysis and the results of this PFS definition are reflected in the SmPC (see section 5.1).

The choice of censoring in the definition of TT1R / TTBR is not supported. Patients were to be censored on the last measurement before PFS event (death, progression) or new therapy. In principle this could lead to overestimation of the TT1R and TTBR. However, the impact of this is expected to be limited given the high response rate and the low number of subjects with an early death. Furthermore, while TT1R and TTBR provide insight into the time needed for treatment to have its (maximal) effect, these parameters are of less importance for the interpretation of the benefit of treatment.

In contrast to previous advice (EMA/CHMP/SAWP/376795/2017) and guidance on PFS as a primary endpoint (CHMP/27994/2008 Rev. 1), an interim analysis for PFS was planned. Only 31% of patients have an event (50% in the final analysis) and this immaturity may hamper conclusions given the heterogeneous prognoses of patients, especially for the patients with better prognosis.
The number of randomisation strata: 2 x 3 = 6 in 300 patients is rather large could be acceptable provided that no empty strata are present. In the stratum with R-ISS unclassified < 10 patients were enrolled in each arm. However the low number of subjects is accepted as this stratum was assumed to be included to better compare the effect in strata with R-ISS stage I or II with R-ISS stage III.
The primary endpoint PFS was to be tested hierarchically for the interim and final analysis. An O'Brien and Fleming α-spending function was used to obtain the nominal significance levels for the interim and final analyses of survival on PFS, CR and MRD negativity rate. ORR and VGPR+ had a Pocock α-spending function. OS is only tested once, approximately 3 years after the primary PFS analysis. The combination

[2] Lancet Oncol. 2014 Nov;15(12):e538-48. doi: 10.1016/S1470-2045(14)70442-5. Epub 2014 Oct 26.

of group-sequential testing for PFS and hierarchically testing the other endpoints group-sequentially after that protects the type I.

During the study the definition of PFS was modified such that the date of initiation of further anti-myeloma treatment was censored, i.e. the primay estimand was changed. This was based on external feedback from the FDA, however in the context of an open-label trial, it cannot be excluded that this may also have been guided by on internal information. As the original planned analysis (without censoring) is in line with the amended analysis, it seems unlikely that internal availability of results informed the MAH in this open-label trial. MRD negativity in patients with VGPR+ was added into the hierarchical testing strategy before CR. As this does not concern the primary endpoint, this is agreed.

The number of protocol deviations relating to in- and exclusion criteria were low (n=5) and are considered unlikely to have significantly impacted the study results. There were a number of protocol deviations related to randomisation (wrong stratum); these were 20 in IKd arm and 13 in Kd arm). These were mostly related to the R-ISS stratum and most likely caused by the complexity of the R-ISS scale, which was only validated in 2015 (i.e. shortly before the study was initiated), and by the urgent need to start treatment. When the sponsor identified the stratification factor error rate, a corrective action was put in place (provision of a R-ISS calculation tool) which decreased the rate of errors. Importantly, the stratification errors did not lead to an imbalance in incidence of patients with R-ISS stratification factor between IKd and Kd arms or PFS analysis as was shown by sensitivity analyses.

Efficacy data and additional analyses

The ITT consists of 302 subjects, with 179 randomised to IKd arm and 123 into the Kd arm, 3 subjects did not receive treatment (2 in IKd and 1 in Kd). At the data cut off for this interim analysis, 168 patients have discontinued study treatment (84 [46.9%] in the IKd arm and 84 [68.3%] in the Kd arm and treatment was ongoing for the remainder of the subjects.

The median age of the ITT population at time of enrolment was 64 years (range 33-90 years), approximately half of the population was > 65 years, only a a few (n=26) subjects older than 75 were enrolled. Slighty more more males were included than females (56 vs 44%), which is a reflection of the slightly different incidence of MM in males vs females. The vast majority of the subjects were white (70%) and approximately half of the population came from Europe. While patients with ECOG stage 2 were allowed to enter the study, only few (n=16) subjects with ECOG 2 were randomised (11 in IKd arm and 5 in Kd arm). Information on the number of subjects with ECOG status 0 or with status 1 could not be found. Most patients (70%) had IgG type of MM, only few had R-ISS stage III (8%) at study entry, while 26% of the subjects had R-ISS stage I and 60% had R-ISS stage II. R-ISS stage could not be classified for 7% of the subjects. Overall, 24.2% of patients had high risk cytogenetic abnormalities. Most patients had bone lesions (71% per eCRF) and/or soft tissue plasmacytoma (94% per eCRF). Overall 61 (20.2%) patients had renal impairment (eGFR <60 mL/min/1.73m^2 at baseline).

The median number of prior lines was 2.0 (range 1 to 4) in both arms, with 44% having received 1 prior line, 33% 2 prior lines and 21% 3 prior lines of therapy. Five subjects (2%) had received > 3 lines of therapy (N=3 in IKd and n=2 in Kd arm) which is a protocol deviation, although in the listing of protocol deviations only 3 subjects are noted. This discrepancy was due to two cases for whom the algorithm used to calculate the number of lines (Rajkumar & Kumar S, 2020) overestimated the number of prior lines, which was corrected upon review by a clinician. In total there were 3 subjects included with >3 prior lines instead of the protocol required 1-3 prior lines of therapy.

The number of prior regiments were higher than the number of prior lines with median of 3 (range 1-11) because a line of therapy can consist of several regimens . All patients had relapsed disease and majority (72%) had relapsed and refractory disease. Most patients had received an PI (90%) and/or IMID (78%),

less than half were refractory to lenalidimide (33%), bortezomib (30%) or both agents (15%). There were 61.3% of patients who had undergone prior ASCT. Only one subject had received prior anti-CD38 directed therapy.

The patient characteristics were well balanced between study arms, except for some minor differences. The patients in the Kd arm were slightly younger and this arm contained slightly more subjects from non-western countries. Also the disease characteristics were sufficiently balanced between the study arms. In the Kd arm there were slightly more subjects had ISS Stage I at study entry (58% vs 50%), but the distribution across the R-ISS stages seems balanced between the arms. Slightly more subjects with serum LDH elevated and with renal impairment (24% vs 14.6%) were included in the IKd arm. Also with regard to the prior-anti-myeloma treatments study arms were reasonably well balanced. A slight difference between the arms is noted in frequency of subjects with 2 prior lines (35.8% in the IKd arm and 29.3% in the Kd arm) and 3 prior lines (18.4% IKd and 24.4% Kd), and who had prior ASCT (64.8% in IKd arm, 56.1% in Kd). There were slightly more relapsed and refractory subjects in the Kd arm than the IKd arm (76% vs 68%).

Overall while some slight imbalances are noted between the treatment arms in some of the parameters, the differences are not consistently favouring the IKd arm nor significantly large to impact the interpretation of the study. It is thus considered that the treatment arms are sufficiently balanced to allow a meaningful comparison.

The enrolled patient population seems an adequate reflection of the target population. The selection of patients based on prior treatment regiments or response to prior treatment regimens was limited to the exclusion of subjects with primary refractory disease, of subjects who were refractory to prior anti-CD38 mAb and of those with prior carfilzomib treatment. These selection criteria do not need to be reflected in the indication, although the target population should be described in section 5.1 of the SmPC. In line with the in/exclusion criteria, the study population included refractory and non-refractory subjects and had a mix of prior treatment therapies, except for prior CD38 directed therapies. Only one subject was enrolled who already had received prior anti-CD38-directed therapy. Although it is recognised that the pharmacological profile of isatuximab and other CD38-directed therapies (daratumumab) differs to some extent, it cannot be excluded that prior exposure would have had an effect on the activity of isatuximab. Therefore the lack of data on the impact of prior CD38 directed therapy on efficacy of IKd regimen is mentioned in section 5.1 of the SmPC. While the patients needed to have RRMM for study entry, the proposed indication does not specify that patients should have relapsed and/or have refractory MM. This omission can be accepted as this is in line with the indication of other products for the same target population (e.g. daratumumab, carfizomib).

Overall the studied population is considered an adaquete reflection of the target population which is appropriately described in the proposed wording of the indication.

The primary endpoint of the study was already met at the interim analysis. Superiority of IKd over Kd was shown in the ITT with a HR of 0.531 (99% CI: 0.318 to 0.889), and a p value (1-sided stratified log rank test) of 0.0007. The curves seem to start separating only after approximately 8-9 months, which may indicate non-proportional hazards, however, this will have a conservative effect on the hazard ratio and the log-rank test. It does however suggest that the effect of adding I to a Kd backbone is small for those with a (very) worse prognosis.

The median PFS was not reached in the Ikd arm and was 19.15 months (95% CI: 15.770 - not reached) in the Kd arm, which is consistent with the protocol assumption of 19 months. The observed effect size is clinically relevant, and is largely independent of the choice for censoring and event rules or stratification rules (so largely independent of what is considered an PFS event) as all 'sensitivity' analyses using resulted in relatively similar HR (0.51-0.595), a median PFS in control arm of 16-20 months and median PFS not reached in IKd arm. This indicates that different estimands of PFS have similar results, and in

that sense the primary endpoint may be considered to be robust. Of note, overall maturity of data is limited (34% of patients in primary analysis and 39% in the analysis recommend by the guideline on PFS as primary endpoint CHMP/27994/2008 Rev. 1), and there is a high degree of censoring after 18 month, so the effect of treatment for those with better prognosis is not established. The study is still ongoing and the final PFS analysis at 159 PFS events will be performed as per protocol this currently estimated to occur in approximately 3Q2021. At this time an update of the duration of response (DoR) and the time from randomisation to the date of second disease progression or death from any cause, whichever happens first (PFS2), will be also provided. With this analysis, overall survival (OS) Kaplan-Meier curves will be provided for information without statistical test, as the protocol pre-specifies that the OS will be tested 3 years after positive PFS analysis (with positive interim PFS analysis in 2020 this OS analysis is planned in 2023). The MAH has committed following the CHMP recommendation to provide final PFS and OS analyses once the analysis have been performed at the protocol specified moment.

In the subgroup analysis a positive effect of adding I to Kd backbone was also seen in most (prespecified) subgroups, with some variability. Although the PFS subgroup analyses was performed according to the PFS definitation of the primary analysis and not according to the EU recommended definition, the performed analysis is accepted given the limited difference in events (15 events) between these two definitions. The subgroup analysis revelad no impact of the number of prior therapies, previous treatment with SCT, PI or IMID on treatment outcome, thus supporting the broad indication. Deviations in HR from the primary analysis are noted in subgroups based on geographical region (with a HR of 1.244 in the population enrolled in the America-region), R-ISS stage (I or II vs III, with HR in population with R-ISS stage III close to 1), and presence/absence of cytogenetic abnormalities. A HR >1 noted in the subgroup enrolled in the America-region is most likely due to an imbalance in a substantial number prognostic facotes in favour of the Kd arm. A numerical difference in the HR point estimate is also noted in the subpopulations based on ECOG status (0 or 1 vs >1), and those on previous therapy with PI and IMID, however this may be explained by the low patient numbers in the subgroups with ECOG status >1 and those having received PI and IMID. Upon request the MAH has submitted a subgroup analysis based on response to prior therapy(CR or sCR and others). The HR in the subgroup of patients with CR or sCR during at least one prior therapy and the subgroup of other patients was 0.507 (95% CI: 0.265 to 0.968) and 0.501 (95% CI: 0.307 to 0.818), respectively. Overall, subgroup analyses for individual prognostic factors did not identify a population which may not benefit from adding I to a Kd regimen, as all HRs were (well) below 1. Thus the subgroup analyses cannot not explain the appearingly late separation of the PFS curves. As only 15% of the PFS-events occur before 9 months the this issue is not longer pursued. Furthermore, while these analyses indicate there may be subgroup who benefit less from the IKd vs Kd than the overall population, in particular those with R-ISS stage III, a detrimental effect of adding I to Kd was not seen in any of the subpopulations analysed.

In the IKd arm a relative large group (15%) discontinued carfilzomib but remained on Id. The MAH provided an exploratory analysis of patiens comparing PFS of patients in the IKd arm who discontinued carfilzomib with those remaining on treatment and with the control arm. The HR in IKd without and with carfilzomib premature discontinuation versus Kd arm were 0.563 (99% CI: 0.332 to 0.957) and 0.268 (99% CI: 0.07 to 1.029), respectively. Although this analysis should be interpreted with great caution because of confounding and limitations in sample size, the data indicate that discontinuation of carfilzomib from the IKd regime does not seem to compromise the efficacy of starting with treatment with IKd.

The treatment effect in secondary endpoints TTP and TTNT was consistent with the effect seen in PFS. Only a limited effect in ORR was noted (86.6% vs 82.9%), but this may be expected with this very active backbone treatment. However, responses in the IKd arm were deeper (VGPR or better 72.6% versus 56.1%, with MRD negativity rate of 29.6% vs 13.0%), and lasted longer (HR 0.425, median DoR not reached in both arms). A higher CR rate was also noted (39.7% vs 27.6%). Of note the CR rate may

have been underestimated in the IKd arm because of the interference of isatuximab with M protein measurement (comigration of isatuximab with M protein could lead to a conclusion of presence of residual M protein which may infact be isatuximab). Correction for this interference (only applicable to I treated subjects) would lead to a CR rate and CR+MRD negativity in the IKd arm of 46% and 24% respectively.

Protocol stipulated MRD results were missing for 49 patients with VGPR+ as per investigator (n=198).For 23 of these 49 cases this was due to lack of BMA sampling, for the others BM sample was not evaluable for MRD e.g. due to lack of knowledge on dominant clone. As in general practice BM sampling is usually done at the time of CR (and not VGPR) and given the invasiness of the sampling procedure, it is acknowledged that there may have been some reluctance to BM sampling at VGPR by investigators. Of note this level of missing data (23 of 198 (12%) with investigator VGPR+) seems similar or lower to what has been reported in literature.

A trend toward longer PFS2 in the IKd arm is noted, and no detriment on OS. While this is reassuring, it is noted that data are still very immature so updated data are to be provided when the analyses have been performed at the protocol specified moment (see RMP?).

Among patients with renal impairment (eGFR <50 mL/min/1.73m^2), a higher percentage experienced a complete renal response ($\geq$ 1 assessment $\geq$ 60 mL/min/1.73m^2) in the Ikd arm than in the Kd arm (52 vs 31%). However, as patient numbers are limited (n=25 in IKd and n=13 in Kd), no clear conclusions on the benefit of adding isatuximab to Kd to improve renal response can be drawn.

Several PROs were performed including the disease-specific EORTC QLQ-Myeloma module (MY20). However, interpretation of PROs in an open label study should be interpreted with caution. Compliance for all PROs was good. Only grouped averages were provided which had high standard deviation on each datapoint thus further hampering interpretation. Nevertheless it is noted that the median and mean (and SD) are very similar between the treatment groups and remain constant in time, except towards the end of the period (> 22 cycles) when only few patients are at risk. So it seems that there are no differences in health related quality of life between the study arms, and that thus adding I to Kd does not seem to negatively affect quality of life.

The analysis of FCGR3A polymorphism on treatment effect is hampered because of limited patients numbers in some genotypic subgroups, and the imbalance in prognostic baseline characteristics between the subpopulations. This particularly relates to the FCGR3A 158V/V subgroup in which the least benefit was noted of the addition of I to Kd, so no conclusion should be drawn based on this analysis.

There were no dedicated studies in special populations.

Regarding age, the median age of the studied population in the pivotal study was 64 years (range 33 to 90) with appoximately half of the population (n=148) being ≥ 65 years. The subgroup analysis on the primary endpoint does not indicate a significant effect of age on efficacy. No separate analyses for efficacy was performed for subjects ≥ 75 years, which is accepted given the low number of subjects (n=26) in this age category. No children were included in this study.

Regarding renal impairment, among patients with eGFR <50 mL/min/1.73m^2 at baseline, more patients in the IKd (13/25, 52%) arm experienced a complete renal response ($\geq$ 1 assessment $\geq$ 60 mL/min/1.73m^2 during Treatment) than in the Kd arm (4 of 13, 31%).

There were few patients with abnormal hepatic function in the pivotal study (n=33), but these were not analysed separately for efficacy. This can be accepted as an impact of hepatic impairment on PK of isatuximab is not expected.

Results from study TCD14079 Part B seem to support the fixed volume infusion. However as this has already been accepted previously (EMEA/H/C/004977/0000) and described in the SmPC, further discussion is not needed here.

Study TED10893 Phase 2 Stage 2 supports the addition of dexamethasone to isatuximab.

Study TCD12795 was submitted to support the addition of carfilzomib to isatuximab. However, as this is a small study lacking a control arm, and considering the heterogeneity of the MM population and the difficulties with cross study comparisons it is difficult to draw firm conlusions.

The complexity of cross study comparison is acknowledged.

Overall, this analysis and the supportive studies are indicative of the activity of isatuximab when combined with dexamethasone of carfilzomib in the MM population and thus provide general support for the indication applied for but do not allow firm conclusions.

2.4.4. Conclusions on the clinical efficacy

The results from the pivotal study show a statistical significant and with a HR of 0.572 also a clinically relevant improvement of PFS when I is added to a Kd backbone. This result is considered robust and is supported by secondary endpoints indicating a deeper and longer response in patients treated with IKd versus Kd. Based on a limited number of events, no detriment seems apparent in OS and also PFS2 suggests a beneficial effect of the IKd combination. These effects are seen across all subgroups tested.

Given the immaturity of the data the treatment effect of IKd for those with good prognosis cannot accurately be determined due to the high level of censoring after 18 months. Therefore, the MAH will provide updated data, when available, to confirm the observed effect and the notion that also PFS2 is improved and there is no detriment on OS.

Overall the studied population is considered an adequate reflection of the target population which is appropriately described in the proposed wording of the indication.

2.5. Clinical safety

Introduction

The MAH presented the safety data from the pivotal Phase 3 study EFC15246 (IKEMA), a randomised, open-label, multicentre study of isatuximab combined with carfilzomib and dexamethasone (IKd) versus carfilzomib and dexamethasone (Kd) in patients with RRMM, together with integrated supportive safety data for all isatuximab-treated patients from 9 company-sponsored MM studies (including EFC15246) that were completed or partially completed with at least one approved clinical study report (CSR) each by the cut-off date of 07 February 2020 for this application.

