26 March 2020
EMA/CHMP/200978/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sarclisa

International non-proprietary name: isatuximab

Procedure No. EMEA/H/C/004977/0000

Note

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

Administrative information

Name of the medicinal product:	Sarclisa
Applicant:	sanofi-aventis groupe 54 rue La Boetie 75008 Paris France
Active substance:	Isatuximab
International Non-proprietary Name/Common Name:	Isatuximab
Pharmaco-therapeutic group (ATC Code):	monoclonal antibodies, (L01XC38)
Therapeutic indication(s):	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.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	20 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial and 3 vials

Table of contents

List of abbreviations

ADA:	anti-drug antibodies
AE:	adverse event
ALT:	alanine amino transferase
ASCT:	autologous stem cell transplant
AST:	aspartate amino transferase
AT:	all-treated
$AUC_{0\text{-}24h}$:	area under the curve over the 24 hour dosing interval
AUC_{1week}:	cumulative AUC over 2 weeks
AUC_{2weeks}:	cumulative AUC over 1 week
AUC_{4weeks}:	cumulative AUC over 4 weeks
AUC_{last}:	area under the curve up to the last measurable concentration
BCC:	basal cell carcinoma
BOR:	best overall response
CA:	chromosomal abnormality
CD38:	cluster of differentiation 38
CI:	confidence interval
CL:	clearance
CLB:	competitive ligand binding
C_{max}:	maximum plasma concentration
$C_{max,c1d1}$:	maximum concentration after the first administration (Cycle 1 Day 1)
$C_{post\text{-}infusion,max}$:	maximum concentration over time
CR:	complete response
CrCl:	creatinine clearance
CRenal:	complete renal response
CSR:	clinical study report
CT1W:	C_{trough} at 1 week
CT2W:	C_{trough} at 2 weeks
CT4W:	C_{trough} at 4 weeks
C_{trough}:	predose concentration during repeated dosing
DDI:	drug-drug interaction
Dex:	dexamethasone
DOR:	duration of response
ECOG:	Eastern Cooperative Oncology Group
e-GFR:	estimated Glomerular Filtration Rate
EOT:	end of treatment
E R:	exposure-response
FcGR:	Fc fragment of IgG Receptor
FcRn	The Fc fragment of IgG receptor and transporter
G-CSF:	granulocyte colony stimulating factor
GOF:	goodness-of-fit
HRQL:	health-related quality of life
IBLd:	isatuximab in combination with bortezomib, lenalidomide, and dexamethasone
ICBd:	isatuximab in combination with bortezomib, cyclophosphamide, and dexamethasone
IFE:	immunofixation electrophoresis
IgG1:	immunoglobulin G1
ILd:	isatuximab in combination with lenalidomide and dexamethasone
IMiDs:	immunomodulatory drugs
IMWG:	international myeloma working group

IPd:	isatuximab in combination with pomalidomide/dexamethasone
IRC:	independent response committee
IRs:	infusion reactions
ISR:	incurred sample reanalysis
ISS:	international staging system
Km:	Michaelis-Menten rate constant
LC-HRMS:	liquid chromatography high resolution mass spectrometry
Ld:	lenalidomide and dexamethasone
LLOQ:	lower limit of quantitation
MDS:	myelodysplastic syndrome
MM:	multiple myeloma
MOFV:	minimum objective function value
MR:	minimal response
MRD:	minimal residual disease
MRenal:	minor renal response
MTD:	maximum tolerated dose
NCA:	non-compartmental analysis
NDMM:	newly diagnosed multiple myeloma
NK:	natural killer
OF:	objective function
ORR:	overall response rate
OS:	overall survival
P1F1:	cell line 1, process 1, formulation 1
P2F2:	cell line 1, process 2, formulation 2
PC:	performance control
Pd:	pomalidomide and dexamethasone
PD:	progressive disease, pharmacodynamic
PEG:	polyethylene glycol
PFS:	progression-free survival
PI:	proteasome inhibitor
PK:	pharmacokinetic
PR:	partial response
PS:	performance status
Q:	inter-compartment distribution clearance
Q2W:	every 2 weeks
Q4W:	every 4 weeks
QTcF:	corrected QT interval by Fredericia
QW/Q2W:	once weekly for the first cycle (28 days; 4 once-weekly administrations) and every 2 weeks thereafter
RD:	receptor density
R ISS:	revised-ISS
RO:	receptor occupancy
RRMM:	relapsed or refractory multiple myeloma
SAE	serious adverse event
SAEM:	stochastic approximation expectation maximization
SCP:	screening cut point
SD:	standard deviation
SPEP:	serum M protein electrophoresis
TCRβ:	T cell receptor beta chain
TD:	time dependency

TEAE:	treatment-emergent adverse event
t_{max}:	time to reach the maximal concentration
TMDD:	target mediated drug disposition
ULN:	upper limit of normal
V_1:	distribution volume of the central compartment in the popPK model
V_2:	distribution volume of the peripheral compartment in the popPK model
V_{max}:	maximum rate of clearance
VGPR:	very good partial response
VPC:	visual predictive checks

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 30 April 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Sarclisa, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2018.

Sarclisa was designated as an orphan medicinal product EU/3/14/1268 on 29 April 2014 in the following condition: Treatment of plasma cell myeloma.

The applicant applied for the following indication: Sarclisa is indicated, in combination with pomalidomide and dexamethasone, for the treatment of patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI).

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 14 May 2020 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Sarclisa.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 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

Similarity

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

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance isatuximab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received Protocol assistance from the CHMP on the development for the indication from the CHMP on 22 January 2015 (EMEA/H/SA/2998/1/2014/PA/III), 13 October 2016 (EMEA/H/SA/2998/1/FU/1/2016/PA/II) and 22 June 2017 (EMEA/H/SA/2998/1/FU/2/2017/PA/II). The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- the proposed analytical comparability plan to characterize the material to use in Phase 2 and 3 clinical studies and the bridging strategy,
- the use of PandA instead of the ELISAtest, to monitor ADAs in clinical studies to support registration and future clinical studies,
- the acceptability of the non-clinical package prior to initiation of Phase 3 clinical studies and for MA,
- the clinical efficacy, safety, and PK/PD data to initiate study EFC14335,
- the adequacy of study EFC14335, in particular the comparator and primary endpoint hazard ratios, as well as the safety database, to support MA,
- the demonstration of non-similarity of isatuximab versus daratumumab, based on (i) the different molecular structure features, in particular paratopes and target binding epitopes, and (ii) the different mechanism of action features, in particular pro-apoptotic activity and inhibition of Cd38 enzymatic activity.

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: Alexandre Moreau

The application was received by the EMA on	30 April 2019
The procedure started on	23 May 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	27 August 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2019
The applicant submitted the responses to the CHMP consolidated List of	10 October 2019

Questions on	
A routine GCP inspection at the sponsor site in the US and two investigator sites, one in Taiwan and one in Greece, between 10 October 2019 and 21 November 2019 took place. The outcome of the inspection carried out was issued on	20 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 February 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	02 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 March 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sarclisa on	26 March 2020
The CHMP adopted a report on similarity of Sarclisa with Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro on	26 March 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple myeloma (MM) is a haematological malignancy resulting from the uncontrolled proliferation of monoclonal plasma cells, which leads to production of monoclonal immunoglobulin (known as M-protein) with substantial immunosuppression and end-organ damage. The proposed target indication of isatuximab is in a later line of therapy in refractory / relapsed multiple myeloma in patients who received at least two prior regimens, including lenalidomide and a proteasome inhibitor (PI).

2.1.2. Epidemiology

Multiple myeloma (MM) is a rare disease that 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.

2.1.3. Biologic features, aetiology and pathogenesis

Multiple myeloma is characterized by marrow plasmacytomas (plasma cell tumours) and overproduction of monoclonal immunoglobulins (IgG, IgA, IgD or IgE) or Bence-Jones protein (monoclonal K or h light chains), while the production of normal immunoglobulin is impaired.

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.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Multiple myeloma is associated with significant disease burden for patients. Patients with MM experience a variety of disease-related events and symptoms, including renal failure, anaemia, fatigue, exertional dyspnoea, bone destruction leading to pain, fractures, and immunodeficiency/recurrent infections. A deterioration in quality of life is particularly marked in elderly frail patients, who represent approximately 30% of patients with MM (Rosko A et al. 2017).

The most common criteria used in diagnosis of symptomatic MM are the presence of ≥10% clonal Bone Marrow plasma cells or biopsy proven bone 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.

The course of MM is highly variable, and the clinical behaviour is heterogeneous. In general, the disease is characterised by a chronic phase lasting several years, and an aggressive terminal phase (Moreau P. et al., 2017).

The International Staging System (ISS) relies on the combination of the level of serum ß2-microglobulin and albumin in 3 different stages. ISS 3 is associated with the poorest outcome. 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 (Moreau P. et al. 2017).

2.1.5. Management

Treatment should be initiated in patients with active myeloma fulfilling the CRAB criteria, i.e. hypercalcaemia (>11.0 mg/dl), renal failure (creatinine >2.0 mg/ml),aAnaemia (Hb <10 g/dl), and active bone lesions. Other indications for treatment include symptomatic hyperviscosity, recurrent bacterial infections, and amyloidosis with organ involvement.

First line treatment options contain at least one of the novel therapies, i.e. proteasome inhibitors and/or immunostimulatory 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 therapy options have increased and outcome has improved in the last decade, most patients with MM will ultimately relapse. Second and later remissions can be achieved with further therapy, however myeloma typically reappears more aggressively after each relapse, leading to decreased duration of response and culminating in treatment-refractory disease with short survival times.

Relapsed and/or refractory patients typically receive salvage therapy; if possible, this could include a (2nd) autologous or allogeneic hematopoietic stem cell transplantation until relapse or toxicity appear and then proceeding to the next salvage option. In this setting, bortezomib- and lenalidomide-based regimens are the most commonly used in combination with corticosteroids, to which sometimes also an alkylating agent or an anthracycline is added. With the introduction of these newer therapies in recent times, median survival has been reported to improve further to 45 to 60 months from the diagnosis of the disease. Despite improvement in Progression Free Survival and Overall Survival for patients with early relapsed MM with these agents, 40-60% of patients do not respond to therapy and nearly all relapse after one of these regimens.

The treatment landscape for patients with Relapsed Refractory MM is rapidly changing following the recent approval of three drugs belonging to two novel classes of agents: the histone deacetylase (HDAC) inhibitor panobinostat (Farydak), and two monoclonal antibodies, daratumumab (Darzalex) and elotuzumab (Empliciti). Furthermore, the addition of the second-generation IMiDs, lenalidomide (Revlimid) and pomalidomide (Imnovid) and the second-generation PIs carfilzomib (Kyprolis) and ixazomib (Ninlaro) provides additional within-class treatment options for patients with R/R MM.

Carfilzomib, elotuzumab, ixazomib and daratumumab have been approved in different combinations for patients with at least one prior line of therapy.

In the very advanced stage of disease (third line setting and beyond) where isatuximab is proposed, pomalidomide, daratumumab and panobinostat have been approved:

- Pomalidomide, the third-in-class IMiD, in combination with low-dose dexamethasone, has been approved in patients who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and whose disease progressed after treatment with these medicines.

- Daratumumab monotherapy has been approved for the treatment of adults with relapsed/refractory MM whose previous treatment included a proteasome inhibitor and an immunomodulatory agent and whose disease worsened after treatment.

- Panobinostat has been also approved in combination with bortezomib and dexamethasone for patients with relapsed and/or refractory multiple myeloma who have received at least two prior

regimens including bortezomib and an immunomodulatory agent. Panobinostat in combination with bortezomib and dexamethasone is associated with a significant toxicity and is not a recommended treatment option in the ESMO clinical practice guideline.

An extension of indication was approved in 2019 for elotuzumab in combination with pomalidomide and low-dose dexamethasone (EPd) for the treatment of patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor (PI), and have demonstrated disease progression on the last therapy.

The choice of therapy in the relapsed 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 the case of biochemical relapse, treatment can be delayed).

About the product

Isatuximab is an immunoglobulin G1 (IgG1) monoclonal antibody that binds to the human cell surface antigen molecule classified as cluster of differentiation 38 (CD38).

CD38 is a transmembrane glycoprotein with ectoenzymatic activity, expressed in haematological malignancies and is highly and uniformly expressed on multiple myeloma cells. Isatuximab acts through IgG Fc-dependent mechanisms including: antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Isatuximab can also trigger tumour cell death by induction of apoptosis via an Fc-independent mechanism (SmPC section 5.1).

In human peripheral blood mononuclear cells (PBMCs), natural killer (NK) cells express the highest CD38 levels. In vitro, isatuximab can activate NK cells in the absence of CD38 positive target tumour cells through a mechanism which is dependent of the Fc portion of isatuximab. Also, isatuximab inhibits Tregs which express higher levels of CD38 in MM patients compared to healthy individuals.

Isatuximab exhibits multiple tumour targeting and immunomodulatory effects that may contribute to a clinical effect in controlling tumour growth of multiple myeloma.