Patient exposure

Pivotal Phase 3 study EFC15246 (IKEMA)

Study EFC15246 randomised a total of 302 patients (179 in IKd arm and 123 in Kd arm). Three of the randomised patients did not receive the study treatment and were excluded from the safety population. The safety population of the study consisted of 177 patients in the IKd arm and 122 patients in the Kd arm.

As of the cut- off date of this analysis, the IKd arm had more patients still ongoing with study treatment than the Kd arm (52.0% versus 30.9%) and had fewer patients who definitively discontinued all study treatments (46.9% versus 68.3%). The main reasons for definitive treatment discontinuation (in the

randomised population) were disease progression (29.1% in IKd arm versus 39.8% in Kd arm) and AEs (8.4% IKd versus 13.8% Kd) (**Table 23**).

***Table** 23 Disposition of patients - EFC15246 - randomised population*

	Kd (N=123)	IKd (N=179)
Randomized and not treated	1 (0.8)	2 (1.1)
Randomized and treated	122 (99.2)	177 (98.9)
Patients still on treatment	38 (30.9)	93 (52.0)
Patients with definitive treatment discontinuation	84 (68.3)	84 (46.9)

	Kd (N=123)	IKd (N=179)
Reason for definitive treatment discontinuation		
Adverse event	17 (13.8)	15 (8.4)
Progressive disease	49 (39.8)	52 (29.1)
Poor compliance to protocol	0	0
Withdrawal by subject	14 (11.4)	11 (6.1)
Other	4 (3.3)	6 (3.4)
Reason for treatment withdrawal by subject		
Adverse event	5 (4.1)	3 (1.7)
Study procedure	1 (0.8)	1 (0.6)
Other	8 (6.5)	7 (3.9)
Status at the cutoff date[a]		
Alive	98 (79.7)	148 (82.7)
Death	25 (20.3)	31 (17.3)
Time from last contact to the cutoff date[b]		
≤ 2 weeks	19 (15.4)	8 (4.5)
> 2 weeks and ≤ 1 month	1 (0.8)	0
> 1 month and ≤ 2 months	0	0
> 2 months	3 (2.4)	7 (3.9)

a Cut-off date for overall survival (07FEB2020).

b For patients censored for overall survival before the Cut-off date.

Note: Definitive treatment discontinuation is defined as the discontinuation of all the study drugs. When all study drugs are not discontinued at the same time, the reason for definitive discontinuation is the reason for discontinuation of the last study drug stopped

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

1 month = 4 weeks

PGM=PRODOPS/SAR650984/EFC15246/DMC 2020 01/REPORT/PGM/dis dispo r t.sas
OUT=REPORT/OUTPUT/dis_dispo_r_t_i.rtf (15JUN2020 10:50)

The definitive treatment discontinuations caused by reasons classified as "Other" were:

• In IKd arm: unconfirmed progressive disease (PD) and/or PD per local laboratory results but not per central laboratory results (4 [2.3%] patients), "poor prognosis due to having reached the maximum expected response of the study treatment" (1 [0.6%]), and autologous stem cell transplant (1 [0.6%]).

• In Kd arm: Investigator's decision based on serum free light chain (FLC) increase (1 [0.8%] patient), Investigator's decision to discontinue corticosteroid therapy due to achieved therapeutic effect and excessive adverse effects of long-term corticosteroid therapy (1 [0.8%]), no evidence of clinical efficacy (1 [0.8%]), and autologous stem cell transplant (1 [0.8%]).

Premature discontinuation of at least one study drug occurred in 19.2% of patients in IKd arm and 4.1% of patients in Kd arm, all due to AEs (Study EFC15246). Only 1 patient (0.6%) in this study had premature discontinuation of isatuximab. Carfilzomib was prematurely discontinued in 14.7% of patients in IKd arm and 0.8% in Kd arm.

Treatment duration:

In study EFC15246, the duration of treatment exposure was longer in the IKd arm than in the Kd arm (median: 80.0 weeks versus 61.4 weeks). The overall extent of treatment exposure was greater in the IKd arm compared to the Kd arm, with longer duration of treatment and more cycles started per patient (median: 19.0 versus 14.5) (Table 24). The percentage of patients with at least 18 cycles of treatment was 57.6% in IKd arm versus 39.3% in the Kd arm.

***Table** 24 Extent of overall exposure - EFC15246 - safety population*

	Kd (N=122)	IKd (N=177)	All (N=299)
Total number of cycles started	1663	2813	4476
Cumulative exposure to treatment (patient-years)	131.4	223.1	354.4
Number of cycles started by patient			
Number	122	177	299
Mean (SD)	13.6 (7.3)	15.9 (7.1)	15.0 (7.2)
Median	14.5	19.0	18.0
Min ; Max	1 ; 28	1 ; 27	1 ; 28

Isatuximab exposure:

The median duration of isatuximab exposure was 79.86 weeks (median 19 cycles), with a median relative dose intensity (RDI) of 94.27% (range: 66.7 to 108.2%) (presented in Table 12 and Table 13 of SCS). Of the 177 patients who received isatuximab infusions, 62.1% had at least 1 dose omission and 38.4% had at least 1 infusion interrupted (due to TEAEs or other reasons). A total of 82 (1.4%) out of 5715 isatuximab infusions were interrupted and almost all were re-started (except for 4 infusions not re-started) (***Table** 25).

***Table** 25 Summary of patients with at least one dose modification for isatuximab - EFC15246 - safety population (selection of Table 13 SCS)*

	IKd (N=177)
Number of treated patients	177 (100)
Patients with at least 1 infusion delay within cycle	44 (24.9)
Patients with at least 1 dose omission	110 (62.1)
Patients with at least 1 dose reduction	3 (1.7)
Patients with at least 1 infusion interrupted	68 (38.4)
Patients with at least 1 infusion interrupted and re-started	67 (37.9)
Patients with at least 1 infusion interrupted and not re-started	4 (2.3)
Patients with at least 2 infusions interrupted	9 (5.1)
Number of isatuximab infusions	5715
Isatuximab infusion interrupted	82 (1.4)
Isatuximab infusion interrupted and re-started	78 (1.4)
Isatuximab infusion interrupted and not re-started	4 (<0.1)
Isatuximab infusion interrupted more than once	6 (0.1)
Infusions interrupted	82
1st infusion	57 (69.5)
2nd infusion	6 (7.3)
Subsequent infusions	19 (23.2)

Carfilzomib exposure:

Carfilzomib exposure was slightly greater in the IKd arm compared to the Kd arm in duration of exposure (median: 65.00 versus 59.57 weeks) and number of cycles started by patient (median: 16 versus 14). The median RDI for carfilzomib was similar between the two arms (91.18% versus 91.35%). The percentage of patients with at least 1 dose omission or dose reduction for carfilzomib was similar between the IKd and Kd arms (71.2% versus 72.1% for dose omission;35.0% versus 35.2% for dose reduction) (***Table** 26). The percentage of patients with at least 1 carfilzomib infusion interrupted was low and similar between the two arms (4.0% versus 3.3%).

Table 26 *Summary of patients with at least one dose modification for carfilzomib - EFC15246*

	Kd (N=122)	IKd (N=177)	All (N=299)
Number of treated patients	122 (100)	177 (100)	299 (100)
Patients with at least 1 infusion delay within cycle	33 (27.0)	45 (25.4)	78 (26.1)
Patients with at least 1 dose omission	88 (72.1)	126 (71.2)	214 (71.6)
Patients with at least 1 dose reduction	43 (35.2)	62 (35.0)	105 (35.1)
Patients with at least 1 infusion interrupted	4 (3.3)	7 (4.0)	11 (3.7)
Patients with at least 1 infusion interrupted and re-started	3 (2.5)	6 (3.4)	9 (3.0)
Patients with at least 1 infusion interrupted and not re-started	1 (0.8)	1 (0.6)	2 (0.7)
Patients with at least 2 infusions interrupted	1 (0.8)	1 (0.6)	2 (0.7)
Number of carfilzomib infusions	9284	14383	23667
Carfilzomib infusion interrupted	5 (<0.1)	9 (<0.1)	14 (<0.1)
Carfilzomib infusion interrupted and re-started	3 (<0.1)	8 (<0.1)	11 (<0.1)
Carfilzomib infusion interrupted and not re-started	2 (<0.1)	1 (<0.1)	3 (<0.1)
Carfilzomib infusion interrupted more than once	0	0	0
Infusions interrupted	5	9	14
Subsequent infusions	5 (100)	9 (100)	14 (100)
Number of patients who did not escalate carfilzomib at 56 mg/m^2 on the third infusion[a]	4 (3.3)	9 (5.1)	13 (4.3)
Number (%) of patients who never escalate the carfilzomib dose to 56 mg/m^2	1 (0.8)	7 (4.0)	8 (2.7)
Number (%) of patients with a delayed carfilzomib dose escalation to 56 mg/m^2	3 (2.5)	2 (1.1)	5 (1.7)
Number of patients who discontinued carfilzomib before C1D8	1 (0.8)	2 (1.1)	3 (1.0)
Time from infusion start to first interruption (minutes)			
Number	5	9	14
Mean (SD)	34.6 (32.7)	17.0 (20.8)	23.3 (25.9)
Median	25.0	10.0	12.5
Q1 ; Q3	12.0 ; 36.0	7.0 ; 15.0	8.0 ; 25.0
Min ; Max	10 ; 90	3 ; 70	3 ; 90

Dexamethasone exposure:

Dexamethasone exposure was also greater in the IKd arm compared to the Kd arm in duration of exposure (median: 76.14 versus 59.07 weeks) and number of cycles started by patient (median: 18 versus 14). The median RDI for dexamethasone was 84.78% in IKd arm versus 88.37% in Kd arm. The percentage of patients with at least 1 dose omission or dose reduction was similar between the IKd and Kd arms (77.4% versus 75.4% for dose omission; 43.5% versus 38.5% for dose reduction).

Table 27 *Summary of patients with at least one dose modification for dexamethasone- EFC15246*

	Kd (N=122)	IKd (N=177)	All (N=299)
Number of treated patients	122 (100)	177 (100)	299 (100)
Patients with at least 1 dose delay [n(%)]	32 (26.2)	53 (29.9)	85 (28.4)
Patients with at least 1 dose reduction [n(%)]	47 (38.5)	77 (43.5)	124 (41.5)
Patients with at least 1 dose omission [n(%)]	92 (75.4)	137 (77.4)	229 (76.6)

A dose is considered as delayed if started more than 1 day after theoretical date.

PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/cdc_modify_s_t.sas
OUT=REPORT/OUTPUT/cdc_modify_dex_s_t_i.rtf (17JUL2020 14:29)

Adverse events

An overview of TEAEs in EFC15246 is presented in (Table 28). Exposure-adjusted overview of TEAEs is provided in **Table** 29 and 30.

Table 28 *Overview of treatment-emergent adverse events - EFC15246 - safety population*

	Kd (N=122)	IKd (N=177)
Patients with any TEAE	117 (95.9)	172 (97.2)
Patients with any grade ≥ 3 TEAE	82 (67.2)	136 (76.8)
Patients with any grade 3-4 TEAE	81 (66.4)	134 (75.7)
Patients with any grade 5 TEAE[a]	4 (3.3)	6 (3.4)
Patients with any treatment emergent SAE[b]	70 (57.4)	105 (59.3)
Patients with any TEAE leading to definitive treatment discontinuation	17 (13.9)	15 (8.5)
Patients with any TEAE leading to premature discontinuation of Isatuximab	NA	1 (0.6)
Patients with any TEAE leading to premature discontinuation of Carfilzomib	1 (0.8)	26 (14.7)
Patients with any TEAE leading to premature discontinuation of Dexamethasone	4 (3.3)	11 (6.2)
Patients with any AESI[c]	0	1 (0.6)
Patients with any IR of grade ≥ 3	0	1 (0.6)
Patients with any treatment-related TEAE[d] (any grade)	98 (80.3)	153 (86.4)
Patients with any treatment-related grade ≥ 3 TEAE	58 (47.5)	87 (49.2)
Patients with any serious treatment-related TEAE	31 (25.4)	44 (24.9)

TEAE: Treatment emergent adverse event, AESI: Adverse event of special interest, SAE: Serious adverse event, IR: Infusion reaction, NIMP: non investigational medicinal product

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

NA: Not Applicable

a TEAE with fatal outcome during the treatment period

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 (female patient or female partner), symtomatic overdose with study treatment or NIMP

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

PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/ae_overview_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_s_t_i.rtf (15JUN2020 16:02)

Table *29 Patient years analysis : overview of TEAEs - EFC15246 - safety population*

	Kd (N=122)		IKd (N=177)	
	n (%)	Event rate per patient year[a]	n (%)	Event rate per patient year[a]
Patients with any TEAE	117 (95.9)	9.41	172 (97.2)	10.94
Patients with any grade ≥3 TEAE	82 (67.2)	1.05	136 (76.8)	1.26
Patients with any grade 5 TEAE[b]	4 (3.3)	0.03	6 (3.4)	0.03
Patients with any treatment emergent SAE	70 (57.4)	0.72	105 (59.3)	0.70
Patients with any TEAE leading to definitive treatment discontinuation	17 (13.9)	0.13	15 (8.5)	0.07

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

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

a Calculated as number of patients with an event divided by total patient years.

b TEAE with fatal outcome during the treatment period

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

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.

PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/ae_overview_pyears_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_pyears_s_t_x.rtf (15JUN2020 16:03)

Most frequent TEAEs by SOC and PT

The most frequently reported TEAEs at SOC level (all grades, in ≥20% of patients in either arm) included: Infections and infestations (86.4% in IKd arm and 80.3% in Kd arm), General disorders and administration site condition (63.8%, 56.6%), Injury, poisoning, and procedural complications (62.7%, 26.2%), Gastrointestinal disorders (61.6%, 49.2%), Respiratory, thoracic and mediastinal disorders (52.0%, 40.2%), Musculoskeletal and connective tissue disorders (48.6%, 55.7%), Vascular disorders (46.3%, 44.3%), Nervous system disorders (39.0%, 43.4%), Psychiatric disorders (32.8%, 26.2%), Skin

and subcutaneous tissue disorders (27.7%, 13.1%), Cardiac disorders (23.7%, 22.1%), and Metabolism and nutrition disorders (23.2%, 17.2%) (***Table** 30*).

At PT level, the TEAEs with higher incidences (≥5% higher) in IKd arm than in Kd arm were: infusion related reaction (44.6% versus 3.3%), hypertension (36.7%, 31.1%), upper respiratory tract infection (36.2%, 23.8%), diarrhea (36.2%, 28.7%), fatigue (28.2%, 18.9%), dyspnea (27.7%, 21.3%), bronchitis (22.6%, 12.3%), cough (19.8%, 13.9%), and vomiting (15.3%, 9.0%). The TEAEs with lower incidences (≥5% lower) in IKd arm than in Kd arm were pyrexia (9.0% versus 14.8%) and thrombocytopenia (2.8% versus 9.8%).

After adjustment for exposure, the type of TEAE and incidence in events per PY was similar and still higher in the IKd arm than in KD. For diarrhea (0.39, 0.35), dyspnea (0.28, 0.24), and cough (0.18, 0.15), the exposure-adjusted incidences were similar between the IKd and Kd arms.

The most frequently reported Grade ≥3 TEAEs (≥10% of patients in either arm) by primary SOC were Infections and infestations (38.4% in IKd arm and 28.7% in Kd arm), Vascular disorders (21.5%, 23.8%), and Metabolism and nutrition disorders (10.7%, 4.9%). At PT level, the most frequent Grade ≥3 TEAEs (in ≥5% of patients) were: hypertension (20.3% in IKd arm and 19.7% in Kd arm), pneumonia (16.4%, 12.3%), thrombocytopenia (2.3%, 8.2%), insomnia (5.1%, 2.5%), and dyspnea (5.1%, 0.8%) (***Table** 30*).