Isatuximab blocks the enzymatic activity of CD38, which catalyzes the synthesis and hydrolysis of cyclic ADP-ribose, a calcium mobilizing agent, and this may contribute to immunoregulatory functions. Isatuximab inhibits the cADPR production from extracellular NAD in multiple myeloma cells.

The combination of isatuximab and pomalidomide in the treatment of multiple myeloma is supported by non-clinical experiments. In vitro, the combination enhances cell lysis of CD38 expressing multiple myeloma cells by effector cells (ADCC), and by direct tumour cell killing compared to that of isatuximab alone. In vivo experiments using a human multiple myeloma xenograft model demonstrated that the combination of isatuximab and pomalidomide results in enhanced antitumor activity compared to the activity of isatuximab and pomalidomide alone.

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.

The proposed posology is 10 mg/kg IV in combination with pomalidomide and dexamethasone once weekly for the first 4 weeks (one cycle), followed by every 2 weeks for the following cycles.

In the clinical studies, isatuximab was administered up to a dose of 20 mg/kg, either once weekly, every 2 weeks, every two weeks for 8 weeks followed by every 4 weeks, or every week for 4 weeks followed by every 2 weeks (the latter being the proposed posology, applied in Phase 3 Study EFC14335).

2.2. Quality aspects

2.2.1. Introduction

Sarclisa is presented as a concentrate for solution for infusion containing 20 mg/mL of isatuximab as active substance and supplied in vials in two presentations: 100 mg/5 mL and 500 mg/25 mL.

Other ingredients are: histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80 and water for injections (WFI).

2.2.2. Active Substance

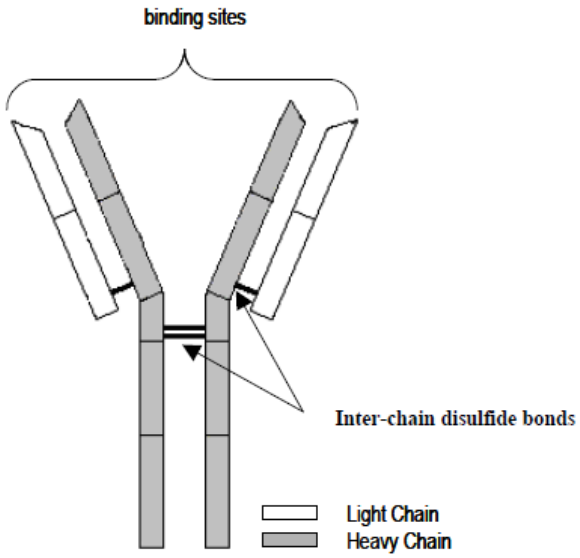
General information

Isatuximab is a chimeric immunoglobulin IgG (IgG1) derived-monoclonal antibody (mAb) expressed in a Chinese hamster ovary (CHO) cell line. Isatuximab binds to a specific extracellular epitope of cluster of differentiation 38 (CD38) receptor and triggers several mechanisms leading to the death of CD38 expressing tumour cells.

The protein structure (Figure 1) is composed of two kappa light chains each with molecular weight of approximately 23 kDa and two IgG1 heavy chains, each with a molecular weight of approximately 49 kDa (deglycosylated form) linked through disulfide bridges.

Each light chain consists of 214 amino acid residues and each heavy chain consists of 450 amino acid residues. The heavy chain N-terminal glutamine residue is fully converted to pyroglutamate. The majority of the heavy chain C-terminal K450 is clipped (between 9 and 11 % of C-terminal K450 using reduced peptide mapping). Isatuximab contains 32 cysteines leading to 16 disulfide bonds and two glycosylation sites located on Asparagine N300 of heavy chain.

Figure 1 - General representation of isatuximab.



Manufacture, process controls and characterisation

Manufacturer(s)

The manufacturers and contract laboratories have been described to perform manufacturing, storage and control of isatuximab formulated drug substance (FDS) and the information provided is found acceptable.

Description of manufacturing process and process controls

FDS materials for the phase 2 and phase 3 clinical trials, as well as the Process Performance Qualification (PPQ) runs, represents the commercial manufacturing process.

The active substance manufacturing process begins with working cell bank (WCB) thawing, cell culture and harvest of CHO cells. The process includes steps for expanding the culture in shake flasks and wave bags followed by expansion bioreactors to inoculate the 10,000L production bioreactor, produce and eventually harvest the isatuximab antibody. The purification of isatuximab is thereafter achieved through a series of chromatographic, filtration and viral inactivation steps. The sequence of purification steps is designed to remove process and product-related impurities, efficiently capture isatuximab protein, concentrate and exchange the drug substance into the final buffering system.

The manufacturing process has been adequately described and justified with a sufficient level of details included covering also in-process controls and process parameters for each process step. The validated process hold times (maximum time limits for production) have been provided for the isatuximab FDS manufacturing process. This is found acceptable.

Control of materials

All materials have been listed and specifications for non-compendial materials have been provided. No material of biological origin, except the CHO production cell line, was used in the manufacturing process.

The Chinese hamster ovary (CHO) host cell line used for expression of isatuximab is a serum-free suspension cell line. The cell line development and cell banking have also been described in enough detail.

Characterisation of master cell bank (MCB), working cell bank (WCB) and cells at the limit of *in vitro* cell age (LIVCA) has been performed in compliance with ICH Q5A and ICH Q5D. Sterility, mycoplasma testing, isoenzyme analysis, control of HC- and LC-chain gene sequences and flanking regions as well as viral testing were performed. The acceptance criteria were met, showing that the cell banks are of hamster origin with the correct gene sequences, sterile and free of detectable mycoplasma and viruses, except for retrovirus like particles, as expected for CHO cells. A protocol containing detailed acceptance criteria for creation of potential future WCB has also been provided. This protocol is found acceptable. In addition, acceptable data confirming genetic stability of the production cell lines have been provided.

Control of critical steps and intermediates

In-process controls (critical or noncritical IPCs) and process parameters (CPPs or non-CPPs) have been defined and summarized for each process step in the manufacturing of isatuximab active substance.

The rationale for the classification and justification of acceptable ranges for the in-process controls and process parameters have been detailed and acceptably justified. Both in-process controls (critical and

non-critical IPCs) and process parameters (CPPs or non-CPPs) are included in this section of the dossier. It should be noted that any future change of both critical and non-critical IPCs and CPPs or non-CPPs should be handled by a variation application.

Acceptance criteria and action limits for the IPCs have been defined based on manufacturing experience and prior knowledge. Safety related IPCs have been established for the process steps of cell culture, harvest, purification, and formulation. These IPCs include bioburden and bacterial endotoxin as well as mycoplasma and virus detection. In addition to the IPCs, specifications are established for active substance lot release for both bioburden and bacterial endotoxins.