***Table** 30 Number (%) of patients with TEAEs with an incidence >=5% in any treatment group by primary SOC and PT (worst grade by patient) - EFC15246 - safety population*

Primary System Organ Class Preferred Term [n(%)]	Kd (N=122)		IKd (N=177)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	117 (95.9)	82 (67.2)	172 (97.2)	136 (76.8)
Infections and infestations	98 (80.3)	35 (28.7)	153 (86.4)	68 (38.4)
Upper respiratory tract infection	29 (23.8)	2 (1.6)	64 (36.2)	6 (3.4)
Pneumonia	24 (19.7)	15 (12.3)	42 (23.7)	29 (16.4)
Bronchitis	15 (12.3)	1 (0.8)	40 (22.6)	4 (2.3)
Nasopharyngitis	14 (11.5)	0	28 (15.8)	0
Influenza	17 (13.9)	5 (4.1)	16 (9.0)	1 (0.6)
Lower respiratory tract infection	10 (8.2)	5 (4.1)	16 (9.0)	7 (4.0)
Respiratory tract infection	8 (6.6)	0	16 (9.0)	2 (1.1)
Urinary tract infection	11 (9.0)	2 (1.6)	12 (6.8)	3 (1.7)
Gastroenteritis	9 (7.4)	2 (1.6)	11 (6.2)	1 (0.6)
Conjunctivitis	8 (6.6)	0	10 (5.6)	0
Rhinitis	3 (2.5)	0	10 (5.6)	0
Sinusitis	4 (3.3)	0	9 (5.1)	1 (0.6)
Blood and lymphatic system disorders	20 (16.4)	11 (9.0)	25 (14.1)	16 (9.0)
Thrombocytopenia	12 (9.8)	10 (8.2)	5 (2.8)	4 (2.3)
Metabolism and nutrition disorders	21 (17.2)	6 (4.9)	41 (23.2)	19 (10.7)
Decreased appetite	4 (3.3)	0	13 (7.3)	0
Psychiatric disorders	32 (26.2)	4 (3.3)	58 (32.8)	11 (6.2)
Insomnia	28 (23.0)	3 (2.5)	42 (23.7)	9 (5.1)
Anxiety	4 (3.3)	0	13 (7.3)	0
Nervous system disorders	53 (43.4)	7 (5.7)	69 (39.0)	5 (2.8)
Headache	21 (17.2)	1 (0.8)	26 (14.7)	0
Peripheral sensory neuropathy	15 (12.3)	1 (0.8)	25 (14.1)	0
Dizziness	7 (5.7)	0	8 (4.5)	0
Eye disorders	23 (18.9)	1 (0.8)	30 (16.9)	6 (3.4)
Cataract	8 (6.6)	1 (0.8)	15 (8.5)	4 (2.3)

Primary System Organ Class Preferred Term [n(%)]	Kd (N=122)		IKd (N=177)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Vascular disorders	54 (44.3)	29 (23.8)	82 (46.3)	38 (21.5)
Hypertension	38 (31.1)	24 (19.7)	65 (36.7)	36 (20.3)
Thrombophlebitis superficial	7 (5.7)	0	9 (5.1)	0
Deep vein thrombosis	10 (8.2)	2 (1.6)	8 (4.5)	0
Respiratory, thoracic and mediastinal disorders	49 (40.2)	7 (5.7)	92 (52.0)	17 (9.6)
Dyspnoea	26 (21.3)	1 (0.8)	49 (27.7)	9 (5.1)
Cough	17 (13.9)	0	35 (19.8)	0
Gastrointestinal disorders	60 (49.2)	7 (5.7)	109 (61.6)	14 (7.9)
Diarrhoea	35 (28.7)	3 (2.5)	64 (36.2)	5 (2.8)
Nausea	20 (16.4)	0	28 (15.8)	0
Vomiting	11 (9.0)	1 (0.8)	27 (15.3)	2 (1.1)
Constipation	12 (9.8)	0	22 (12.4)	1 (0.6)
Dyspepsia	5 (4.1)	0	15 (8.5)	1 (0.6)
Gastrooesophageal reflux disease	3 (2.5)	0	11 (6.2)	0
Abdominal pain	8 (6.6)	0	6 (3.4)	0
Skin and subcutaneous tissue disorders	16 (13.1)	0	49 (27.7)	6 (3.4)
Rash	6 (4.9)	0	12 (6.8)	1 (0.6)
Musculoskeletal and connective tissue disorders	68 (55.7)	6 (4.9)	86 (48.6)	16 (9.0)
Back pain	25 (20.5)	1 (0.8)	39 (22.0)	3 (1.7)
Muscle spasms	19 (15.6)	0	25 (14.1)	0
Arthralgia	10 (8.2)	2 (1.6)	22 (12.4)	3 (1.7)
Pain in extremity	15 (12.3)	1 (0.8)	19 (10.7)	0
Bone pain	9 (7.4)	0	10 (5.6)	0
Musculoskeletal pain	3 (2.5)	0	10 (5.6)	1 (0.6)
Musculoskeletal chest pain	7 (5.7)	0	8 (4.5)	0
Muscular weakness	8 (6.6)	0	3 (1.7)	1 (0.6)
Renal and urinary disorders	19 (15.6)	4 (3.3)	19 (10.7)	3 (1.7)
Acute kidney injury	7 (5.7)	2 (1.6)	5 (2.8)	2 (1.1)
General disorders and administration site conditions	69 (56.6)	9 (7.4)	113 (63.8)	16 (9.0)
Fatigue	23 (18.9)	1 (0.8)	50 (28.2)	6 (3.4)
Asthenia	20 (16.4)	4 (3.3)	32 (18.1)	3 (1.7)
Oedema peripheral	21 (17.2)	0	23 (13.0)	1 (0.6)
Pyrexia	18 (14.8)	0	16 (9.0)	2 (1.1)
Non-cardiac chest pain	8 (6.6)	0	12 (6.8)	4 (2.3)
Injury, poisoning and procedural complications	32 (26.2)	4 (3.3)	111 (62.7)	8 (4.5)
Infusion related reaction	4 (3.3)	0	79 (44.6)	1 (0.6)
Fall	10 (8.2)	0	20 (11.3)	3 (1.7)
Accidental overdose	7 (5.7)	0	16 (9.0)	0
Traumatic fracture	5 (4.1)	2 (1.6)	13 (7.3)	4 (2.3)
Contusion	5 (4.1)	0	10 (5.6)	0

Treatment-related TEAEs

Overall, the IKd and Kd arms were balanced in the incidences of treatment-related TEAEs (86.4% versus 80.3% for all grades; 49.2% versus 47.5% for Grade ≥3). The most frequent treatment-related TEAEs (all grades, ≥15%) were infusion related reaction (44.6% in IKd arm and 3.3% in Kd arm), hypertension (23.7%, 27.9%), fatigue (21.5%, 13.9%), insomnia (20.3%, 19.7%), and dyspnea (18.6%, 17.2%). The most frequent treatment-related Grade ≥3 TEAEs (all grades, ≥5%) were hypertension (13.0%, 18.9%), pneumonia (5.1%, 4.9%), and thrombocytopenia (2.3%, 6.6%). The IKd arm had higher incidence of treatment-related infusion related reactions (all grades), fatigue (all grades), but lower incidence of treatment-related hypertension (all grades and Grade ≥3) and thrombocytopenia (all grades).

Post-treatment AEs: In study EFC15246, 5 (2.8%) patients in IKd arm and 4 (3.3%) patients in Kd arm reported post-treatment AEs (all grades); of them, 4 in IKd arm and 2 in Kd arm were both Grade ≥3 and serious. No single post-treatment AE (by PT) was experienced by more than 1 patient.

Serious adverse events

The incidence of patients with serious TEAEs was similar between the IKd and Kd arms (59.3% versus 57.4% for all grades; 53.1% versus 47.5% for Grade ≥3) (Table 31).

Table 31 *Treatment emergent SAEs with an incidence >= 2% in any treatment group by primary SOC and PT (worst grade by patient) - EFC15246 - safety population*

Primary System Organ Class Preferred Term [n(%)]	Kd (N=122)		IKd (N=177)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	70 (57.4)	58 (47.5)	105 (59.3)	94 (53.1)
Infections and infestations	37 (30.3)	32 (26.2)	67 (37.9)	60 (33.9)
Pneumonia	14 (11.5)	14 (11.5)	32 (18.1)	27 (15.3)
Lower respiratory tract infection	5 (4.1)	5 (4.1)	7 (4.0)	7 (4.0)
Upper respiratory tract infection	2 (1.6)	1 (0.8)	5 (2.8)	4 (2.3)
Respiratory tract infection	1 (0.8)	0	4 (2.3)	2 (1.1)
Viral upper respiratory tract infection	0	0	4 (2.3)	4 (2.3)
Influenza	5 (4.1)	4 (3.3)	1 (0.6)	1 (0.6)
Cardiac disorders	6 (4.9)	5 (4.1)	13 (7.3)	11 (6.2)
Cardiac failure	2 (1.6)	2 (1.6)	5 (2.8)	4 (2.3)
Vascular disorders	8 (6.6)	6 (4.9)	5 (2.8)	3 (1.7)
Deep vein thrombosis	3 (2.5)	2 (1.6)	2 (1.1)	0
Musculoskeletal and connective tissue disorders	6 (4.9)	4 (3.3)	10 (5.6)	8 (4.5)
Pathological fracture	1 (0.8)	0	4 (2.3)	4 (2.3)
Renal and urinary disorders	5 (4.1)	4 (3.3)	5 (2.8)	3 (1.7)
Acute kidney injury	3 (2.5)	2 (1.6)	3 (1.7)	2 (1.1)
Injury, poisoning and procedural complications	4 (3.3)	4 (3.3)	11 (6.2)	7 (4.0)
Traumatic fracture	2 (1.6)	2 (1.6)	5 (2.8)	3 (1.7)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term, SAE: Serious adverse event
MedDRA 22.1
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 IKd group
TEAEs with a start date before the operational Cut-off date and becoming serious after the operational Cut-off date were excluded from this analysis.
Only SOC with at least one PT ≥ 2% in at least one treatment group are presented.
PGM=PRODOPS/SAR650984/EFC15246/DMC 2020 01/REPORT/PGM/ae socpt s t.sas
OUT=REPORT/OUTPUT/ae_socpt_serious2_s_t_i.rtf (15JUN2020 16:03)

Deaths

In study EFC15246, during both treatment and post-treatment periods, 30 [16.9%] patients in IKd arm and 25 [20.5%] patients in Kd arm had died; mostly due to disease progression (18 [10.2%] in IKd arm and 19 [15.6%] in Kd arm). The majority of deaths (45 of 55) occurred during the posttreatment period. During the treatment period, 10 patients died; the incidence was similar between the IKd and Kd arms (6 [3.4%] and 4 [3.3%]). Adverse event was the cause of deaths for 5 (2.8%) patients in IKd arm and 2 (1.6%) patients in Kd arm.

During the posttreatment period, the main cause of death was disease progression, with lower incidence in the IKd arm than in the Kd arm (9.6% versus 14.8%). Adverse event was the cause of death for 1 patient (in IKd arm) during the posttreatment period. Nine patients (6 [3.4%] in IKd arm and 3 [2.5%] in Kd arm) died due to "Other" reasons (unrelated AEs or death from unknown cause).

Of the 55 patients who died during the study, Grade 5 AEs (ie, AEs with fatal outcome during the study) regardless of causality of death were reported in 16 patients overall, with similar incidence between the 2 arms (10 [5.6%] in IKd arm and 6 [4.9%] in Kd arm). Treatment-related Grade 5 TEAEs were reported in 2 patients (both in IKd arm): atypical pneumonia in 1 patient (during treatment period) and pneumocystis jirovecii pneumonia in another (during posttreatment period).

Two patients (1 in each group) experienced fatal AEs in the context of disease progression. Fatal AEs in context other than disease progression (regardless of causality of death) were reported in 6 (3.4%) patients in IKd arm and 3 (2.5%) patients in Kd arm.

Table 32 *AEs leading to death in context other than disease progression by primary SOC and PT - EFC15246 - safety population*

Primary System Organ Class Preferred Term [n(%)]	Kd (N=122)		IKd (N=177)	
	All	Related	All	Related
Any fatal AE in context other than disease progression[a]	3 (2.5)	0	6 (3.4)	2 (1.1)
Infections and infestations	1 (0.8)	0	4 (2.3)	2 (1.1)
Pneumonia	1 (0.8)	0	2 (1.1)	0
Atypical pneumonia	0	0	1 (0.6)	1 (0.6)
Pneumocystis jirovecii pneumonia	0	0	1 (0.6)	1 (0.6)
Septic shock	1 (0.8)	0	0	0
Cardiac disorders	1 (0.8)	0	2 (1.1)	0
Cardiac failure	0	0	2 (1.1)	0
Acute myocardial infarction	1 (0.8)	0	0	0
Renal and urinary disorders	0	0	1 (0.6)	0
Acute kidney injury	0	0	1 (0.6)	0
General disorders and administration site conditions	1 (0.8)	0	0	0
Death	1 (0.8)	0	0	0

AE: Adverse event, SOC: System organ class, PT: Preferred term

a Deaths within 30 days from last dose with cause of death not equal to disease progression, or death more than 30 days from last dose with cause of death equal to AE

MedDRA 22.1

n (%) = number and percentage of patients with at least one fatal AE in context other than progressive disease

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

PGM=PRODOPS/SAR650984/EFC15246/DMC 2020 01/REPORT/PGM/ae socpt fatal s t.sas
OUT=REPORT/OUTPUT/ae_socpt_fatal_notpd_s_t_i.rtf (15JUN2020 16:02)

Other significant adverse events

Infusion reactions

Infusion reactions of any grades were reported more frequently in the IKd arm (in 81 [45.8%] of patients) than in the Kd arm (4 [3.3%]). In the IKd arm, IRs were mostly reported as induced by isatuximab. All IRs were Grade 1 or Grade 2 except for 1 patient (in IKd arm) who developed a Grade 3 IR which was reported as carfilzomib induced. Of the 81 (45.8%) patients who experienced IRs, 76 (42.9%) patients experienced IRs during the first 2 days of study treatment. Ten (5.6%) patients in IKd arm experienced IR episodes beyond Cycle 1. Five patients (2.8%) in IKd arm experienced 3 or more episodes of IRs. All IRs in EFC15246 were reversible and recovered without sequelae (with or without corrective treatment). Most IR episodes recovered within 1 or 2 days from onset (in IKd arm, 73.8% within 1 day, 23.8% within 2 days). Four IR episodes (3 [2.5%] in IKd arm and 1 [16.7%] in Kd arm) lasted for more than 2 days and recovered.

Infusion reaction resulted in isatuximab discontinuation in 1 (0.6%) patient. Infusion reactions led to isatuximab dose interruption in 53 (29.9%) patients, isatuximab dose omission in 1 (0.6%) patient, carfilzomib dose interruption in 2 patients (1 in IKd arm and 1 in Kd arm), and carfilzomib dose reduction in 4 patients (3 [1.7%] in IKd arm and 1 [0.8%] in Kd arm). Although 29.9% of patients in IKd arm experienced at least one isatuximab dose interruption due to infusion reaction, the overall rate of isatuximab dose interruption due to any reason was 1.4% (82 interruptions out of a total of 5715 infusions).

In IKd arm, out of the 81 (45.8%) patients with IRs, 78 (44.1%) patients had IRs reported as induced by isatuximab, including 3 patients with IRs reported as induced by both isatuximab and carfilzomib. Three other patients had IRs reported as induced by carfilzomib alone. One patient in IKd group experienced Grade 1 cytokine release syndrome and another patient in IKd group experienced Grade 2 hypersensitivity. In IKd arm, the most frequent IR symptoms (in ≥5% of patients) were cough (11.3%), dyspnea and (10.2%), nasal congestion (10.2%), vomiting (6.8%), and nausea (6.2%).

In study EFC15246, all 177 (98.9%) treated patients in the IKd arm and 23 (18.7%) patients in the Kd arm received medications reported as IR prophylactic medication (in addition to IMP dexamethasone). In addition, 7 patients in IKd arm and 2 patients in Kd arm received GCSF/GMCSF for IR prophylaxis.

Most patients in both arms had at least 1 TEAE within 24 hours of isatuximab or carfilzomib administration (92.1% in IKd arm and 91.0% in Kd arm for all grades; 50.3% and 37.7% for Grade≥3). Treatment-related TEAEs within 24 hours of infusion were reported in 81.9% of patients in IKd arm and 74.6% of patients in Kd arm (31.6% versus 27.0% for Grade ≥3). The most frequent TEAEs within 24 hours of infusion (in >15% of patients) included infusion related reaction (44.6% in IKd arm versus 3.3% in Kd arm), hypertension (28.2%, 23.0%), diarrhoea (21.5%, 15.6%), fatigue (23.7%, 11.5%), dyspnoea (20.9%, 16.4%), insomnia (16.9%, 18.9%), and upper respiratory tract infection (16.4%, 7.4%), which is consistent with the overall safety profile of isatuximab and carfilzomib.

TEAEs from the "Hypersensitivity and CRS" CMQ were reported more frequently in the IKd arm (55.4%) than in the Kd group (16.4%); the difference was primarily driven by infusion related reaction which occurred more frequently in the IKd arm (44.6% versus 3.3%). Most of these TEAEs started within 24 hours of isatuximab or carfilzomib infusion (52.0% versus 11.5%). Majority of these TEAEs were treatment-related (49.2% versus 8.2%); and almost all were Grade 1 or 2 except for 4 patients with Grade ≥3 events (3 in IKd arm and 1 in Kd arm). Besides infusion related reaction, rash was the second most frequent TEAE from the "Hypersensitivity and CRS" CMQ, reported in 12 (6.8%) patients in IKd arm and 6 (4.9%) patients in Kd arm (8 [4.5%] versus 3 [2.5%] within 24 hours of infusion). One patient in IKd arm experienced a Grade 1 cytokine release syndrome and another patient in IKd arm experienced a Grade 2 hypersensitivity. Both events occurred within 24 hours of infusion and both were considered treatment-related.

Cardiac and vascular disorders AEs

Overall, the addition of isatuximab to Kd did not increase the incidence of TEAEs (both all grades and Grade ≥3) in cardiac CMQ (ie, cardiac disorders SOC), in cardiac failure SMQ (narrow), in ischemic heart disease SMQ (narrow), in embolic and thrombotic events (venous and arterial) SMQ (narrow), and in cardiac arrhythmias HLGT. TEAEs belonging to cardiac disorders SOC were reported with similar incidences in IKd and Kd arms (23.7% versus 22.1% for all grades; 7.3% versus 7.4% for Grade ≥3). Congestive cardiac failure (ie, congestive heart failure [CHF]) was reported in 3 (1.7%) patients in the IKd arm (none in Kd arm). Pulmonary edema was reported in 1 (1.0%) patient in the Kd arm (none in IKd arm). Two of the 3 patients with CHF had relevant medical history of hypertension (for 1 patient) and emphysema and smoking (for another patient), while the third patient with CHF had no relevant medical history. The patient with pulmonary edema had medical history of asthma and type 2 diabetes. There were no TEAEs in cardiomyopathy SMQ (narrow) reported in this study.

TEAEs in vascular hypertensive disorders HLGT (all grades) were reported with higher incidence in the IKd arm than in the Kd arm. The incidence of patients with hypertension (all grades) was 36.6% in the IKd arm versus 30.4% in the Kd arm in patients without prior history, and 38.1% versus 32.6% in patients with prior history. Overall, the incidence of all grade hypertension was 36.7% in IKd arm versus 31.1% in Kd arm. The incidence of Grade ≥3 hypertension, however, was similar between the 2 arms: 20.3% in IKd versus 19.7% in Kd. Two patients, 1 in each arm, experienced hypertension crisis. No patient in IKd arm had definitive treatment discontinuation due to hypertension, while 2 patients in Kd arm had hypertension leading to definitive treatment discontinuation. Regarding the observed >5% difference between the IKd and Kd arms in all grade hypertension assessments of the mean and standard deviation of systolic and diastolic blood pressure over the course of the study did not reveal a difference between the two arms.

Thromboembolic events, venous or arterial, were reported with slightly lower incidence in the IKd arm than in the Kd arm (15.3% versus 16.4% for all grades; 4.0% versus 5.7% for Grade ≥3). Most thromboembolic events were venous events (13.6% and 14.8% in IKd and Kd groups, respectively). The most frequently reported venous events were thrombophlebitis superficial (5.1% and 5.7%; no Grade ≥3) and deep vein thrombosis (4.5% and 8.2%; with 1.6% in Kd group Grade ≥3). Pulmonary embolism was the most frequently reported Grade ≥3 venous event (2.3% and 2.5%). The incidence of arterial thromboembolic events was also slightly lower in the IKd arm than in the Kd arm (1.7% versus 3.3% for all grades; 1.1% versus 2.5% for Grade ≥3). The reported arterial events (all grades) included acute myocardial infarction (0.6% versus 0.8%), coronary artery occlusion (0.6% in IKd), peripheral arterial occlusive disease (0.6% versus 0.8%), ischemic stroke (1.6% in Kd), and peripheral embolism (0.8% in Kd).

Infections

Overall, TEAEs in the SOC Infections and infestations were reported in 86.4% and 80.3% of patients in the IKd and Kd arms, respectively. Most infections were in the HLGT" infections - pathogen unspecified" (83.1% in IKd group and 76.2% in Kd group). The most frequently reported infections (all grades) in either arm were upper respiratory tract infection, pneumonia, and bronchitis. Serious infections were reported in 37.9% and 30.3% of patients in the IKd and Kd arms, respectively (33.9% and 26.2% for Grade ≥3). When adjusted for exposure, the difference in serious infections between the 2 arms was reduced but remained higher in the IKd arm than in the Kd arm (0.38 versus 0.33 event per PY). Most infections TEAEs (respiratory infections included) were reversible and manageable with supportive care (prophylaxis or curative) and few resulted in definitive treatment discontinuation (2.8% of patients in IKd arm and 4.9% in Kd arm). Infections with fatal outcomes not in the context of disease progression occurred to 4 patients in IKd arm and 1 patient in Kd arm. One patient in Kd arm (and no patient in IKd

group) reported hepatitis B reactivation. Two patients in the IKd arm had primary infections of hepatitis B virus.

The addition of isatuximab to Kd increased the incidence of respiratory infections, both all grades (83.1% versus 73.8%) and Grade ≥3 (32.2% versus 23.8%), driven by higher incidence of upper respiratory infection (36.2% versus 23.8%) and bronchitis (22.6% versus 12.3%) in the IKd arm than in the Kd arm. Pneumonia was reported in 23.7% of patients in IKd arm and 19.7% of patients in Kd arm.

Lower respiratory TEAEs

In study EFC15246, lower respiratory TEAEs excluding infections (in" lower respiratory events" CMQ) were reported more frequently in the IKd arm than in the Kd arm (46.3% versus 36.1% all grades; 9.0% versus 3.3% Grade ≥3), with dyspnea and cough being the main contributors to the imbalance. Of the 9 patients with Grade ≥3 dyspnea in the IKd arm, 4 had a history of respiratory disease or as evidenced by the medical history or the use of respiratory medications.

Second primary malignancies

Second primary malignancies (SPMs) were reported in 13 (7.3%) patients in IKd arm and 6 (4.9%) patients in Kd arm. All SPMs were solid tumours (skin cancers or non-skin solid tumours). There were no haematologic malignancies reported in either arm. Skin cancers as SPM were reported in 9 (5.1%) patients in IKd arm and 3 (2.5%) patients in Kd arm. Among the 12 patients with skin cancers, medical history of skin cancer(s) was reported in 3 patients (all in IKd arm). All patients with skin cancers were able to continue in the study after resection. Other solid tumours as SPM (other than skin cancers) were reported in 5 (2.8%) patients in IKd arm and 4 (3.3%) patients in Kd arm. Among them, 4 patients discontinued study treatment due to SPMs (3 in IKd arm and 1 in Kd arm).

Neutropenia and neutropenic complications

In study EFC15246, the overall incidence of patients with Grade 3 neutropenia (regardless of baseline status) was higher in the IKd arm (17.5%) than in the Kd arm (6.6%). The incidence of Grade 4 neutropenia was low and similar between the two arms (1.7% versus 0.8%). The incidence of Grade 3 neutropenia was higher among patients with pre-existing Grade 2 neutropenia at baseline, as compared to patients with lower grade or no neutropenia at baseline. Compared to IPd combination, the IKd combination had much lower rate of Grade 3-4 neutropenia, especially Grade 4 neutropenia. In study EFC15246, neutropenia events were well managed with supportive care and were reversible in most subjects with few cases of neutropenic complications. No patients had definitive treatment discontinuation due to neutropenia or neutropenic complication. Neutropenic complications were experienced by 5 (2.8%) patients overall, 2 (1.1%) with febrile neutropenia and 3 (1.7%) with neutropenic infection (gastroenteritis, pneumonia, chronic sinusitis), all in IKd arm. Three patients with neutropenic complications (2 with febrile neutropenia and 1 with neutropenic infection) received GCSF/GMCSF. One patient in IKd arm had premature discontinuation of carfilzomib due to neutropenia.

Thrombocytopenia

The incidences of patients with Grade 3 and Grade 4 laboratory thrombocytopenia were similar between the IKd and Kd arms (18.6% versus 15.6% for Grade 3; 11.3% versus 8.2% for Grade 4), and were higher among patients with pre-existing thrombocytopenia (Grade 1 or 2) at baseline as compared to patients with no abnormality at baseline. Thrombocytopenia as a TEAE was reported with lower incidence in the IKd arm than in the Kd arm (5 [2.8%] versus 12 [9.8%] all grades; 2.3% versus 8.2% Grade ≥3). Thrombocytopenia TEAE led to 1 definitive treatment discontinuation in the Kd arm (and none in IKd

arm). There were no cases of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome reported.

Overall, haemorrhages (all grades) were reported more frequently in the IKd arm (19.8%) than in the Kd arm and (12.3%). The incidence of Grade 3 or 4 haemorrhages was low. Five patients experienced Grade 3 haemorrhages (4 [2.3%] in IKd arm and 1 [0.8%] in Kd arm). One patient in IKd arm experienced a Grade 4 haemorrhage. Haemorrhages following Grade 4 thrombocytopenia were reported in 4 (2.3%) patients, all in the IKd arm (Grade 1 haemorrhage in 1 patient, Grade 2 in 2 patients, and Grade 3 in 1 patient). There appeared to be no correlation between Grade 3-4 thrombocytopenia and haemorrhages.

Interference with cross-matching and red blood cell antibody screening

Because anti-CD38 antibody treatment has the potential to interfere with the indirect antiglobulin test (IAT, also known as indirect Coombs test) performed for blood bank typing, patients in the IKd arm in EFC15246 and those in the IPd arm in EFC14335 underwent IAT testing during screening, and were tested again at least once during treatment. In study EFC15246, IAT was performed in 168 (94.9%) patients at baseline and 162 (91.5%) patients during the treatment period in the IKd arm.

A positive Coombs test was perfomed in 94.9% (168 patients) at baseline and 91.5% (162 patients) during the treatment period in the IKd arm. In the IKd arm, a positive Coombs test was reported during study treatment in 95 of the 150 patients (63.3%) with both a negative test at baseline and at least one test during study treatment. No haemolytic disorder was reported in patients with positive indirect Coombs receiving red blood cell transfusions.

Laboratory findings

Overall, the majority of patients in both IKd and Kd arms experienced some degree of laboratory anaemia, lymphopenia (lymphocyte count decreased), and thrombocytopaenia (platelet count decreased) (Table 33). The overall incidences (all grades) were similar between the two arms, but the incidences of Grade 3 neutropenia was higher in the IKd arm than in the Kd arm. No patients in either arm experienced Grade 4 anaemia. The majority of patients in both arms with anaemia during on-treatment period had pre-existing anaemia at baseline. The IKd arm had more patients with pre-existing Grade 3 anaemia (13 [7.3%]) than the Kd arm (4 [3.3%]).

Table 33 *Hematology - Abnormalities during the on-treatment period (worst grade per patient)*

Laboratory parameter n/N1 (%)	Kd (N=122)	IKd (N=177)
Anemia		
All Grades	121/122 (99.2)	176/177 (99.4)
Grade 1	44/122 (36.1)	52/177 (29.4)
Grade 2	53/122 (43.4)	85/177 (48.0)
Grade 3	24/122 (19.7)	39/177 (22.0)
Grade 4	0/122	0/177
Lymphocyte count decreased		
All Grades	116/122 (95.1)	167/177 (94.4)
Grade 1	10/122 (8.2)	8/177 (4.5)
Grade 2	36/122 (29.5)	37/177 (20.9)
Grade 3	53/122 (43.4)	92/177 (52.0)
Grade 4	17/122 (13.9)	30/177 (16.9)
Neutrophil count decreased		
All Grades	53/122 (43.4)	97/177 (54.8)
Grade 1	15/122 (12.3)	29/177 (16.4)
Grade 2	29/122 (23.8)	34/177 (19.2)
Grade 3	8/122 (6.6)	31/177 (17.5)
Grade 4	1/122 (0.8)	3/177 (1.7)
White blood cell decreased		
All Grades	93/122 (76.2)	154/177 (87.0)
Grade 1	44/122 (36.1)	63/177 (35.6)
Grade 2	42/122 (34.4)	61/177 (34.5)
Grade 3	6/122 (4.9)	28/177 (15.8)
Grade 4	1/122 (0.8)	2/177 (1.1)
Platelet count decreased		
All Grades	107/122 (87.7)	167/177 (94.4)
Grade 1	50/122 (41.0)	78/177 (44.1)
Grade 2	28/122 (23.0)	36/177 (20.3)
Grade 3	19/122 (15.6)	33/177 (18.6)
Grade 4	10/122 (8.2)	20/177 (11.3)

Note: % calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) during the on-treatment period
PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/lab_allgrade_hema_s_t.sas
OUT=REPORT/OUTPUT/lab_allgrade_hema_ontrt_s_t_i.rtf (15JUN2020 11:49)

Clinical chemistry in metabolism and electrolytes were generally similar between the IKd and Kd arms (Table 34). Most of the abnormalities were of Grade 1 or 2. Grade 3 hyperglycemia, Grade 3 hyponatremia, and Grade 3 hypophosphatemia were noted with higher incidence in the IKd arm than in the Kd arm: 6.1% versus 2.9% for hyperglycemia; 7.9% versus 4.1% for hyponatremia; 9.7% versus 5.8% for hypophosphatemia. The incidence of Grade 4 abnormalities was very low (<2% in either arm).

Table 34 Metabolic function - Abnormalities during the on-treatment period (worst grade per patient)

Laboratory parameter n/N1 (%)	Kd (N=122)	IKd (N=177)
Hypoalbuminemia		
All Grades	55/122 (45.1)	86/176 (48.9)
Grade 1	33/122 (27.0)	59/176 (33.5)
Grade 2	20/122 (16.4)	25/176 (14.2)
Grade 3	2/122 (1.6)	2/176 (1.1)
Grade 4	0/122	0/176
Hypoglycemia		
All Grades	8/104 (7.7)	27/163 (16.6)
Grade 1	7/104 (6.7)	19/163 (11.7)
Grade 2	0/104	8/163 (4.9)
Grade 3	1/104 (1.0)	0/163
Grade 4	0/104	0/163

Laboratory parameter n/N1 (%)	Kd (N=122)	IKd (N=177)
Hyperglycemia		
All Grades	39/104 (37.5)	58/163 (35.6)
Grade 1	20/104 (19.2)	33/163 (20.2)
Grade 2	15/104 (14.4)	13/163 (8.0)
Grade 3	3/104 (2.9)	10/163 (6.1)
Grade 4	1/104 (1.0)	2/163 (1.2)

Note: % calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) during the on-treatment period.
PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/lab_allgrade_meta_s_t.sas
OUT=REPORT/OUTPUT/lab_allgrade_meta_ontrt_s_t_i.rtf (15JUN2020 11:49)

Liver function: The IKd and Kd arms were similar in the overall incidences of ALT increased and AST increased (all grades). The incidence of Grade 3 ALT increased was 4.0% in IKd arm and 2.5% in Kd arm. The incidence of Grade 3 AST increased was 4.0% and 0.8% in IKd and Kd arms, respectively. One patient in IKd arm experienced a transient Grade 4 ALT increased. The IKd arm had lower incidence of Grade 2 blood bilirubin increased than the Kd arm (4.5% versus 12.3%). One patient in IKd arm experienced a Grade 3 blood bilirubin increased, which did not meet the criteria for Hy's Law. There was higher incidence of Grade 1 ALP increased in the IKd arm than in the Kd arm (28.2% versus 19.7%). This may be hypothesised to be of bone rather than of liver origin within the context of tumour response, as has been observed with other active myeloma agents.

Renal function: The addition of isatuximab to Kd did not result in an increase in renal dysfunction. Compared to the Kd arm, the IKd arm had similar or lower incidences of renal impairment (based on eGFR [MDRD]), creatinine increased, and hyperuricemia at each grade. This may be attributed to better myeloma control in the IKd arm leading to less renal dysfunction. End-stage renal disease (eGFR <15 mL/min/1.73m2) was reported in 3 (1.8% of 163) patients in the IKd arm and 3 (2.7% of 110) patients in the Kd arm. Of note, race was not reported for 14 patients in IKd arm and 12 patients in Kd arm due to legal considerations and eGFR was therefore not calculated for these patients. Of the 6 patients with end-stage renal disease during study treatment, 3 in IKd arm and 1 in Kd arm recovered to at least baseline status. End-stage renal disease occurred in the context of an AE to 1 patient in the IKd arm (bronchitis) and 2 patients in the Kd arm (hypertension with cardiac failure for one patient; urinary tract infection with pulmonary infection for another patient), in the context of disease progression to 1 patient in the IKd arm, and in the context of and AE and disease progression to 1 patient in the IKd arm (flu like syndrome with diarrhoea) and 1 patient in the Kd arm (fatal pneumonia with septic shock). In TEAEs related to

renal toxicity, the IKd arm had a lower incidence of TEAEs in the HLT of renal failure and impairment than the Kd arm: 5.1% versus 8.2% all grades; 1.1% versus 2.5% Grade ≥3. The IKd arm had lower incidence of acute kidney injury than the Kd arm (2.8% versus 5.7%).

Safety in special populations

Age groups

In both the IKd and Kd arms the incidence of Grade ≥3 increased with age and incidence of serious TEAEs was higher in patients ≥65 years old. Definitive treatment discontinuations only increased by age in the Kd arm. In the IKd arm, TEAEs leading to premature discontinuation of carfilzomib also increased with increasing age. A similar profile in TEAE overview was observed in subgroups by increasing age versus the overall safety population presented by a higher incidence of patients with Grade ≥3 TEAEs, but this did not result in an increase in the incidence of patients with serious TEAEs, fatal TEAE during study treatment, or TEAEs leading to definitive treatment discontinuation in the IKd arm versus the Kd arm.

Table 35 *Overview of TEAEs by age - EFC15246 - Safety population*

	Age <65 (N=152)		Age ≥65 to <75 (N=121)		Age ≥75 (N=26)	
	Kd (N=65)	IKd (N=87)	Kd (N=47)	IKd (N=74)	Kd (N=10)	IKd (N=16)
Patients with any TEAE	61 (93.8)	83 (95.4)	46 (97.9)	73 (98.6)	10 (100)	16 (100)
Patients with any grade ≥ 3 TEAE	41 (63.1)	60 (69.0)	33 (70.2)	62 (83.8)	8 (80.0)	14 (87.5)
Patients with any grade 3-4 TEAE	41 (63.1)	59 (67.8)	32 (68.1)	61 (82.4)	8 (80.0)	14 (87.5)
Patients with any grade 5 TEAE[a]	1 (1.5)	1 (1.1)	3 (6.4)	5 (6.8)	0	0
Patients with any treatment emergent SAE[b]	32 (49.2)	46 (52.9)	31 (66.0)	48 (64.9)	7 (70.0)	11 (68.8)
Patients with any TEAE leading to definitive discontinuation	5 (7.7)	6 (6.9)	8 (17.0)	8 (10.8)	4 (40.0)	1 (6.3)
Patients with any TEAE leading to premature discontinuation of Isatuximab	NA	0	NA	1 (1.4)	NA	0
Patients with any TEAE leading to premature discontinuation of Carfilzomib	0	9 (10.3)	1 (2.1)	13 (17.6)	0	4 (25.0)
Patients with any TEAE leading to premature discontinuation of Dexamethasone	2 (3.1)	4 (4.6)	1 (2.1)	5 (6.8)	1 (10.0)	2 (12.5)
Patients with any AESI[c]	0	1 (1.1)	0	0	0	0
Patients with any treatment-related TEAE[d] (any grade)	53 (81.5)	77 (88.5)	35 (74.5)	63 (85.1)	10 (100)	13 (81.3)
Patients with any treatment-related grade ≥3 TEAE	32 (49.2)	36 (41.4)	22 (46.8)	40 (54.1)	4 (40.0)	11 (68.8)
Patients with any serious treatment-related TEAE	13 (20.0)	17 (19.5)	14 (29.8)	20 (27.0)	4 (40.0)	7 (43.8)

Gender

No consistent trends by gender were observed for the incidence of TEAEs, serious TEAEs, and treatment-related serious TEAEs. Grade ≥3 TEAEs occurred at a higher incidence in males in the IKd arm (80.8%) than in the female (72.2% KD and 71.8% IKd) with the lowest incidence in males in the Kd arm (63.2%). Even though higher incidence of patients with Grade ≥3 TEAEs was observed in males in the IKd arm (not in females), this did not result in an increase in the incidence of patients with serious TEAEs, fatal TEAEs during study treatment, or TEAEs leading to definitive treatment discontinuation in the IKd arm compared to the Kd arm.

Race and ethnicity

In general, there did not appear to be any trends in the incidence of TEAEs by race. The incidence of Grade ≥3 and Grade 3-4 TEAEs was higher in the IKd arms regardless of race. The incidence of serious TEAEs was similar between IKd and Kd arms of Caucasian and non-Caucasian patients, but was lower overall in non-Caucasian patients in the IKd (48.5% non-caucasican versus 63.1% caucascian) and Kd arms (51.9% non-caucasican versus 60.2% caucascian). There was a higher incidence of patients with Grade ≥3 TEAEs, but this did not result in an increase in the incidence of patients with serious TEAEs, with fatal TEAEs during study treatment, or with TEAEs leading to definitive treatment discontinuation in the IKd arm versus the Kd arm.