The information given in the section on Control of critical steps and intermediates is found acceptable.

Process validation and/or evaluation

The commercial manufacturing process for isatuximab FDS has been validated by demonstrating that the process met pre-defined acceptance criteria for performance when run within defined process parameters. The process validation and evaluation data are comprehensive and in support for a consistent performance of the manufacturing process. Acceptable ranges for the process parameters and quality attributes selected for evaluation of the process as well as the rationale for selection of critical quality attributes (CQAs) and CPPs have been provided.

The validation and evaluation were performed on several Process performance qualification (PPQ) batches. The results for both critical and non-critical process parameters and quality attributes were provided and summarized per manufacturing step for the four PPQ batches. The PPQ batches met all specification acceptance criteria and demonstrated a consistent clearance of product and process related impurities. Process validation PPQ batches were run at commercial scale but some validation aspects were run at reduced scale such as viral clearance and resin lifetime studies. The reduced scale studies were performed using qualified scale-down models and their qualification has been provided. Shipping of the active substance to the finished product manufacturing site has been validated and an efficient shipping process has been demonstrated.

The information provided concerning the process validation is found acceptable.

Manufacturing process development

The studies on manufacturing process development including process development and changes of processes used over development as well as the demonstration of comparability has been thoroughly described. In addition, process characterization of the commercial process, the identification of CQAs for the process and some information regarding the suitability of the container closure have been provided. The rationale for the classification and justification of acceptable ranges for the in-process controls (critical or non-critical IPCs) and process parameters (CPPs or non-CPPs) have been detailed and justified.

Development and changes of processes used over development

The process development history has been described in sufficient detail. The intended commercial process of isatuximab active substance manufacturing and this process has been used to produce active substance material used in clinical Phase II and Phase III studies. The same cell line was used throughout the different development phases.

Comparability of processes used over development has been studied. Based on the results presented, the active substance bathes produced from different processes showed overall comparable profiles and the information provided in the section on comparability is found adequately justified and acceptable.

Control strategy

The process control strategy has been thoroughly described including a series of systematic studies in multiple phases for the development of the commercial manufacturing process. Critical control attributes have been identified through a multidisciplinary risk assessment including the impact on the safety and/or efficacy of the final finished product. All CQAs and non-CQA have been provided.

Process characterization of the commercial process

The initial risk assessment originates from prior knowledge and development and manufacturing history. Process characterization studies were performed including qualified small-scale models of the process steps and proven acceptable ranges (PARs) were established. Results from process characterization were also used to define the CPPs and non-CPPs for the process as well as the acceptance criteria and action limits for CPPs and non-CPPs, respectively. Proven acceptable ranges were determined by models based on Design of Experiment (DOE) methodology. The Process performance qualification (PPQ) batches were successfully manufactured to demonstrate reproducibility of the manufacturing process. All the final CPPs and non-CPPs have been summarized. The rationale and justification for the selection of CPPs have been provided. The strategy to use multivariate understanding to increase process knowledge and establish ranges for process parameters is supported. In this case, sufficient data have been provided and the proposed process parameters are fixed and therefore it is concluded that the proven acceptable ranges (PARs) proposed for the isatuximab manufacturing process steps are found to be acceptably justified.

The information provided for control strategy, identification of CQAs and process characterization studies of the commercial manufacturing process is found acceptable.

Characterisation

Comprehensive characterization studies are reported on isatuximab active substance using state-of-the-art methods. All the characterization studies were conducted on isatuximab material representative of the commercial manufacturing process.

Impurities

The active substance has been tested for potential process-related and product-related impurities.

All impurities were considered to be well-controlled by the manufacturing process, recommended storage conditions and associated analytical monitoring.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specification for the active substance includes appearance, identity, potency, purity, bacterial endotoxins. The proposed tests and acceptance criteria are acceptable.

The acceptance criteria are valid both for release and end-of-shelf-life except for some tests that are only performed at release. This is found acceptable.

The acceptance criteria in the active substance specification are based on process capability for the commercial manufacturing process characterization outcomes and safety data.

All process- and product-related impurities were considered to be well-controlled by the manufacturing process, recommended storage conditions and associated analytical monitoring since they were all

demonstrated to be reduced to low or non-detectable levels in active substance at commercial scale manufacturing.

Analytical procedures

The analytical methods used to test active substance have been described. The method descriptions are found acceptable and sufficiently detailed. The validation of the methods as well as transfer validations where relevant, are adequately addressed and the methods are found appropriately validated. In addition, reports to verify the suitability of the compendial methods for microbiological examination and bacterial endotoxins for isatuximab active substance have been provided.

Batch analyses

Batch analysis data for isatuximab active substance has been presented for all batches manufactured over the development. All data comply with the proposed active substance specification acceptance criteria. Analytical results have been provided for all PPQ batches. A summary is provided on the evolution of analytical procedures over development as well as results from bridging studies for comparison between procedures. The information provided is found sufficient and acceptable.

Reference Standards or Materials

In-house primary and working standard have been established. Both current standards originate from a batch manufactured according to the proposed commercial process. The reference standards have been well described, characterized and motivated, considered as representative of the commercial manufacturing process.

Container closure system

The chosen container closure system is adequate, complies with relevant standards and has been described in sufficient detail.

Stability

Stability data have also been presented on accelerated and stressed storage conditions as well as stability under daylight exposure. All batches included in the stability studies are representative of the commercial manufacturing process.

No trend towards degradation can be seen for any control parameter in the stability data reported under long term storage condition.

Based on the stability results under long term storage condition, results from accelerated and stress studies the proposed shelf-life for isatuximab active substance is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product (FP) is provided as a sterile concentrate for solution for infusion containing 20 mg/mL of isatuximab as active substance. Other ingredients are: histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80 and water for injections (WFI). No novel excipients were used.

Sarclisa finished product is supplied in 2 single-use vial presentations: 500 mg/25 mL and 100 mg/5 mL:

- The 100 mg/5 mL presentation is provided in a 6 mL single use glass vial in 2 pack sizes: 1 vial and 3 vials. The fill volume (5.4 mL) has been established to ensure removal of 5 mL.
- The 500 mg/25 mL presentation is provided in a 30 mL single use glass vial in 1 pack size: 1 vial. The fill volume (26.0 mL) has been established to ensure removal of 25 mL.

Pharmaceutical development

Formulation development

The formulation development has been adequately addressed and the chosen formulation sufficiently justified. There is no overage of active substance or excipients, only overfill which has been acceptably justified.

Manufacturing process development

A comprehensive manufacturing process development has been performed and is adequately described and discussed. The chosen development approach is found appropriate.