Renal status (<60 mL/min/1.73m^2, ≥60 mL/min/1.73m2)

Among patients with eGFR ≥60 mL/min/1.73m2, Grade ≥3 TEAEs occurred less frequently in the Kd arm than in the IKd arm. In the Kd arm, patients with eGFR < 60 mL/min/1.73m2 had higher incidence of serious TEAEs versus patients with eGFR ≥60 mL/min/1.73m2 (77.8% versus 54.3%) while in the IKd arm, a similar incidence of serious TEAEs was reported in patients with eGFR <60 mL/min/1.73m^2 and in patients with eGFR ≥60 mL/min/1.73m^2 (6.8% versus 59.2%). A similar profile in TEAE overview was observed in subgroups by renal function to the overall TEAE overview in safety population. There was a higher incidence of patients with TEAEs Grade ≥3 for patients with eGFR ≥60 mL/min/1.73m2 in the IKd arm (not for patients with eGFR <60 mL/min/1.73m2), but it did not result in an increase in the incidence of patients with serious TEAEs, with fatal TEAE during study treatment, or with TEAE leading to definitive treatment arm discontinuation.

Hepatic status

Although there were few patients with abnormal hepatic function in the IKd and Kd arms (17 and 16 patients, respectively), there were no trends observed in the incidence of TEAEs in patients based on hepatic function, except for a higher incidence of patients with serious TEAEs in the Kd arm with abnormal liver function versus with normal liver function in the Kd arm (75.0% versus 54.7%).

A similar profile in TEAE overview was observed in subgroups by liver function versus the TEAE overview in the overall safety population. There was a higher incidence of patients with TEAEs Grade ≥3, but not for patients with abnormal hepatic function, which was slightly lower in the IKd arm. This did not result in an increase in the incidence of patients with serious TEAEs, with fatal TEAEs during study treatment, or with TEAEs leading to definitive treatment discontinuation in the IKd arm versus the Kd arm.

Extrinsic factors

Overall, in all isatuximab treated patients, there were no marked and consistent differences across different geographic regions (Western and Eastern Europe [N=359], North and South America [N=489], Asia [N=81], and Other countries [N=118]) in the incidences of TEAEs (any grades, Grade ≥3, by SOC and PT, Grade 5 with fatal outcome, serious, leading to treatment discontinuation, treatment-related) and the incidences of Other important AEs (IRs, lower respiratory and respiratory infections, neutropenia, and thrombocytopenia). In all isatuximab treated patients, there were approximately equal number of patients who received 1 to 3 prior lines of therapy (N=508) and those who received >3 prior lines of therapy (N=522).

There were no marked and consistent differences between the two groups by prior lines of therapy in the incidences of TEAEs (any grades, Grade ≥3, by SOC and PT, Grade 5 with fatal outcome, serious, leading to treatment discontinuation, treatment-related) and the incidences of Other important AEs (IRs, lower respiratory and respiratory infections, neutropenia, and thrombocytopenia).

Discontinuation due to adverse events

Definitive treatment discontinuation was defined as discontinuation of all study medications or the last ongoing study drug. The incidence of patients with TEAEs leading to definitive treatment discontinuation was lower in the IKd arm (15 [8.5%]) than in the Kd arm (17 [13.9%]) (***Table 36***).

Premature discontinuation of isatuximab due to TEAE was reported in 1 (0.6%) patient (infusion related reaction) (≤ grade 3). Premature discontinuation of carfilzomib due to TEAEs was reported in 26 (14.7%) patients in IKd arm and 1 (0.8%) patient in Kd arm. Cardiac disorders TEAEs were the main reason for premature carfilzomib discontinuation (7.3% in IKd arm), with cardiac failure PT being the most frequent (5 [2.8%]) (Table 37). Premature discontinuation of dexamethasone due to TEAEs occurred to 6.2% of patients in the IKd arm and 3.3% of patients in the Kd arm.

Table 36 *Number (%) of patients with TEAE(s) leading to definitive treatment discontinuation by Primary SOC and PT - EFC15246 - safety population*

Primary System Organ Class Preferred Term [n(%)]	Kd (N=122)		IKd (N=177)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	17 (13.9)	10 (8.2)	15 (8.5)	11 (6.2)
Infections and infestations	6 (4.9)	5 (4.1)	5 (2.8)	5 (2.8)
Pneumonia	4 (3.3)	3 (2.5)	3 (1.7)	3 (1.7)
Atypical pneumonia	0	0	1 (0.6)	1 (0.6)
Pneumocystis jirovecii pneumonia	0	0	1 (0.6)	1 (0.6)
Abdominal abscess	1 (0.8)	1 (0.8)	0	0
Lower respiratory tract infection	1 (0.8)	1 (0.8)	0	0
Septic shock	1 (0.8)	1 (0.8)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	1 (0.8)	3 (1.7)	3 (1.7)
Colon cancer	1 (0.8)	1 (0.8)	1 (0.6)	1 (0.6)
Pancreatic carcinoma metastatic	0	0	1 (0.6)	1 (0.6)
Uterine cancer	0	0	1 (0.6)	1 (0.6)
Blood and lymphatic system disorders	1 (0.8)	1 (0.8)	1 (0.6)	0
Microangiopathic haemolytic anaemia	0	0	1 (0.6)	0
Thrombocytopenia	1 (0.8)	1 (0.8)	0	0
Nervous system disorders	1 (0.8)	1 (0.8)	3 (1.7)	1 (0.6)
Dementia	0	0	1 (0.6)	0
Embolic cerebral infarction	0	0	1 (0.6)	0
Intracranial mass	0	0	1 (0.6)	1 (0.6)
Encephalopathy	1 (0.8)	1 (0.8)	0	0
Cardiac disorders	3 (2.5)	1 (0.8)	1 (0.6)	1 (0.6)
Cardiac failure	0	0	1 (0.6)	1 (0.6)
Acute myocardial infarction	1 (0.8)	1 (0.8)	0	0
Atrial fibrillation	1 (0.8)	0	0	0
Sinus bradycardia	1 (0.8)	0	0	0
Vascular disorders	3 (2.5)	1 (0.8)	0	0
Deep vein thrombosis	1 (0.8)	0	0	0
Hypertension	2 (1.6)	1 (0.8)	0	0
Respiratory, thoracic and mediastinal disorders	2 (1.6)	0	1 (0.6)	1 (0.6)
Dyspnoea	1 (0.8)	0	1 (0.6)	1 (0.6)
Chronic obstructive pulmonary disease	1 (0.8)	0	0	0
Gastrointestinal disorders	1 (0.8)	1 (0.8)	0	0
Large intestine perforation	1 (0.8)	1 (0.8)	0	0
General disorders and administration site conditions	1 (0.8)	1 (0.8)	1 (0.6)	0
General physical health deterioration	0	0	1 (0.6)	0
Death	1 (0.8)	1 (0.8)	0	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 22.1
n(%) = number and percentage of patients with at least one TEAE leading to definitive treatment discontinuation
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IKd group
PGM=PRODOPS/SAR650984/EFC15246/DMC_2020_01/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_defdisc_s_t_i.rtf (15JUN2020 16:02)

Table 37 *TEAEs leading to premature discontinuation of carfilzomib by Primary SOC and PT - EFC15246 - safety population*

Primary System Organ Class Preferred Term [n(%)]	Kd (N=122)		IKd (N=177)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	1 (0.8)	0	26 (14.7)	13 (7.3)
Infections and infestations	0	0	3 (1.7)	2 (1.1)
Abdominal sepsis	0	0	1 (0.6)	1 (0.6)
Pneumonia	0	0	1 (0.6)	1 (0.6)
Respiratory tract infection	0	0	1 (0.6)	0
Blood and lymphatic system disorders	1 (0.8)	0	1 (0.6)	0
Neutropenia	0	0	1 (0.6)	0
Haemolysis	1 (0.8)	0	0	0
Metabolism and nutrition disorders	0	0	1 (0.6)	1 (0.6)
Mineral metabolism disorder	0	0	1 (0.6)	1 (0.6)
Nervous system disorders	0	0	1 (0.6)	0
Peripheral sensory neuropathy	0	0	1 (0.6)	0
Cardiac disorders	0	0	13 (7.3)	7 (4.0)
Cardiac failure	0	0	5 (2.8)	2 (1.1)
Cardiac failure congestive	0	0	2 (1.1)	1 (0.6)
Supraventricular tachycardia	0	0	2 (1.1)	1 (0.6)
Acute myocardial infarction	0	0	1 (0.6)	1 (0.6)
Atrial fibrillation	0	0	1 (0.6)	1 (0.6)
Coronary artery occlusion	0	0	1 (0.6)	0
Coronary artery stenosis	0	0	1 (0.6)	1 (0.6)
Vascular disorders	0	0	1 (0.6)	1 (0.6)
Hypertension	0	0	1 (0.6)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	0	0	3 (1.7)	2 (1.1)
Pulmonary hypertension	0	0	2 (1.1)	1 (0.6)
Dyspnoea	0	0	1 (0.6)	1 (0.6)
Hepatobiliary disorders	0	0	1 (0.6)	0
Hyperbilirubinaemia	0	0	1 (0.6)	0
Skin and subcutaneous tissue disorders	0	0	1 (0.6)	0
Diabetic ulcer	0	0	1 (0.6)	0
Renal and urinary disorders	0	0	1 (0.6)	0
Renal impairment	0	0	1 (0.6)	0
General disorders and administration site conditions	0	0	1 (0.6)	0
Oedema peripheral	0	0	1 (0.6)	0
Investigations	0	0	1 (0.6)	0
Electrocardiogram t wave abnormal	0	0	1 (0.6)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term

MedDRA 22.1

n(%) = number and percentage of patients with at least one TEAE leading to premature treatment discontinuation of carfilzomib

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

PGM=PRODOPS/SAR650984/EFC15246/DMC 2020 01/REPORT/PGM/ae socpt s t.sas

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Dose reduction/omission of isatuximab due to TEAEs was reported in 53.1% of patients in the IKd arm, most frequently due to TEAEs in the SOC of Infections and Infestations (with upper respiratory tract infection, bronchitis, and pneumonia being the most frequent). Other TEAEs leading to isatuximab dose reduction/omission (in ≥2% of patients) included hypertension dyspnea, and asthenia (each with 4 [2.3%] patients). Dose interruption (ie, infusion interruption) of isatuximab due to TEAEs occurred in 32.8% of patients in IKd arm, primarily due to infusion related reactions (29.9%).

Carfilzomib dose reductions/omissions due to TEAEs were reported in 67.2% of patients in the IKd arm and 75.4% of patients in the Kd arm. The most frequently reported TEAEs leading to carfilzomib dose reduction (≥10% in either group) were upper respiratory tract infection (12.4% in IKd arm and 9.8% in Kd arm) and hypertension (11.9%, 14.8%). Carfilzomib dose interruptions due to TEAEs occurred in 7 (4.0%) patients in the IKd arm and 2 (1.6%) patients in the Kd arm, mainly due to TEAEs in the General disorders and administration site conditions SOC (administration site extravasation and infusion site extravasation for 2 patients each in IKd arm, and infusion site erythema and infusion site pain for 1 patient each). One patient each in both IKd and Kd arms had carfilzomib interruption due to infusion related reaction. No patient had a carfilzomib infusion interruption due to a Grade ≥3 TEAE.

Dexamethasone dose reductions/omissions due to TEAEs were reported in 75.1% of patients in the IKd arm and 77.0% of patients in the Kd arm. The most frequently reported TEAEs leading to dexamethasone dose reduction (≥10% in either arm) included upper respiratory tract infection (13.0% in IKd arm and 10.7% in Kd arm), insomnia (11.9%, 8.2%), bronchitis (10.7%, 6.6%), pneumonia (10.2%, 9.8%), and hypertension (7.3%, 13.9%). Dose interruption was not applicable to dexamethasone when given orally.

Dose delay of any drug due to TEAEs was reported more frequently in the IKd arm (59.9%) than in the Kd arm (45.1%). The most frequent TEAEs leading to dose delay of any drug was in the SOC of Infections and Infestations.

Supportive study TCD12795

Safety data from the ongoing investigator-sponsored Phase 1b TCD12795 study for isatuximab-carfilzomib combination are presented (cut-off May 2020). In total, 33 patients received isatuximab and carfilzomib (27 mg/m^2), without dexamethasone, at 3 isatuximab dose regimens (10 mg/kg Q2W, 10 mg/kg QW/Q2W, and 20 mg QW/Q2W), including 24 patients at the 10 mg/kg QW/Q2W dose regimen used in the pivotal EFC15246 study. Per the study protocol, all patients had at least 2 prior lines of therapy and had confirmed disease progression or were refractory to their last prior line of therapy. At the time of data cut-off, 4 patients remained on-treatment and 28 patients had discontinued study treatment due to disease progression with a median duration of follow-up of 26.7 months (range 13.3 to 61 months).

No dose-limiting toxicities were reported in this study. There were no treatment-related deaths or treatment discontinuations due to an AE. The most common Grade 3 or 4 AEs were lymphopenia (55%), hypertension (15%), anaemia (9%), and neutropenia (9%). One patient experienced a Grade 3 deep vein thrombosis, but there were no other severe haematologic, vascular or cardiac AEs.

There were IRs reported in 18 patients (55%), with the majority occurring during the first infusion (17 of 18) and most attributed to isatuximab (17 of 18). These AEs were mostly Grade 1-2 (only 1 Grade 3), and did not lead to treatment discontinuation in any patient. Ten patients experienced 12 SAEs, all due to infection: upper respiratory infection (6 patients), gastroenteritis (2 patients), pneumonia (2 patients), febrile neutropenia (1 patient), and hepatitis B reactivation (1 patient). All SAEs resolved with appropriate treatment and all patients resumed study treatment.

Pooled Analysis (All ISA-pool)

The pooled analysis safety dataset contains the supportive safety data from the initial dossier (submitted to FDA and EMA on 30 April 2019 and approved by FDA on 2 March 2020 and by EMA on 30 May 2020) (N=576), plus new data from EFC15246 and 5 additional company-sponsored MM studies (TED10893 Phase 2 Stage 2, TED14154 Part B, TED14095, TCD14079 Part B, and TCD14906). The integrated supportive safety dataset does not include data from studies or parts of studies that are still ongoing at the dossier cut-off date (i.e. 7 company-sponsored MM studies and 4 company-sponsored non-MM studies, and 5 investigator-sponsored studies [4 MM studies and 1 non-MM study]) (Table 38). For ongoing studies, only the serious adverse event (SAE) data collected in the pharmacovigilance database up to the common technical document (CTD) SAE cut-off date (07 February 2020) are provided in the CTD.

Table 38 *Summary of completed company-sponsored studies (or parts of studies)*

Study	Study design and indication	Isatuximab dose/schedule	# of patients (isatuximab)	Dossier Inclusion	Completed CSRs as of cut-off date
Pivotal study: Isatuximab + carfilzomib/dexamethasone (IKd) combination study in multiple myeloma					
EFC15246	Phase 3 randomized, open-label, multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib and dexamethasone versus carfilzomib with dexamethasone in patients with RRMM previously treated with 1 to 3 prior lines	10 mg/kg QW/Q2W	177[a]	New	Completed CSR for 65% PFS (cutoff 07-Feb-2020) Study still ongoing
Isatuximab + pomalidomide/dexamethasone (IPd) combination studies in multiple myeloma					
EFC14335	Phase 3 randomized, open-label, multicenter study comparing isatuximab in combination with pomalidomide and dexamethasone versus pomalidomide and dexamethasone in patients with RRMM (previously treated with at least 2 prior lines)	10 mg/kg QW/Q2W	152	Original	Completed CSR for final PFS and interim OS analyses (cutoff 22-Nov-2018)
TCD14079	Phase 1b study of isatuximab in combination with pomalidomide and dexamethasone in patients with RRMM	Part A: 5-20 mg/kg QW/Q2W	45	Original	Completed Part A CSR (DBL 10-Nov-2017)
		Part B: 10 mg/kg QW/Q2W	47	New[b]	Completed Part B CSR (cutoff 30-Oct-2019)
Single-agent isatuxmab (+/-dexamethasone) studies in multiple myeloma or other hematological malignancies					
TED10893	Phase 1/2 dose escalation and expansion safety, PK, and efficacy study of multiple intravenous administrations of isatuximab in patients with selected CD38+ hematological malignancies (NHL, CLL)	Phase 1: Up to 20 mg/kg Q2W or QW/Q2W	89[c]	Original	Completed Phase 1 CSR (DBL 09-Jan-2017)
		Phase 2 Stage 1: 3, 10 or 20 mg/kg QW/Q2W or Q2W/Q4W	97	Original	Completed P2S1 CSR (DBL 26-Apr-2017)
		Phase 2 Stage 2: 20 mg/kg QW/Q2W ((+/-dexamethasone)[d]	93	Original	Completed P2S2 interim CSR (cutoff: 15-Nov-2017)
			71	New[e]	Completed P2S2 final analysis (DBL 22-Aug-2019)
TED14095	Phase 1/2 multicenter study of isatuximab administered as a single agent in Japanese patients with RRMM	Phase 1: 10-20 mg/kg QW/Q2W	8	New	Completed CSR (cutoff: 10-Dec-2019)
		Phase 2: 20 mg/kg QW/Q2W	28	New	
TED14154	(Phase 1) Open-label, dose-escalation (Part A) and multicenter (Part B) study to evaluate the safety, PK, and efficacy of SAR650984 (isatuximab) in patients with RRMM	Part A: 10 or 20 mg/kg QW/Q2W	26	Original	Completed Part A CSR (DBL 06-Jul-2017)
		Part B: 20 mg/kg QW/Q2W	32	New	Completed Part B CSR (DBL 20-Dec-2018)
Other combination studies with isatuximab in multiple myeloma					
TCD11863	Phase 1b dose escalation and expansion study of isatuximab in combination with lenalidomide and dexamethasone (ILd) for the treatment of RRMM	3, 5, 10 or 20 mg/kg Q2W or QW/Q2W	57	Original	Completed CSR (cutoff 26-May-2016)
TCD13983 ICBd	Phase 1b dose escalation, expansion, safety, PK, and PD study of isatuximab administered intravenously in combination with bortezomib based regimens in adult patients with newly diagnosed MM non eligible for transplantation	ICBd Part: 10 or 20 mg/kg QW/Q2W	17	Original	Completed ICBd CSR (DBL 25-Sep-2017)
TCD14906	Phase 1/2 study to evaluate safety, PK, and efficacy of isatuximab in combination with cemiplimab in patients with RRMM (with at least 3 prior lines of therapy)	Phase 1: 10 mg/kg QW/Q2W	3	New	Completed interim CSR (cutoff 14-Feb-2020)
		Phase 2: 10 mg/kg QW/Q2W	105	New	
			Total: 1047		

MM = multiple myeloma; RRMM = relapsed and/or refractory multiple myeloma; CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin lymphoma; IKd = isatuximab/carfilzomib/dexamethasone; IPd = isatuximab/pomalidomide/dexamethasone; ILd = isatuximab/lenalidomide/ dexamethasone; ICBd = isatuximab/cyclophosphamide/bortezomib/dexamethasone; Q2W = bi-weekly throughput the treatments; QW/Q2W = weekly for the first cycle, and then bi-weekly after the first cycle; Q2W/Q4W = bi-weekly for the first cycle, then every 4 weeks after first cycle; PK = pharmacokinetics; PD = pharmacodynamics; PFS = progression-free survival; OS = overall survival.

a Safety population, IKd arm.

b The CSR presented only the safety results.

c 84 MM, 3 NHL, 2 CLL.

d Total 164 patients: 109 Isatuximab alone, 55 Isatuximab+dexamethasone.

e Included in the integrated safety database and SCS/ISS only (CSR not approved at the dossier cutoff date).