The process characterization studies at laboratory scale and at industrial scale together with the risk assessment at different stages is found to acceptably justify the final chosen CQAs, CPPs and control strategy.

The risk for extractables and leachables from the equipment has been acceptably addressed. None of the components was found to pose a high risk concerning potential extractables and leachables. Furthermore, the complementary filter evaluation demonstrated the suitability of the sterile filter chosen.

The rationale for the selection of the primary package materials has been acceptably described and justified. The primary packaging materials (colourless clear glass type I vials and type I coated rubber closures) are in compliance with compendial requirements of the Ph. Eur.

The results from the extractables and leachable assessment show that there are no concerns related to organic compounds and elemental impurities.

Compatibility

Different combinations of materials and pumps used in clinical practice have been used in the study. The results verify acceptable physico-chemical stability for 48 hours at 5°C and additional 8 hours at room temperature, after dilution in 0.9% sodium chloride and 5% dextrose.

Furthermore, an assessment of bacteriostatic and fungistatic activities of the infusion solutions was performed by a challenge test with the conditions of the European Pharmacopoeia. The wording in section 6.3 of the SmPC is in line with the wording in the EMA GL CPMP/QWP/159/96 Note for guidance on maximum shelf -life for sterile products for human use after first opening or following reconstitution. Extended in-use storage time longer than given by the guideline (24 hours at 2-8°C) will be on the responsibility of the user.

Manufacture of the product and process controls

The manufacturing process and process controls have been acceptably described and summarised in a flow chart. In brief, the manufacturing process consists of the following steps: thawing the isatuximab formulated drug substance (FDS), pooling of FDS and homogenization, pre-filtration of the solution,

sterile filtration, aseptic filling, inspection and finally labelling and packaging. No reprocessing has been described.

Controls of critical steps and intermediates

The control strategy chosen has been properly described and is based on the conclusions of the manufacturing process development. The final CQAs, CPPs and manufacturing control strategy are found acceptably justified by the pharmaceutical development. Also, the set points and ranges proposed for CPPs and non-CPPs are found acceptably justified. The listed critical process parameters were assessed in the final risk assessment. The rational for the classifications in CPPs and non-CPPs was clearly addressed.

Process validation and/or evaluation

The process validation followed a traditional approach and covered three consecutive production scale batches manufactured per presentation, i.e. 100 mg/ 5 mL and 500 mg/ 25 mL vials. The validation covers different batch volumes for the two presentations as well as routine and maximum processing time. This also includes holding times and the allowed time out of refrigeration (TOR). All validation results complied with the acceptance criteria and no differences between batches manufactured with routine or maximum processing and holding times (also including planned process interruptions) could be observed. The time out of refrigeration (TOR) for the whole manufacturing process was monitored during PPQ. After the completion of the process additional time out of refrigeration was applied on batches which were manufactured with maximum processing time. These samples were placed on stability and available data complied with the specification.

In conclusion, the process validation is found to be acceptable and demonstrates that the finished product complies well with the acceptance criteria and specification and can be consistently manufactured within the defined processing and holding times.

Filter validation and Media fills

The maximum holding time of the pre-filtered solution has been acceptably justified from a physico-chemical point of view and by media fills.

Acceptable information about the pre-filter and sterile filter has been provided describing adequately the material, pore size, surface area and sterilizing process.

In the filter validation study, the filter integrity, chemical compatibility, particle release test, bacterial challenge test with viability test, adsorption, pH and extractables were studied. The parameters for the validation studies reflected a worst-case scenario of the filtration process. The results demonstrate the suitability of the chosen filter for pre-filtration and sterile filtration.

The media fill test covers the holding time after pre-filtration, filtration of the product bulk solution and filling of the finished product solution. The results show no positive units and the applicant claims that the maximum filtration time is justified.

Shipping validation study

This study was conducted to test the impact of transport. The results of the finished product after the simulated shipping validation comply with the acceptance criteria. The packaging configuration of the two presentations 100 mg/5mL and 500 mg/25 mL is found acceptably validated for the commercial product.

Product specification, analytical procedures, batch analysis

Specification

The specification for the finished product includes appearance, identity, potency, purity, sterility, bacterial endotoxins and extractable volume. The proposed tests and acceptance criteria are acceptable.

The specification chosen complies in general with the requirements in the general Ph. Eur. monograph for Monoclonal antibodies for human use. Furthermore, tests for sterility, endotoxin, volume in container and particulate matter are included in line with Ph. Eur. 0520 on parenteral preparations and injections.

Impurities

Both potential process-related impurities and product-related substances are adequately addressed as well as the control strategy in place for each impurity. Elemental impurities are monitored as required in ICH Q3D guideline. A summary of the risk assessment was provided. No organic compound above the Analytical Evaluation Threshold, and no elemental impurity above the ICH Q3D limit for parenteral compounds were detected during the studies.

A comparison of the levels of each impurity or substance between the FDS and finished product PPQ batches has been provided.

Analytical procedures

The analytical methods are validated successfully in accordance with ICH Q2 guideline. The validation results were acceptable and showed that the analytical methods are suitable for their intended use and valid.

Batch analysis

Batch analyses data are provided for the commercial P2F2 process (500 mg/25 mL and 100 mg/5 mL). There are several P2F2 batch results presented covering primary stability and clinical batches as well as the PPQ batches, which also are used for the on-going confirmatory stability studies.

PPQ batches complied well with the acceptance criteria and demonstrate a satisfactory batch to batch consistency. This is also applicable to the additional batch results provided (covering the primary stability and clinical batches).

Reference standards

The same reference standard is used as for the analysis of the active substance. This is acceptable.

Container closure system

The Sarclisa finished product is supplied in Type I glass vials closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stopper. The vials are crimped with an aluminium seal with a grey flip-off button. The fill volume has been established to ensure removal of 5 mL and 25 mL (i.e. 5.4 mL and 26 mL, respectively).

Stability of the product

The proposed shelf life for the finished product is 36 months when stored between 2-8°C and protected from light.

Stability results from batches manufactured according to commercial process as well as pilot scale batches have been provided. The studies are performed in accordance with ICH Q5C (Stability testing of Biotechnological/Biological products).

Results from accelerated and stress studies have been provided.

Primary stability batches

After 36 months storage at 5°C all results are within the acceptance criteria.

Confirmatory stability study on PPQ batches

The PPQ batches have been put on stability under the same conditions as for primary stability batches, also including photostability testing on one of the batches for each presentation. The results from the PPQ batches demonstrate similar trends between the PPQ batches and the primary stability batches. The photostability study verifies the need for the protection from light for the unopened vials.

Conclusion

The proposed 36-months shelf life at 2-8°C for both package sizes is found approvable.

After dilution chemical and physical in-use stability of Sarclisa infusion solution has been demonstrated for 48 hours at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Adventitious agents

No material of animal or human origin is in direct use in the manufacturing process of isatuximab except the CHO cells. Information has been provided as well as confirmation that the manufacturing processes is in compliance with EMA/410/01 rev.3 guidance minimising the risk of TSE transmission.

Adequate information has been provided regarding the control and testing of bacteria, fungi and mycoplasma. Sufficient information has also been provided with regard to the testing of MCB, WCB and limit of *in vitro* cell age for production (LIVCA). In conclusion, appropriate tests have been performed in accordance with ICH Q5A and Q5D.

Testing of unprocessed bulk (UPB) for adventitious agent is performed for every lot as in-process control. Information of the tests performed is sufficient and acceptable. Data from several batches of UPB has also been provided. No adventitious agents could be detected, only retrovirus-like particles (RVLP), which is expected for CHO cells.

Virus clearance studies

The information provided on the virus clearance studies is acceptable. The design of the virus clearance studies is in accordance with ICH Q5A. Relevant model viruses have been used. Worst-case conditions have been chosen for the experiments. Detailed information has been provided on the downscaling of the steps tested for virus clearance.

The quantitative virus risk assessment demonstrates a significant safety margin for retrovirus in the manufacturing process.

The data presented indicates control of the starting and raw materials, adequate IPC for viral contamination in unprocessed bulk and the results indicate effective reduction of a broad spectrum of

virus in the isatuximab manufacturing process which together ensures a safe product with regards to adventitious agents contamination.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The overall quality documentation provided for Sarclisa in the marketing authorisation application is of adequate quality. No major objections were identified during the assessment. As discussed and agreed during the evaluation determination of post-translational modifications will be included in comparability assessments upon future changes to the active substance and finished product manufacturing process and future stability studies.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory way. There is a good control strategy in place to guarantee consistent quality of the finished product. The results of tests carried out indicate that the active substance and finished product are manufactured in a validated and well-controlled process.

The overall quality of Sarclisa is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the data provided, the marketing authorisation application for Sarclisa is considered approvable from a quality point of view.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The effect of isatuximab on the production of cGDPR from nicotinamide guanine dinucleotide was measured in vitro and in vivo in a xenograft model. The disposition of isatuximab (SAR650984) was studied in the animal species and strains used in the toxicology program (cynomolgus monkeys) and in the pharmacology program (immunosuppressed mice with and without human tumour xenografts). The pivotal repeat-dose toxicity study in Non-Human Primates (study tsk0154), the local tolerance study in rabbits (study tol1117) and the in vitro compatibility study with human whole blood and plasma (study hem0123) have been performed under GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Isatuximab (SAR650984) is a humanized anti-CD38 antibody, derived from murine variant mu38SB19 Isatuximab, (hu38SB19 v1.00), which bears the constant regions of human immunoglobulin G1 (IgG1). Isatuximab binds to human CD38 with a dissociation constant (KD) of 0.12 nM. CD38 is a membrane protein, which also appears in a soluble form. Isatuximab affects the ecto-enzymatic function of CD38 blocking the conversion of nicotinamide guanine dinucleotide (NGD) or NAD into cyclic guanosine diphosphate ribose (cGDPR) or cADPR respectively.

In vitro

The effect of isatuximab on the production of cGDPR from nicotinamide guanine dinucleotide was measured in vitro (study IMV23-009). 20 nM isatuximab reduces the production of cGDPR from nicotinamide guanine dinucleotide to approximately 12% of control values.

The antibody is able to induce cell death in various ways. It is capable of inducing Antibody Dependent Cell mediated Phagocytosis (ADCP), Antibody Dependent Cell mediated Cytotoxicity (ADCC), Complement dependent Cytotoxicity (CDC) and direct apoptosis. The different antibody functionalities have been tested using panels of different cell lines (studies ONVT0117, IMV23-012, IMV23-014). The applicant showed the isatuximab-mediated effect (percentage of cell death) via ADCP, ADCC, CDC and apoptosis using Multiple Myeloma cell lines (LP-1, MOLP-8 & NCI-H929), while for an in vitro MABEL determination other cell lines (Ramos, SU-DHL-8 & DND-41) have been used to assess the effect of isatuximab-mediated ADCP, ADCC, CDC.

Direct apoptotic effect of isatuximab on mononuclear cells from bone marrow aspirates from relapsed MM patients was investigated in study IVT0058. Isatuximab pro-apoptotic action was effective in cells from 4/7 patients (28-40% compared to basal values) and moderate (14-16% compared to basal values) in cells from 3/7 patients. Adding plasma and/or macrophages to induce ADCC or ADCP showed that cell killing could be increased in 1 out of 2 samples. This illustrates that cells from various MM patient do not react identical upon isatuximab incubation.

Based on the literature data patient derived peripheral blood mononuclear cells (PBMCs) with pomalidomide, and in some cases, albeit to a lower extent, also with lenalidomide, enhances isatuximab-mediated direct cytotoxicity and lysis of CD38 positive MM cells by effector cells (ADCC) compared to incubation with isatuximab alone. The effect size seems to be patient dependent. Whether the different reaction of MM cells from the 7 MM patients upon incubation with isatuximab with or without PBMC is related to the CD38 levels on the specific MM cells or whether other factors are underlying this different effect is not known.

In vivo

A xenograft model with a Non-Hodgkin Lymphoma (NHL) cell line in severe combined immunodeficient (SCID) mice (SU DHL-8 tumours; study IMP23-018) was used to provide in vivo POC for isatuximab. SAR650984 Ab was active at all dose levels tested (2.5, 10 and 40 mg/kg/injection). A clear dose response was seen for the activity of SAR650984.

Immunomodulatory potential

The applicant investigated the effect of isatuximab on NK cells (study ONVT0152), which express the target, but are also involved in isatuximab-mediated ADCC. The applicant showed that the antibody itself was capable of inducing NK cells to release cytokine IFN-γ and TNF-α, indicating NK cell activation. When adding a tumour cell line, not expressing CD38, isatuximab activated NK-related cytolysis. The effect of isatuximab was also investigated in primary NK cells isolated from 7 healthy donors. Pre-incubating primary NK cells with isatuximab at 1 µg/mL versus IgG at 1 µg/mL, increased the average cytolysis in 3/7 donors.

Monocytes also express CD38. Polarization of monocytes towards a M1 or M2 phenotype does not occur directly upon isatuximab incubation. However, in co-culture with NK cells, isatuximab appears to indirectly polarize monocytes towards M1 monocytes probably by means of activating NK cells and the subsequent IFN-Y release by these activated NK cells (study ONVT0150).