The safety population in All-Isa pool consisted of 1047 patients in total, all of whom received isatuximab treatment, either in combination with Kd (n=177) or with Pd (n=244), or as single-agent with or without dexamethasone (n=477), or in other combination therapies (not separately listed and discussed in this SCS). Of all 1047 patients in the All-Isa pool, 27.3% were still ongoing with study treatments at the cutoff date for this SCS (**Table 39**). In IKd group, 52.5% of the patients were still ongoing. The leading reason for definitive treatment discontinuation was progressive disease (56.0% overall, 29.4% in the IKd group). The incidence of definitive treatment discontinuation due to AEs was similar across the IKd, IPd,

Isa (+/-Dex), and All groups (8.5%, 7.4%, 6.7%, and 8.0%, respectively). Adverse event was the reason for all premature discontinuation of at least one study drug (isatuximab or other) reported so far. The category of " Other reason" for discontinuations was reviewed and found to be predominantly related to Investigators decision, patient decision/withdrawal of consent, or unconfirmed disease progression.

***Table 39** Disposition of patients - All-Isa pool - safety population*

n (%)	IKd (N=177)	IPd (N=244)	Isa (+/- Dex) (N=477)	All (N=1047)
Enrolled/Randomized and treated patients	177 (100)	244 (100)	477 (100)	1047 (100)
Ongoing treatment	93 (52.5)	106 (43.4)	50 (10.5)	286 (27.3)
Main reasons for definitive treatment discontinuation				
Adverse event	15 (8.5)	18 (7.4)	32 (6.7)	84 (8.0)
Progressive disease	52 (29.4)	99 (40.6)	352 (73.8)	586 (56.0)
Poor compliance to protocol	0	1 (0.4)	1 (0.2)	2 (0.2)
Withdrawal by subject	11 (6.2)	5 (2.0)	1 (0.2)	20 (1.9)
Other reason	6 (3.4)	15 (6.1)	41 (8.6)	69 (6.6)
Main reasons for premature treatment discontinuation of isatuximab				
Adverse event	1 (0.6)	4 (1.6)	0	5 (0.5)
Other reason	0	0	0	0
Main reasons for premature treatment discontinuation of dexamethasone				
Adverse event	11 (6.2)	2 (0.8)	3 (0.6)	21 (2.0)
Other reason	0	0	0	0
Main reasons for premature treatment discontinuation of carfilzomib				
Adverse event	26 (14.7)	-	-	26 (2.5)
Other reason	0	-	-	0

IKd: Isatuximab in combination with carfilzomib and low-dose dexamethasone; IPd: Isatuximab in combination with pomalidomide and dexamethasone; Isa: isatuximab; Dex: dexamethasone.

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

Definitive treatment discontinuation is defined as the discontinuation of all the study treatments (ie, discontinuation of all study treatments or the last ongoing study treatment), and premature treatment discontinuation is defined as the discontinuation of at least one of the study treatment and continuation of at least one study treatment.

PGM=PRODOPS/SAR650984/OVERALL/POOL_MM_SUB_2/REPORT/PGM/dis_dispo_s_t.sas
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Exposure

Of all 1047 patients in the All-Isa pool, 27.3% were still ongoing with study treatment at the cutoff date. The leading reason for definitive treatment discontinuation was progressive disease (56.0% overall, 29.4% in IKd group). The incidence of definitive treatment discontinuation due to AEs was similar across the IKd, IPd, Isa(+/-Dex), and All groups (8.5%, 7.4%, 6.7%, and 8.0%, respectively).

Overall, a total of 9273 isatuximab infusions were administered to the 1047 patients in the All-Isa pool. The median number of cycles started per patient was 7.0 and the median duration of isatuximab exposure was 26.14 weeks. The number of patients having at least 12 months, at least 18 months, and more than 24 months of isatuximab treatment was 288 (27.5%), 128 (12.2%), and 15 (1.4%), respectively. Comparing with the IPd group, the IKd group had greater isatuximab exposure with more cycles started (median number of cycles started: 19.0 versus 10.0), longer duration of exposure (median: 79.86 versus 41.00 weeks), and more patients having at least 12 and 18 months of isatuximab treatment (121 versus 67 for at least 12 months, 91 versus 7 for at least 18 months). The Isa(+/-Dex) group, in comparison to the IKd and IPd groups, had much less isatuximab exposure in median number of cycles started (median 4) and median duration of exposure (median: 15.71 weeks). The percentage of patients with at least 1 isatuximab infusion omitted or infusion interrupted was generally comparable between the IKd group and the IPd group.

TEAE

An overview of TEAEs in All-Isa pool is presented in Table 40. Treatment-related TEAEs (any grade) were reported in 78.6% of patients, Grade ≥3 TEAEs in 67.7% (36.6% treatment-related), serious TEAEs in 50.6% (18.2% treatment-related), TEAEs leading to definitive treatment discontinuation in 7.8%, and

TEAEs with fatal outcome during the treatment period in 73 (7.0%) patients (5 [0.5%] treatment-related). IRs (any IR, excluding symptoms) were reported in 44.3% (2.2% Grade ≥3).

Compared to the IPd group, the IKd group had notably lower (more than 5% lower) incidence in treatment-related TEAEs (86.4% versus 93.4%), any Grade ≥3 TEAEs (76.8% versus 84.4%), treatment-related Grade ≥3 TEAEs (49.2% versus 70.1%), AESIs (0.6% versus 20.5%), treatment-related serious TEAEs (24.9% versus 33.2%), and TEAEs with fatal outcomes (3.4% versus 9.0%) (Table 40).

Compared to the IKd and the IPd groups, the Isa(+/-Dex) group had lower incidence in treatment-related TEAEs (66.5%), Grade ≥3 TEAEs (54.5%), treatment-related Grade ≥3 TEAEs (13.0%), and treatment-related serious TEAEs (7.8%), but higher incidence in AESIs (44.0%). The higher incidence of AESIs was probably because in EFC14335 and EFC15246 only IRs of Grade ≥3 were considered AESIs.

Table 40 *Overview of treatment-emergent adverse events - All-Isa pool - safety population*

N(%)	IKd (N=177)	IPd (N=244)	Isa (+/- Dex) (N=477)	All (N=1047)
Patients with any TEAE (any grade)	172 (97.2)	243 (99.6)	453 (95.0)	1014 (96.8)
Patients with any treatment-related TEAE (any grade)	153 (86.4)	228 (93.4)	317 (66.5)	823 (78.6)
Patients with any TEAE of grade ≥ 3	136 (76.8)	206 (84.4)	260 (54.5)	709 (67.7)
Patients with any treatment-related TEAE of grade ≥ 3	87 (49.2)	171 (70.1)	62 (13.0)	383 (36.6)
Patients with any TEAE of grade 3-4	134 (75.7)	202 (82.8)	251 (52.6)	688 (65.7)
Patients with any AESI	1 (0.6)	50 (20.5)	210 (44.0)	332 (31.7)
Patients with any AESI of grade ≥ 3	1 (0.6)	13 (5.3)	11 (2.3)	33 (3.2)
Patients with any IR (excluding symptoms)	81 (45.8)	96 (39.3)	214 (44.9)	464 (44.3)
Patients with any IR of grade ≥ 3 (excluding symptoms)	1 (0.6)	5 (2.0)	11 (2.3)	23 (2.2)
Patients with any serious TEAE	105 (59.3)	147 (60.2)	203 (42.6)	530 (50.6)
Patients with any serious treatment-related TEAE	44 (24.9)	81 (33.2)	37 (7.8)	191 (18.2)
Patients with any TEAE with fatal outcome during the treatment period	6 (3.4)	22 (9.0)	31 (6.5)	73 (7.0)
Patients with any treatment-related TEAE with fatal outcome during the treatment period	1 (0.6)	1 (0.4)	2 (0.4)	5 (0.5)
Patients with any TEAE leading to definitive discontinuation	15 (8.5)	18 (7.4)	30 (6.3)	82 (7.8)
Patients with any TEAE leading to premature discontinuation of isatuximab	1 (0.6)	4 (1.6)	1 (0.2)	6 (0.6)
Patients with any TEAE leading to premature discontinuation of pomalidomide	-	9 (3.7)	-	9 (0.9)
Patients with any TEAE leading to premature discontinuation of dexamethasone	11 (6.2)	3 (1.2)	2 (0.4)	21 (2.0)
Patients with any TEAE leading to premature discontinuation of carfilzomib	26 (14.7)	-	-	26 (2.5)

IKd: Isatuximab in combination with carfilzomib and low-dose dexamethasone; IPd: Isatuximab in combination with pomalidomide and dexamethasone; Isa: isatuximab; Dex: dexamethasone.

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.

PGM=PRODOPS/SAR650984/OVERALL/POOL_MM_SUB_2/REPORT/PGM/ae_overview_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_p2_s_t_i.rtf (21JUL2020 8:11)

Most frequent TEAEs by SOC and PT

In all isatuximab treated patients, the most frequent SOCs with TEAEs (in ≥30% of patients) were Infections and infestations (67.7% of patients), General disorders and administration site conditions (56.8%), Injury, poisoning and procedural complications (54.5%), Gastrointestinal disorders (52.4%), Musculoskeletal and connective tissue disorders (52.0%), Respiratory, thoracic and mediastinal disorders (42.2%), Nervous system disorders (39.0%), and Blood and lymphatic system disorders (30.0%). The most frequent SOCs with Grade ≥3 TEAEs (≥10% of patients) were Infections and infestations (27.5% of patients), Blood and lymphatic system disorders (25.7%), and General disorders and administration site conditions (11.1%) (SCS Table 32). Compared to the IPd group, the IKd group had notably lower (≥10% lower) incidence of TEAEs in the SOCs of Blood and lymphatic system disorders (14.1% versus 59.0%,

primarily driven by high incidence of neutropenia in the IPd group), Musculoskeletal and connective tissue disorders (48.6% versus 63.1%), and Nervous system disorders (39.0% versus 50.4%). The IKd group had higher (≥10% higher) incidence of TEAEs in the SOCs of Vascular disorders (46.3% versus 17.2%, primarily driven by high incidence of hypertension in IKd group) and Injury, poisoning and procedural complications (62.7% versus 52.5%).

At the PT level, the most frequent TEAEs (in ≥15% of all isatuximab treated patients) were: infusion related reactions (44.3%), fatigue (27.7%), diarrhea (26.9%), upper respiratory infection (25.8%), nausea (18.5%), back pain (18.4%), cough (16.0%), neutropenia (15.9%), and pneumonia (15.4%). The most frequent Grade ≥3 TEAEs (≥5% of patients) were neutropenia (14.9%), pneumonia (11.5%), anemia (8.1%), and thrombocytopenia (7.1%), and hypertension (5.2%).

The notable TEAEs with higher incidences (≥5% higher) in the IKd and the IPd groups than in the single-agent Isa(+/-Dex) group (SCS Table 32) included: Upper respiratory tract infection (36.2% in IKd group and 33.2% in IPd group versus 18.0% in Isa(+/-Dex) group), diarrhea (36.2% and 29.1% versus 20.3%), pneumonia (23.7% and 22.1% versus 9.6%), bronchitis (22.6% and 18.0% versus 6.7%), insomnia (23.7% and 16.8% versus 9.0%), dyspnea (27.7% and 20.9% versus 7.8%), peripheral sensory neuropathy (14.1% and 11.5% versus 4.2%), muscle spasms (14.1% and 12.3% versus 3.1%), edema peripheral (13.0% and 13.5% versus 8.0%), fall (11.3% and 8.2% versus 3.1%).

The notable TEAEs with similar incidences between the IKd group and the Isa(+/-Dex) group but different (≥5% different) from the IPd group included:neutropenia (4.5% in IKd group and 4.4% in Isa(+/-Dex) group versus 48.8% in IPd group), febrile neutropenia (1.1% and 0.6% versus 7.4%), thrombocytopenia (2.8% and 6.3% versus 12.3%), infusion related reactions (44.6% and 45.5% versus 38.1%), urinary tract infection (6.8% and 5.0% versus 12.7%), dizziness (4.5% and 5.0% versus 10.7%), constipation (12.4% and 8.0% versus 22.1%).

For Grade ≥3 TEAEs, the IKd group had lower (more than 5%) incidence compared to the IPd group in neutropenia (4.0% versus 48.4%), thrombocytopenia (2.3% versus 11.1%), febrile neutropenia (1.1% versus 7.4%), and disease progression (0.6% versus 6.1%). The IKd group had higher incidence of Grade ≥3 hypertension (20.3% versus 2.5%). The higher incidence of hypertension in IKd group compared to the IPd group and the Isa(+/-Dex) group was related to the known side-effect of carfilzomib.

AEs by duration of exposure

- Patients with 24+ months treatment

As of the data cutoff for the pooled analysis, a total of 15 patients out of 1047 isatuximab treated patients had more than 24 months of isatuximab exposure, including 2 in the IKd group, 1 in the IPd group, and 8 in the Isa(+/-Dex) group. During the continued isatuximab treatment after the first 24 months, 8 (53.3%) of the 15 patients had additional TEAEs reported and 2 (13.3%) had Grade ≥3 TEAEs. No patients from the IKd and IPd groups had any post-24 months TEAEs.

Most of the post-24 months TEAEs occurred to no more than 1 patient, except for upper respiratory tract infection, back pain, and musculoskeletal chest pain, each with 2 patients. Grade ≥3 TEAEs after 24 months were reported in 2 patient in the group Isa(+/-Dex) (myelodysplastic syndrome and anemia in 1 patient and subarachnoid hemorrhage in another). The event of myelodysplastic syndrome was considered to be related to study treatment. The event of subarachnoid hemorrhage reported at Cycle 32 was Grade 5 and the patient died.

- Patients with 18+ months treatment

A total of 128 patients (out of 1047 all isatuximab treated patients) had more than 18 months of isatuximab exposure, including 91 in IKd group, 7 in the IPd group, and 18 in the Isa(+/-Dex) group.

Overall, majority of patients had TEAEs (any grade and Grade ≥3) during the first 18 months (68.8%) of isatuximab treatment and fewer patients had TEAEs after 18 months (14.1%). There were no particular TEAEs with markedly higher incidences after 18 months than during the first 18 months. Most of the post-18 months TEAEs occurred to no more than 1 patient, except 3 cases of pneumonia, 2 cases of anemia, 3 cases of dyspnoea and 2 cases of traumatic fracture.

- Patients with 12+ months treatment

A total of 288 patients (out of 1047 all isatuximab treated patients) had more than 12 months of isatuximab exposure, including 121 in the IKd group, 67 in the IPd group, and 71 in the Isa(+/-Dex) group. Overall, the majority of patients had TEAEs (any grade and Grade ≥3) during the first 12 months of isatuximab treatment and fewer patients had TEAEs after 12 months. There were no particular TEAEs with markedly higher incidences after 12 months than during the first 12 months. The most frequent TEAEs (in ≥5% of patients) occurring after 12 months of isatuximab treatment were upper respiratory tract infection (20.1%), diarrhoea (13.9%), fatigue (7.6%), bronchitis (7.3%), cough (6.9%), back pain (6.6%), arthralgia (6.3%), and (between 5 to 6%) pneumonia, insomnia, pain in extremity, dyspnea, nausea, vomiting, and nasopharyngitis. These TEAEs was also among the most frequent TEAEs with onset during ≤12 months of isatuximab treatment. The most frequent Grade ≥3 TEAEs (reported in 3 or more patients) with onset after 12 months of isatuximab treatment were pneumonia, hypertension, anemia, upper respiratory tract infection, neutropenia, urinary tract infection, insomnia, syncope, dyspnea, pathological fracture, traumatic fracture, and viral upper respiratory tract infection.

SAE

Serious TEAEs occurred to 50.6% of all isatuximab treated patients, with similar incidences between the IKd group (59.3%) and IPd group (60.2%) and lower incidence in Isa(+/-Dex) group (42.6%). The most frequent serious TEAE was pneumonia (11.5% overall, with similar incidence between the IKd and the IPd group), followed by disease progression (3.9% overall, with much lower incidence in IKd group [0.6%] than in IPd group [5.7%]). Treatment-related serious TEAEs were experienced by 191 (18.2%) patients overall (24.9% in the IKd group, 33.2% in the IPd group, and 7.8% in the Isa(+/-Dex) group). The most frequent treatment-related serious TEAE (any grade, in ≥1% of patients) was pneumonia (4.9%), followed by infusion related reaction (2.4%), febrile neutropenia (1.4%), and neutropenia (1.1%).

Deaths

Of the 1047 patients treated with isatuximab, 73 (7.0%) patients died during the treatment period (41 of 73 within 60 days from the first dose of study treatment) and 228 (21.8%) died during the post-treatment period. Disease progression was the predominant cause of death in the post-treatment period (178 of 228 deaths) while AEs and disease progression were comparable contributors to the deaths during the treatment period (37 of 73 due to disease progression and 32 of 73 due to AEs).