In addition, regulatory T-cells and conventional T-cells express CD38. Among the regulatory T-cells, a higher percentage express high levels of CD38 (CD38 high) as compared to the conventional T-cells. In

MM patients, the percentage of high CD38 expressing regulatory T-cells is even higher as compared to healthy persons.

Potential for Cytokine release

Cytokine release by normal peripheral blood mononuclear cells (PBMCs) or white blood cells (WBCs) preparations was assessed from 14 independent donors after isatuximab treatment (study IMV23-003). Cytokines were detected by ELISpot (for IFN-γ, TNF-α, and IL-6 [interleukin-6]) and cytometry bead array (CBA) assay (for IFN-γ, TNF-α, IL-12p70, IL-10, IL-8, IL-6, IL-4, IL-2, and IL-1β). In all assays, the positive control antibody OKT3 induced a strong release of all the cytokines tested for each donor (except IL-12p70). No significant release of cytokines was observed after isatuximab incubation under any of the various assays and conditions used and for any of the donors tested.

Binding to normal human blood cells and its effect

Isatuximab specifically binds to 22 to 40% of CD3-positive T-lymphocytes (KD of 0.19 nM), 24 to 67% of CD19-positive B-lymphocytes, 37 to 65% of NK cells and 31 to 97% of CD14+ monocytes (KD of 0.45 nM). Isatuximab did not bind to platelets or RBCs from the 3 different donors.

Incubation of PBMCs from two donors with isatuximab did not induce a measurable effect on proliferation of PBMCs as measured in 5-(and-6)-carboxyfluorescein diacetate (CFDA) assay, which was in contrast to results obtained with a positive control antibody (anti-CD3, OKT3) in this assay (study IMV23-004).

The effect of immobilized isatuximab on the proliferation of freshly isolated human PBMCs as measured by thymidine incorporation showed that it did not cause proliferation of PBMCs compared to the positive control of PBMCs stimulated by immobilized anti-CD3 (OKT3) alone (study GVT0107).

The effect of soluble isatuximab on the proliferation of freshly isolated human PBMCs as measured by thymidine incorporation was also assessed (study GVT0107). Addition of soluble positive control anti-CD3 antibody induced PBMCs proliferation. Addition of soluble isatuximab alone, as well as the other antibodies tested did not cause proliferation of human PBMCs at the concentrations tested. Addition of soluble isatuximab to human PBMCs stimulated with soluble anti-CD3 did not increase the proliferation of PBMCs compared to anti-CD3 alone.

In studies assessing the effect of isatuximab on peripheral blood mononuclear cell depletion and apoptosis it was shown that isatuximab caused less than 10% depletion of any of the cells of WBC (whole blood after lysis of RBC) examined after a 1-hour incubation in the 2 different donors tested. Isatuximab caused an increase in the number of apoptotic NK cells, while B-cells, T-cell and monocytes were unaffected. Under the same conditions, isatuximab increased the percentage of apoptotic Ramos tumour cells (CD38+) by 50%. The pro-apoptotic effect seems to be more specific for tumour cells.

C1P1F1 and C1P2F2 formulations

In order to complement chemistry, manufacturing and control assessment, C1P1F1 and C1P2F2 isatuximab formulation batches were evaluated head to head in vitro and in vivo.

ADCP, ADCC and CDC capacity of isatuximab for two formulations, C1P1F1 and C1P2F2 are compared *in vitro* and are regarded to be similar (studies ONVT0115, ONVT0116, ONVT0117, ONVT0118, ONVT0119). Anti-tumour effect of isatuximab for two formulations, C1P1F1 and C1P2F2 are compared in vivo in a xenograft model with subcutaneously injected SU-DHL-8 cells in matrix (NHL cell line) into SCID mice lacking functional T and B cells (study ONVV0095). The anti-tumour response seems not significantly different.

Relevant animal model for toxicity testing

To identify a relevant animal model for toxicity studies, a CD38 sequence comparison was undertaken followed by cross reactivity assay on tissues from a variety of species followed by generation and testing of isatuximab surrogates, two monkey reactive antibodies.

The percentages of identity with the human sequence are comprised from 53% with the rabbit to 99% with chimpanzee. When compared to human CD38, percentages of identity/similarity in monkey species (other than chimpanzee) suggested that these species (namely the cynomolgus monkey that is a commonly used species in toxicology) could be considered for toxicity testing (please see discussion on Non-clinical aspects).

Immunohistochemistry (IHC) labelling using isatuximab on a representative list of tissues from human and a wide range of laboratory animal species confirmed the specific binding of isatuximab on human spleen, prostate gland and lymph node and demonstrated specific binding of isatuximab to prostate gland and lymph node from the chimpanzee with a comparable staining pattern as in human. There was no observed isatuximab binding in tissues from the other tested species, except sporadically in hamster (prostate gland) and ferret (pulmonary bronchial glands).

Therefore, two monkey reactive antibodies (ch38SB25 and chOKT10) were generated and evaluated as potential reactive surrogate antibodies for toxicity testing in monkeys. Three criteria were used to evaluate the relevance of each surrogate in the monkey: binding affinity, in vitro functional activity and tissue cross-reactivity. The two monkey reactive antibodies ch38SB25 and chOKT10 bound both human and cynomolgus monkey CD38 antigen with a similar affinity. In comparison to isatuximab, their affinity for CD38 was slightly lower as compared to the affinity of the human antibody for the human CD38 protein but was comparable between the 2 monkey antibodies. Both antibodies displayed similar and potent ADCC activity and slightly lower (ch38SB25) or much lower (chOKT10) CDC activity in human tumour cell lines, as compared to isatuximab. However, only isatuximab mediated pro-apoptotic activity. The pattern of tissue cross-reactivity of both ch38SB25 and chOKT10 surrogates in monkey tissues was significantly different from the pattern of tissue-cross-reactivity observed with isatuximab in human tissues, in particular with regards to endothelial cell staining observed in several organs, which could be related to a different distribution of CD38 antigen between monkey and human.

Isatuximab plus pomalidomide

Support for co-treatment with pomalidomide is obtained from incubation of a MOLP-8 xenografted NOD SCID gamma (NSG) mouse model with isatuximab (study ONVV0145). Given that in the NSG mice the macrophages and dendritic cells are defective, and the NK cells are not functional and that mice other than NSG-Hc1 were used, only direct apoptosis mediated by isatuximab could be evaluated. With regard to pomalidomide, upregulation of interferon gamma, IL-2 and IL-10 as well as downregulation of IL-6 have been reported. These changes may contribute to pomalidomide's anti-angiogenic and anti-myeloma activities. Whether pomalidomide immunomodulatory function in NSG mice is or can be fully representative for the human situation is not clear. Although the mechanism is not completely clear, a synergistic anti-tumour effect was observed upon use of isatuximab in combination with an immunemodulatory drug (IMiD), providing support for clinical investigation of the co-administration of pomalidomide and isatuximab.