Compared to the IPd group and the Isa(+/-Dex) group, the IKd group had lower death rates during both treatment period (3.4% versus 9.0% and 6.5%) and post-treatment period (13.6% versus 18.4% and 28.3%), and lower death rate due to disease progression. Fatal TEAEs or Grade 5 post-treatment AEs (including disease progression AE) were reported in 95 (9.1%) patients combined (5.3.5.3 ISS Appendix 1 [Section 2.4.1.1]); of them, 91 were fatal TEAEs and 4 were Grade 5 post-treatment AEs Of the 91 patients with fatal TEAEs (5.3.5.3 ISS Appendix 1 [Section 2.4.1.1]), 45 (4.3%) were in the context of disease progression, with 1 (0.6%) patient from the IKd group compared to 14 (5.7%) from the IPd group and 23 (4.8%) from the Isa(+/-Dex) group. None of the fatal TEAEs in the context of disease progression were treatment-related. Of the 91 patients with fatal TEAEs, 46 (4.4%) were not in the context of disease progression (9 [5.1%] in the IKd group, 13 [5.3%] in IPd group, and 16 [3.4%] in the Isa(+/-Dex) group). The most frequent fatal TEAEs not in the context of disease progression were in the Infections and infestations SOC, with sepsis (7 patients) and pneumonia (6 patients) being the most

frequent, followed by acute kidney injury, sudden death, and death (each with 3 patients) and septic shock, atrial fibrillation, cardiac failure, and respiratory tract infection (each with 2 patients). Seven were treatment-related (all in the Infections and infestations SOC) with sepsis being the most frequent treatment-related fatal TEAE (3 patients).

Adverse events leading to treatment discontinuation or modification

Of all 1047 isatuximab treated patients, 82 (7.8%) patients experienced TEAEs leading to definitive treatment discontinuation, with infusion related reaction (18 [1.7%]) being the most frequent, followed by pneumonia (6 [0.6%]), sepsis (4 [0.4%]), and death and sudden death (3 [0.3%] each). Across the 3 subgroups, the incidence of TEAEs leading to definitive treatment discontinuation was slightly higher in the IKd group (8.5%) compared to the IPd group (7.4%) which in turn was slightly higher than the Isa(+/-Dex) group (6.3%). No patients in the IKd group had definitive treatment discontinuation due to infusion related reaction compared to 1 (0.4%) patient in the IPd group and 10 (2.1%) patients in the Isa(+/-Dex) group.

Premature discontinuations of isatuximab due to TEAEs were reported in 6 (0.6%) patients overall (1 [0.6%] in the IKd group, 4 [1.6%] in the IPd group, and 1 [0.2%] in Isa(+/-Dex) group) (5.3.5.3 ISS Appendix 1). Premature discontinuations of carfilzomib due to TEAEs were reported in 26 patients overall, applicable to the IKd group only (26 [14.7%]), with 13 patients due to TEAEs in the Cardiac disorders SOC. Premature discontinuations of dexamethasone due to TEAEs were reported in 21 (2.0%) patients overall, with 11 (6.2%) in the IKd group compared to 3 [1.2%] in the IPd group and 2 [0.4%] in the Isa(+/-Dex) group). There was no particular pattern in TEAEs leading to premature discontinuation of dexamethasone.

TEAEs leading to any dose modification of isatuximab were reported in 65.7% of patients overall (84.7% in the IKd group, 81.1% in the IPd group, and 49.1% in the Isa(+/-Dex) group). The most frequent TEAEs leading to any dose modification of isatuximab (in ≥5% of patients) were infusion related reaction (33.1%), neutropenia (10.9%), upper respiratory tract infection (9.6%), and pneumonia (8.6%).

Compared to the IPd group, the IKd group had notably lower (more than 5% lower) incidence of TEAEs leading to any isatuximab dose modifications in neutropenia (4.5% versus 33.6%); and notably higher incidence (more than 5% higher) in bronchitis (11.9% versus 5.7%) and respiratory tract infection (7.9% versus 1.2%). TEAEs leading to dose reduction (ie, dose omission) of isatuximab were reported in 23.9% of patients overall (53.1% in the IKd group, 48.4% in the IPd group, and 2.5% in the Isa(+/-Dex) group). The most frequent TEAEs leading to isatuximab dose omission were upper respiratory tract infection (4.9%), followed by pneumonia (3.4%), and neutropenia (3.2%). TEAEs leading to dose interruption of isatuximab were reported in 35.1% of patients overall (32.8% in the IKd group, 34.0% in the IPd group, and 34.2% in the Isa(+/-Dex) group). The single most frequent TEAE leading to isatuximab dose interruption was infusion related reaction (33.0%).

TEAEs leading to dose delay of isatuximab were reported in 40.1% of patients overall (57.6% in the IKd group, 57.0% in the IPd group, and 24.3% in the Isa(+/-Dex) group). The most frequent TEAEs leading to isatuximab dose delays (in ≥5% of patients) were neutropenia (8.9%), upper respiratory tract infection (6.7%), and pneumonia (6.0%).

2.5.1. Discussion on clinical safety

The main safety data for this application are provided by study EFC15246. As of the cut- off date (07 February 2020), the IKd arm had more patients still ongoing with study treatment than the Kd arm (52.0% versus 30.9%) and had fewer patients that definitively discontinued study treatments (46.9% versus 68.3%). The main reasons for definitive treatment discontinuation (in the randomised population) were disease progression (29.1% in the IKd arm versus 39.8% in the Kd arm) and AEs (8.4% versus 13.8%), with pneumonia, hypertension, neoplasm most frequently leading to a treatment discontinuation. In line with this, the overall extent of treatment exposure was greater in the IKd arm compared to the Kd arm, with longer duration of treatment and more cycles started per patient (median: 19.0 versus 14.5 cycles). The percentage of patients with at least 18 cycles of treatment was 57.6% in IKd arm versus 39.3% in the Kd arm. There is no exposure safety relation. The longer treatment duration on IKd was likely a reflection of prolonged disease control compared to Kd. AEs by duration of exposure of IKd was provided for < or > 12 months (n=121), < or > 18 months (n=91), < or > 24 months (n=2) which is considered sufficient for this application. Overall, the majority of patients had TEAEs (any grade and Grade ≥3) occurred during the first 12 months of isatuximab treatment and fewer patients had TEAEs after 12, 18 or 24 months. There were no particular TEAEs with markedly higher incidences after 12, 18 or 24 months of exposure.

Supportive safety data is provided from completed studies evaluating isatuximab in combination with pomalidomide dexamethasone (IPd) or dexamethasone (Id).

Almost all patients in either the IKd or KD arm experienced an treatment-emergent AE (95.9% vs 97.2%), most patients experienced an AEs grade ≥3 TEAEs and reported in a higher incidence in the IKd arm (76.8%) than in the Kd arm (67.2%). In the majority of patients with a grade≥3 TEAEs, AEs were judged as treatment related (treatment-related grade ≥3 TEAEs 47.5% IKd vs 49.2%Kd). Treatment emergent SAE were reported in app. 60% of the patients in both arms of which only 25% of patients has a treatment related SAE as judged by the investigator**.**

The most frequently reported all-grade TEAEs observed with higher incidence (≥10% higher) in the IKd arm than in the Kd arm included infusion related reaction (44.6% versus 3.3%), upper respiratory tract infection (36.2% versus 23.8%), and bronchitis (22.6% versus 12.3%). The exposure-adjusted incidences (events per patient-year) were similar between the IKd and Kd arms for all-grades TEAEs, Grade 5 TEAEs, and serious TEAEs. The IKd arm had higher exposure-adjusted incidence than the Kd arm for Grade ≥3 TEAEs (1.26 versus 1.05), but lower incidence for TEAEs leading to definitive treatment discontinuation (0.07 versus 0.13).

The most frequently reported serious TEAEs were in the SOC Infections and infestations, with highest incidence of PT pneumonia (18.1% in IKd arm versus 11.5% in Kd arms). Other TEAEs with an incidence of ≥4% included lower respiratory tract infection (4.0% versus 4.1%) and influenza (0.6% versus 4.1%). The most frequently reported Grade ≥3 TEAEs (at PT level; ≥10% of patients in either arm) reported were hypertension (20.3% in IKd arm and 19.7% in Kd arm), pneumonia (16.4%, 12.3%), thrombocytopenia (2.3%, 8.2%), insomnia (5.1%, 2.5%), and dyspnea (5.1%, 0.8%).

Overall, the IKd and Kd arms were balanced in the incidences of treatment-related TEAEs (86.4% versus 80.3% for all grades; 49.2% versus 47.5% for Grade ≥3) with as most frequent treatment-related Grade ≥3 TEAEs hypertension, pneumonia, and thrombocytopenia. The applicant provided details with respect to classification of AEs as treatment related as upper respiratory tract infection, diarrhoea, fatigue, dyspnoea, bronchitis, cough, and vomiting were not defined as treatment related but were reported ≥5% more frequent in IKd arm than in Kd arm. In order to avoid or minimise investigator bias in the context of an open label trial, the safety profile of IKd and Kd was presented in the EFC15246 CSR regardless to

study treatment and importantly the SmPC contains the relevant information and percentages of the ADR reported.

In study EFC15246, 30 [16.9%] patients in IKd arm and 25 [20.5%] patients in Kd arm had died during both treatment and post-treatment periods, mostly due to disease progression (18 [10.2%] in IKd arm and 19 [15.6%] in Kd arm). The majority of deaths (45 of 55) occurred during the posttreatment period. During the treatment period, AE was the cause of death for 5 patients (2.8%) in IKd and 4 (3.3%) patients in the Kd arm, during the posttreatment period 1 patient died due to an AE in the IKd arm. Fatal TEAEs (other than disease progression) in the IKd arm were pneumonia for 2 patients (atypical pneumonia (1 patient), pneumocystis jirovecii pneumonia (1 patient), cardiac failure for 2 patients, and acute kidney injury (1 patient), The AEs with fatal outcome regardless of the assessment are listed in Section 4.8 of the SmPC**.** Compared to other isatuximab combination regimens IKd had lower death rates during both treatment period (3.4% versus 9.0% IPd and 6.5% Id) and post-treatment period (13.6% versus 18.4% and 28.3%) despite a longer duration of exposure in IKd patients (median 80 weeks) compared to IPd patients (median 41.0 weeks) or single-agent Isa(+/-Dex) patients (median 15.7 weeks). In general the cause of death was similar to other I combination regimens, although numbers are too low to allow proper comparison.

Definitive treatment discontinuation was defined as discontinuation of all study medications or the last ongoing study drug. The incidence of patients with TEAEs leading to definitive treatment discontinuation was lower in the IKd arm (15 [8.5%]) than in the Kd arm (17 [13.9%]) with pneumonia as leading cause of discontinuation. More patients with IKd treatment had TEAE leading to premature Carfilzomib discontinuation (14.7% vs 0.8%), with cardiac disorders TEAEs as the main reason for premature carfilzomib discontinuation (7.3% in IKd arm) and premature dexamethasone discontinuation (6.2% IKd and 3.3.% Kd). Subjects in the IKd arm could continue with Id or I monotherapy and patients in the Kd arm would proceed to next line treatment. Among 26 (14.7%) patients who prematurely discontinued carfilzomib in IKd arm, 19 patients were still on study treatment (Id only) at the time of the interim analysis. The rate of discontinuation in the IKd patients appears in line with that observed in the pooled analysis for IPd (7.4%) and Id (6.5%). Dose delay of any drug due to TEAEs was reported more frequently in the IKd arm (59.9%) than in the Kd arm (45.1%), the most frequent TEAEs leading to dose delay of any drug was in the SOC of Infections and Infestations (with upper respiratory tract infection, bronchitis, and pneumonia being the most frequent).

Cardiotoxicity is a known toxicity reported with carfilzomib, the addition of isatuximab to Kd did not increase the incidence of TEAEs (both all grades and Grade ≥3) related to cardiotoxicity (23.7% versus 22.1% for all grades; 7.3% versus 7.4% for Grade ≥3). There were no definitive treatment discontinuation due to hypertension in the IKd arm, while 2 patients in Kd arm had hypertension leading to definitive treatment discontinuation.

Infusion reactions (IRs) of any grade occurred in 45.8% of the subjects in almost all cases on the infusion day during the first cycle. All IRs were reversible and Grade 1-2 except for 1 patient who developed a Grade 3 IR which led to premature discontinuation of ISA treatment. The IRs were managed with premedication and/or with temporary infusion interruption (see SmPC section 4.2).

Both isatuximab and carfilzomib can induce infusion associated reactions (IARs) or infusion reactions (IRs). Therefore, dexamethasone was to be administered prior to isatuximab and/or carfilzomib on the days of isatuximab and/or carfilzomib administration (see SmPC section 4.2, 4.4). Also, premedications and guidelines and medications to be administered to patients who developed IRs were provided in the protocol.

Isatuximab with Kd caused neutropenia (17.5% Grade 3 and 1.7% Grade 4; versus 6.6% grade 3 and 0.8% grade 4 for Kd) and increased the risk for infections such as pneumonia and other respiratory infections. Neutropenic complications were experienced by 5 (2.8%) patients overall, 2 (1.1%) with

febrile neutropenia and 3 (1.7%) with neutropenic infection (gastroenteritis, pneumonia, chronic sinusitis), all in IKd arm. The addition of isatuximab to Kd increased the incidence of respiratory infections, both all grades (83.1% versus 73.8%) and Grade ≥3 (32.2% versus 23.8%), mainly driven by higher incidence of upper respiratory infection and bronchitis. The high occurrence of respiratory infections was also found in the ICARIA registrational study (combination with Pomalidomide dexamethasone) and described in 4.4. and 4.8 of the SmPC with similar incidence. Most infections TEAEs (respiratory infections included) were reversible and manageable with supportive care (e.g. G-CSF) and dose delays, few resulted in definitive treatment discontinuation (2.8% of patients in IKd arm and 4.9% in Kd arm). Infections with fatal outcomes not in the context of disease progression occurred to 4 patients in IKd arm and 1 patient in Kd arm. The safety information in the SmPC sections 4.4 and 4.8 reflects the risk for infections, especially respiratory infections, and recommendations for management (including management of neutropaenia).

Second primary malignancies (SPMs) were reported more frequently in the IKd arm (13 subjects (7.3%) vs 6 (4.9%) in Kd arm), all SPMs were solid tumours and consisted mainly of skin cancers (9 subjects (5.1%) in IKd arm and 3 (2.5%) patients in Kd arm). The incidence of SPM for the combination IKd (7.3%) was higher than observed in the IPd (3.3%) or Id (2.9%) even though the population treated with IPd /Id was more heavily pre-treated. SPMs were skin cancers in 9 patients (5.1%) treated with Isa-Kd and in 3 patients (2.5%) treated with Kd, and were solid tumours other than skin cancer in 5 patients (2.8%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd. One patient (0.6%) in the Isa-Kd group and one patient (0.8%) in the Kd group had both skin cancer and solid tumours other than skin cancer (see SmPC sections 4.4 and 4.8). Patients with skin cancer continued treatment after resection of the skin cancer. Solid tumours other than skin cancer were diagnosed within 3 months after treatment initiation in 3 patients (1.7%) treated with Isa-Kd and in 2 patients (1.6%) treated with Kd.

Haemorrhages (all grades) were reported more frequently in the IKd arm (19.8%) than in the Kd arm (12.3%). The incidence of Grade 3 (4 [2.3%] in IKd arm and 1 [0.8%] in Kd arm) or 4 (1 patient in IKd arm) haemorrhages was low. There appeared to be no correlation between Grade 3-4 thrombocytopenia and haemorrhages.

More grade 3 adverse events with imbalanced laboratory values were reported in the IKd arm compared to Kd, e.g. grade 3 hyperglycemia (6.1% versus 2.9%), grade 3 hyponatremia (7.9% versus 4.1%), and grade 3 hypophosphatemia (9.7% versus 5.8%). More severe liver function abnormalities (grade 3) were reported in the IKd arm (4.0% ALT increased and 4.0% AST increased) then the Kd arm (2.5% for Grade 3 ALT increased, 0.8% AST increased). One patient in IKd arm experienced a transient Grade 4 ALT increase. The difference between IKd and Kd could not be explained by pre-existing baseline values and whether these AEs were transient was not presented. A relation between isatuximab and these specific laboratory abonormalities has not been found.

As expected, the incidence of Grade ≥3 AEs increased with age in both the IKd and Kd arms and incidence of serious TEAEs was higher in patients ≥65 years old. The pooled isatuximab safety analysis showed that there are no major differences across 3 age groups in SOCs of Grade ≥3 TEAEs (<65 years (N=461), 65 to 74 years (N=423), and ≥75 years (N=163)). In the SOCs of "Infections and infestations","Injury, poisoning and procedural complications", and "Cardiac disorders", the incidence of Grade ≥3 TEAEs was lower (~6% to 3% lower) in the <65 years age group than in the 65 to 74 years and ≥75 years age groups and a trend of decrease incidences in any IRs across the age groups was observed: 49.9%, 41.4%, 36.2% for any IRs in respective age groups. For lower respiratory infection AEs and respiratory infection AEs (during and post-treatment), the incidence was similar between the <65 years and 65 to 74 years age groups and was lower in the ≥75 years age group. Overall, although an increase in Grade ≥3 AEs was observed with increasing age, a similar TEAE profile was observed, and a similar increase in AEs was seen in the control arm, thus this does not raise concerns.

There were no clinically meaningful differences in the subgroup analyses for race, gender, ECOG PS, renal status, and hepatic status. A similar pattern was seen in the Kd arm and therefore no concerns were raised. In study EFC15246, a higher incidence of patients with Grade ≥3 TEAEs was observed in males in the IKd arm (not in females), but did not result in an increase in the incidence of patients with serious TEAEs, fatal TEAEs during study treatment, or TEAEs leading to definitive treatment discontinuation in the IKd arm compared to the Kd arm. Additionally, there were no marked differences between the two groups by prior lines of therapy in the incidences of TEAEs (any grades, Grade ≥3, by SOC and PT, Grade 5 with fatal outcome, serious, leading to treatment discontinuation, treatment-related) and the incidences of Other important AEs (IRs, lower respiratory and respiratory infections, neutropenia, and thrombocytopenia).

In summary, the described safety profile for isatuximab presents with as most frequent adverse reactions (>20%) neutropenia (46.7%), infusion reactions (38.2i%), pneumonia (30.9%), upper respiratory tract infection (28.3%), diarrhoea (25.7%) and bronchitis (23.7%). The most frequent serious adverse reactions are pneumonia (9.9%) and febrile neutropenia (6.6%). Warnings and precautions for use are presented for infusion reactions (38.2%), grade 3-4 neutropenia reported as laboratory abnormalities (84.9%), and neutropenic complications (30.3%), and a higher incidence of infections including grade ≥ 3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis.

Additional precautions are listed for the interference of ISA with serological testing (indirect antiglobulin test) and the interference with determination of complete response due to interference in the immunofixation assay.

2.5.2. Conclusions on clinical safety

Based on data from study EFC15246 (cut- off date: 07 February 2020) it is shown that toxicity increases when combining isatuximab with Kd therapy compared to Kd with an increase in Grade ≥3 TEAEs. The type of AEs are, in general, as expected based on the working mechanisms of the products used and consistent with that of the all-isatuximab treated patients pool with infusion related reactions (predominantly Grade 1-2), neutropenia, and (respiratory) infections as the most frequent TEAE. These risks are readily managed with routine interventions such as dose modifications of concomitant agents, use of growth factors, baseline blood typing, and use of antibiotics/antivirals.

Overall, the type of AEs are in line with the known toxicity of Kd backbone therapy and anti-CD38 therapy.

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. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 1.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable. RMP version 1.2 remains as the latest approved.

The CHMP endorsed this advice without changes. The CHMP endorsed the Risk Management Plan version

1.2 with the following content:

Safety concerns

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

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1-Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 -Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3-Required additional pharmacovigilance activities				
Non-interventional PASS survey to evaluate the effectiveness of the isatuximab educational materials, to minimise the risk of interference for blood typing (minor antigen) (positive Coombs' test) Planned	To assess the effectiveness of the isatuximab educational materials in term of implementation, knowledge and behaviour with respect to the key safety messages conveyed in the educational materials.	Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Protocol submitted to PRAC Protocol approval by PRAC Start of data collection (the EU PAS register: before data collection starts) End of data collection Final report of study results	December 2020 (based on EC decision in Jun2020) Estimated Q2 2021 Estimated Q3-Q4 2021 (within 6 months after PRAC approval or protocol) Estimated Q4 2022-Q1 2023 Estimated Q2-Q3 2023 (within 6 months after end of data collection)
A Phase 1b/2 study to evaluate the safety, pharmacokinetics, and preliminary	**Primary objectives:** ○ Phase 1: to characterise the	Interference for blood typing (minor antigen) (positive	Final report of study results	2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
efficacy of isatuximab (SAR650984) in patients awaiting kidney transplantation (Study TED16414) Ongoing (the current protocol has already implemented mandatory indirect coombs test data collection at screening and at C2D1. In this trial, patients are followed up until 6 months after the last isatuximab dose. A protocol amendment is planned to add blood samples collection up to 6 months after stopping treatment to confirm how long the interference will persist)	safety and tolerability of isatuximab in kidney transplant candidates. ○ Phase 2: to evaluate the efficacy of isatuximab in desensitisation of patients awaiting kidney transplantation. **Secondary objectives:** ○ Phase 2: to characterise the safety profile of isatuximab in kidney transplant candidates. ○ To characterise the PK profile of isatuximab in kidney transplant candidates. ○ To evaluate the immunogenicity of isatuximab. ○ To assess the overall efficacy of isatuximab in desensitisation of patients awaiting kidney transplantation.	indirect Coombs' test)		

C2D1: Cycle 2 Day 1; EC: European Commission; EU: European Union; PAS: Post-Authorisation Study; PASS: Post-Authorisation Safety Study; PK: Pharmacokinetic; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Interference for blood typing (positive indirect Coombs' test) sion haemolysis)	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.5. PL Section 2. **Legal status**: Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** • Non-interventional PASS survey to evaluate the effectiveness of the isatuximab educational

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
	Additional risk minimisation measures: Healthcare Professionals and blood banks educational material (including brochure and patient card).	materials, to minimise the risk of interference for blood typing (minor antigen) (positive indirect Coombs' test) . • Study TED16414
Viral reactivation	**Routine risk minimisation measures:** SmPC and PL: not labelled **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Specific adverse reaction follow-up questionnaire. **Additional pharmacovigilance activities:** None
Missing Information		
Not applicable		

HCP: Healthcare Professional; PAC: Patient Alert Card; PASS: Post-Authorisation Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The MAH took the opportunity to introduce minor changes in the SmPC sections 4.9, 6.3 and 6.6. Additionally, editorial changes have been also introduced to the Annex II key elements of the RMMs.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Slovenia and the Netherlands.

2.7.1. User consultation

A justification for not performing a 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:

- consultation with target patient groups for adult patients with multiple myeloma who have received at least two prior therapies was performed for the initial MAA.

- the updates to the Package Leaflet following the current EoI are minimal and will not affect its readability.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

Almost all patients with multiple myeloma (MM) who survive initial treatment will eventually relapse and require further therapy. The treatment landscape for patients with RRMM is rapidly changing following the recent approval of new treatment options. There are several regimens approved in EU as second line treatment in RRMM, but further improvement in prolonged disease control is still needed.

3.1.3. Main clinical studies

This application is based on the first interim analysis of the pivotal study (EFC15246), a randomised, open-label, multicenter study comparing the combination of isatuximab with carfilzomib and dexamethasone (IKd) versus carfilzomib and dexamethasone (Kd) in patients with relapsed and/or refractory multiple myeloma (RRMM). In this study 302 patients were included and randomly assigned to treatment with I (10 mg/kg QW/Q2W) added to the Kd backbone or Kd backbone alone in a 3:2 ratio, stratified according to number of prior lines (1 versus >1), and R-ISS (I or II versus III versus not classified). For all three products the dose and dose schedule are the same as for already authorised indications.

The target population consisted of MM patients with measurable disease with at least 1 but no more than 3 prior lines of therapy. Patients who had primary refractory disease, were refractory to prior anti-CD38 mAb, with free light chain (FLC) measurable disease only, or had prior carfilzomib treatment were excluded from the study. At the data cut off for this interim analysis 168 patients have discontinued study treatment (84 [46.9%] in the IKd arm and 84 [68.3%] in the Kd arm and treatment was ongoing for the remainder of the subjects.

3.2. Favourable effects

The study met its primary endpoint PFS: superiority of IKd over Kd was shown in the ITT with a HR of 0.531 (95% CI: 0.318 to 0.889), and a p value (1-sided stratified log rank test) of 0.0007. The robustness of this observation is supported by sensitivity analyses. The median PFS in the Kd arm of 19 months is consistent with the protocol assumption, and the increase in PFS in IKd arm (median not reached, HR <0.6) is considered clinically relevant. In the subgroup analysis for the primary endpoint also a positive effect of adding I to Kd backbone was also seen in most (prespecified) subgroups.

The treatment effect in secondary endpoints TTP and TTNT was consistent with the effect seen in PFS, and the charachterasion of the responses indicted that responses are deeper (increased VGPR+, VGRP+ + MRD negativity and CR rate) and more durable in the IKd arm versus the Kd arm (HR < 0.5 for DoR).

Based on the available data, no detriment is OS is noted, and PFS2 is indicative for benefit of treatment.

3.3. Uncertainties and limitations about favourable effects

Overall maturity of data is limited (34% of patients in primary analysis and 39% in the analysis recommend by of CHMP/27994/2008 Rev. 1), the median PFS and DoR are not reached for the experimental arm and there is a high degree of censoring after 18 month. So further confirmation of the treatment effect and in particular on the notion that also PFS2 is improved and that there is no detriment on OS is needed. The MAH will submit mature data when available.

As the curves for PFS seem to separate later, the benefit of adding I to Kd for those patient with rapid progression is not as evident. Subgroup analyses focussing on worst prognostic markers was not able to explain this apparent disproportional hazard, however subjects with cytogenetic abnormalities seem to benefit less from IKd than the overall population.

3.4. Unfavourable effects

- In study EFC15246 in 8.4% (IKd) vs 13.8% (Kd) of patients an AE led to treatment discontinuation. AEs that most frequently led to a treatment discontinuation were pneumonia, hypertension, neoplasm.

- Almost all patients in either IKd or KD arm experienced an treatment-emergent AE (95.9% vs 97.2%), most of these AEs were grade ≥3 TEAEs and reported in a higher incidence in the IKd arm (76.8%) than in the Kd arm (67.2%). The most frequently reported all-grade TEAEs observed with higher incidence (≥ 10% higher) in the IKd arm than in the Kd arm were infusion related reaction (44.6% versus 3.3%), upper respiratory tract infection (36.2% versus 23.8%), and bronchitis (22.6% versus 12.3%).

- The most frequently reported serious TEAEs were in the SOC Infections and infestations SOC, with PT pneumonia (18.1% in the IKd arm versus 11.5% in the Kd arms). The most frequently reported Grade ≥ 3 TEAEs (at PT level; ≥10% of patients in either arm) reported more often in the IKd arm were hypertension (20.3% in the IKd arm and 19.7% in the Kd arm), pneumonia (16.4%, 12.3%), thrombocytopenia (2.3%, 8.2%), insomnia (5.1%, 2.5%), and dyspnoea (5.1%, 0.8%).

- In study EFC15246, 30 [16.9%] patients in the IKd arm and 25 [20.5%] patients in the Kd arm had died during both treatment and post-treatment periods, during the treatment period an AE was the cause of death for 5 patients (2.8%) in the IKD and 4 (3.3%) patients in the Kd arm and during the post-treatment period 1 patient died due to an AE in the IKd arm. Compared to other isatuximab combination regimens, IKd had lower death rates with similar AEs leading to death, although numbers are too low to allow a proper comparison.

- Cardiotoxicity is a known toxicity reported with carfilzomib, the addition of isatuximab to Kd did not increase the incidence of TEAEs (both all grades and Grade ≥3) related to cardiotoxicity (23.7% versus 22.1% for all grades; 7.3% versus 7.4% for Grade ≥3).

- Reversible and low grade infusion reactions (IRs) of any grades occurred in 45.8% of the subjects in almost all cases on the infusion day during the first cycle. The IRs were managed with premedication as stated in the SmPC and/or with temporary infusion interruption.

- Isatuximab with Kd caused neutropenia (with 17.5% Grade 3 and 1.7% Grade 4) and increased infections such as pneumonia and other respiratory infections. Neutropenic complications were observed and the addition of isatuximab to Kd increased the incidence of respiratory infections (all grades (83.1%) and Grade ≥3 (32.2%), mainly driven by higher incidence of upper respiratory infection and bronchitis. Most infections TEAEs (respiratory infections included) were reversible and manageable with supportive care (prophylaxis or curative) and few resulted in definitive treatment discontinuation (2.8% of patients

in IKd arm and 4.9% in Kd arm), no patients had definitive treatment discontinuation due to neutropenia or neutropenic complication. The high occurrence of severe respiratory infections was also found in the ICARIA registrational study (combination with Pomalidomide dexamethasone). The safety information in the SmPC reflects the risk for infections, especially respiratory infections, and recommendations for management (including management of neutropaenia).

- Second primary malignancies (SPMs) were reported more frequently in the IKd arm (13 subjects (7.3%) vs 6 (4.9%) in Kd arm), all SPMs were solid tumours and consisted mainly of skin cancers. The incidence of SPM for the combination IKd was higher than observed in the IPd (3.3%) or Id (2.9%).

- Haemorrhages (all grades) were reported more frequently in the IKd arm (19.8%) than in the Kd arm (12.3%). The incidence of Grade 3 (4 [2.3%] in the IKd arm and 1 [0.8%] in the Kd arm) or 4 (1 patient in IKd arm) haemorrhages was low. There appeared to be no correlation between Grade 3-4 thrombocytopenia and haemorrhages.

- There were no patients in the immunogenicity population (168 evaluable patients treated with IKd) were ADA-positive, either pre-existing or during the treatment.

- Within the IKd arm, the safety profile showed some differences in subgroups. The incidence of Grade ≥3 AEs increased with age with an higher incidence of serious TEAEs in patients ≥65 years old. A similar TEAE profile was observed, moreover as a similar increase in AEs was seen in the control arm, this does not raise concerns. There were no marked differences between the two groups by prior lines of therapy.

3.5. Uncertainties and limitations about unfavourable effects

- Second primary malignancies (SPMs) were reported more frequently (7.3%) than previously reported for IPd and Id combination regimens and higher than expected from the background incidence of SPMs in MM treated patients (between 1.7% and 6.6%). Long term safety including SPMs will be further monitored through routine Pharmacovigilance and PSUR reporting.

3.6. Effects Table

Effects Table for Sarclisa in combination with carfilzomib and dexamethasone versus carfilzomib and dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Progression free survival Median At 1 year At 2 years	 Months % %	 NC 81 69	 19 70 46		CSR Ikema (EFC15246)
	PFS (PEP definition)		HR 0.531 (95% CI 0.318-0.889)		p=0.0007	
	PFS (EMA guidance)		HR 0.5725 (95%CI 0.354-		p=0.0012	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence		References
			0.925)		- Supported by secondary time to event endpoints (TTNT,TTP DoR) and most subgroup analyses - Non-proportional hazard suggest less benefit in subjects with early progression - High level of censoring provides uncertainty of treatment effect beyond 18 months - Data is immature (< 35% of events), median PFS is not reached in active arm		
ORR	Proportion of subjects with PR, VGPR, CR CRs	%	87	83	Non statistically different		CSR
VGPR+	Proportion of subjects with VGPR or better	%	73	56	Stratified odds ratio 2.185, statistically different Nominal p value = 0.0011		CSR
VGPR+ and MRD neg	Proportion of subjects with VGPR+ who are MRD negative	%	30	13	Stratified odds ratio 2.812, statistically different Nominal p value = 0.001		CSR
CR	Proportion of subjects with CR and stringent CR	%	40	28	Stratified odds ratio 1.792, statistically different Nominal p value =0.0004		CSR
Unfavourable Effects							
Grade ⩾3 AEs	treatment-emergent Grade ⩾3 AEs	%	76.8	67.2	most frequently reported Grade ⩾3 TEAEs (at PT level; ⩾10% of patients in either arm) reported more often in the IKd arm were hypertension (20.3% in the IKd arm and 19.7% in the Kd arm), pneumonia (16.4%, 12.3%), thrombocytopenia (2.3%, 8.2%), insomnia (5.1%, 2.5%), and dyspnoea (5.1%, 0.8%).		CSR
SAEs	treatment-emergent SAEs	%	59.3	57.4	The most frequently reported serious TEAEs (in ≥5% of patients in either treatment group) by primary SOC were: Infections and infestations (37.9% in IKd arm and 30.3% in Kd arm), Cardiac disorders (7.3%, 4.9%), Injury, poisoning and procedural complications		CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence		References
					(6.2%,3.3%), Musculoskeletal and connective tissue disorders (5.6%, 4.9%), and Vascular disorders (2.8%, 6.6%).		

Abbreviations:AE=adverse event, SAE= serious adverse event, CSR= clinical study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results from the pivotal study show a statistically significant and a clinically relevant improvement of PFS in MM patients who have had min 1 and maximal 3 prior lines of therapy are treated with IKd instead of Kd (PFS according to definition PEP: HR 0.531 (95% CI 0.318-0.889), p=0.0007, according to EMA guidance) HR 0.5725 (95%CI 0.354-0.925, p=0.0012, median PFS not-reached vs 19 months). The observed effect size is considered robust in the sense that it is largely independent of the reason for censoring and event or stratification rules. The improvement in PFS is seen across all subgroups tested. However the non-proportional hazard in the PFS curve suggests that the net effect of the addition to a Kd backbone may be less for subjects with early progression (i.e. within 6-9 months after start of treatment), and for those with good prognosis treatment effect cannot accurately be determined due to the high level of censoring after 18 months.

The treatment effect is supported by secondary endpoints indicating a deeper and longer response in patients treated with IKd when compared to Kd. Based on the available data, no detriment is noted in OS and also PFS2 indicates a beneficial effect of the IKd combination.

Overall, although confirmation on the treatment effect is requested as data is immature, the efficacy of treatment seems established, and the IKd combination seems a valuable addition to the treatment options for MM patients with measurable MM who have received at least 1 prior line of treatment.

The addition of I to a Kd backbone results in increased toxicity as is evident from a higher incidence of Grade ≥3 TEAEs compared to Kd treatment. However, this did not result in an increase in SAEs, fatal events during study treatment, or definitive treatment discontinuation due to a TEAE. Apparently, the increased toxicity can be managed with interventions such as dose modifications of concomitant agents, use of growth factors, baseline blood typing, and use of antibiotics/antivirals.

The type of AEs are in general as expected based on the working mechanisms of the drugs and consistent with that of the all-isatuximab treated patients pool with infusion related reactions (predominantly Grade 1-2), neutropenia, and (respiratory) infections as the most common AEs. As already described, isatuximab interferes with serological testing (introducing possible false positive reactions in indirect antiglobulin tests, antibody detection tests, antibody identification panels, and antihuman globulin (AHG) crossmatches) and also interferes with Serum Protein Electrophoresis and Immunofixation Tests (interfering with accurate response classification based on International Myeloma Working Group (IMWG) due to the detection of isatuximab). These interferences are described in the SmPC and educational material.

3.7.2. Balance of benefits and risks

The efficacy of isatuximab in combination with carfilzomib and dexamethasone in the target population is considered clinically relevant. The safety profile is consistent with that known of isatuximab and the background therapy. As the added toxicity of I to a Kd backgound is maneagable and given the substantial improvement in PFS the benefits are considered to outweigh the combined risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Sarclisa for the target population is positive, and this variation is approvable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, 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 approved one	Type II	I, II and IIIB

An Extension of indication for Sarclisa to add combination with carfilzomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. As a consequence the sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 have been updated. The PL is updated accordingly. The MAH took the opportunity to introduce minor changes in the SmPC sections 4.9, 6.3 and 6.6 and update the details of local representatives. Editorial changes have been also introduced to the Annex II key elements of the RMMs. The RMP version 1.2 has been updated.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sarclisa is not similar to Blenrep, Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro 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-0003'