Secondary pharmacodynamic studies

TCR (*tissue cross-reactivity) on human tissue*

The GLP study of tissue cross-reactivity on normal human tissues indicated that isatuximab specific binding was detected in the lymphoid tissues (spleen, thymus, lymph node and tonsil) and in the bone marrow as expected and in the pituitary gland (endothelial cells, confirmed by a co-localization of the

binding with that of CD31), and prostate gland (glandular epithelial cells). Most of the staining observed in these different tissues is overall consistent with the known CD38 protein expression in human. Staining of non-lymphoid tissue elements (epithelial cells of the acini in prostate and endothelial cells lining the sinusoids in pituitary glands), was interpreted as evidence of cross-reactivity that may possibly indicate potential unintended target sites. Staining of epithelial cells in the bronchi and Astrocytes in the brain were only observed in the non-GLP TCR study.

Isatuximab versus daratumumab

From sequence comparisons of the antibodies' Complementarity Determining Regions [CDR] and the CD38 sequence, it can be concluded that isatuximab and daratumumab bind to different CD38 epitopes and consequently need to have different paratopes, which is confirmed by X-ray cristallograpical investigation.

It appeared that both antibodies bind similarly well to CD38 expressed by several multiple myeloma and lymphoma cancer cell lines. Isatuximab did bind to Red Blood Cells (RBCs) from 3 healthy donors. It can also be concluded that isatuximab is different from daratumumab with regard to target recognition and with regard to antibody mediated cell killing. Whether in the patient this will result in a favourable efficacy profile for isatuximab cannot be foreseen as all investigative assays presented above occurred in cell lines of which the level of representation for the disease is not clear.

Safety pharmacology programme

The safety pharmacology has been addressed in a toxicology study (please see Toxicology section).

Pharmacodynamic drug interactions

No pharmacological drug interaction studies were submitted (see discussion on Non-clinical aspects).

2.3.3. Pharmacokinetics

No specific absorption, distribution, metabolism, elimination studies were conducted with isatuximab as it is a monoclonal antibody (mAb), and is only recognized by the human CD38 receptor. No PK interaction studies were performed non-clinically. Potential interactions were evaluated clinically.

Single dose studies

The Applicant has compared the plasma concentrations of the two clinical formulations over time in SCID mice, in which the target for the antibody is not present. Both formulations showed the same profile after single administration. Statistical analysis of the C0 and AUC0-49 did not reveal considerable pharmacokinetic differences between both formulations. Based on the single i.v. administration data, "cell line 1, process 1, formulation 1" C1P1F1 and "cell line 1, process 2, formulation 2" C1P2F2 can be considered bio-equivalent (please refer also to the PD section above).

The Applicant also compared the effect of changing the storage conditions of C1P2F2. The statistical analysis data show that 3-month storage at 25C (instead of 4C) did not significantly affect PK parameters (please refer also to the PD section above).

Repeat dose studies

Mouse

In SCID tumour-bearing mice following repeated bi-weekly IV doses (on Days 11, 14, 18, 21 and 26 post- tumour implantation; study data from IMI23-002) at 2.5, 10 or 40 mg/kg, clearance (CL) decreased with increasing dose from 0.795 mL/day at the lowest dose (2.5 mg/kg) to 0.171 mL/day at

the highest dose (40 mg/kg). Consequently, a greater than dose proportional increase in exposure (AUC) after the 5th administration from 2.5 to 40 mg/kg was observed: AUC increased by 75-fold for a 16-fold increase in dose. Based upon estimated accumulation following repeated bi-weekly dosing (estimated using modeling approach), the increase in exposure was approximately 3-fold at 10 mg/kg and approximately 4-fold at 40 mg/kg dose levels.

Monkey

In the repeat-dose toxicology study in cynomolgus monkeys (study TSK0154), animals (3 animals/sex/group) received isatuximab at 20, 50 or 100 mg/kg/week as a 0.5-hour intravenous infusion once a week for 3 weeks. Plasma samples for toxicokinetic determinations were drawn after the first administration over 1 week and after the 3rd administration over 3 days. In both female and male monkeys, exposure increased in an approximately dose-proportional manner over the dose range of 20 to 100 mg/kg/week, at both Week 1 (AUC0-7d) and Week 3 (AUC0-3d).

Following the first IV infusion of isatuximab at 20-100 mg/kg/week, isatuximab exposure (AUC0-7d) increased by 4.42-fold and 4.60-fold in male and female monkeys, respectively, for a 5-fold increase in dose. After 3 once weekly infusions of isatuximab, exposure (AUC0-3d) increased by 5.04-fold and 4.55-fold in male and female monkeys respectively, for a 5-fold increase in dose. Similar increases in Cmax with dose were also observed. Regardless of the sex and dose level, a 1.84 to 2.27-fold accumulation of isatuximab AUC was observed at Week 3 (AUC0-3d) compared to Week 1 (AUC0-7d). No obvious sex differences in AUC were observed at either Week 1 or Week 3, at any of the doses evaluated.

MABEL and First-In-Human starting dose

The selection of the starting dose for the first-in-man study in patients was based on the Minimal Anticipated Biological Effect level (MABEL) approach and in vitro receptor occupancy. This approach was used due to the absence of a relevant animal model of multiple myeloma for toxicity testing. To support the MABEL approach, a PK study in severe combined inmmunodeficient (SCID) mice, as well as a PK/pharmacodynamic (PD) study in tumour-bearing SCID mice (human SU-DHL-8 lymphoma cells subcutaneously implanted), a CD38-sensitive xenograft model, were conducted (studies IMI23-002 and IMI23-003, with corresponding pharmacodynamic data from study IMP23-018). The MABEL calculated with the most sensitive in vitro model (ADCC) led to an extremely low starting dose in patients (0.000005 mg/kg) and <0.5% receptor occupancy. In contrast, the dose corresponding to the lowest activity in a relevant in vivo PK/PD model (0.2 mg/kg) led to 99.7% theoretical receptor occupancy. Based on the overall data, the recommended starting human dose for the first-in-human study was 0.0001 mg/kg, which is approximately 10% of the predicted CD38 receptor occupancy measured in normal human B and T cells. This dose was 2000-fold lower than the predicted active dose of 0.2 mg/kg based on the in vivo PK/PD model.

Methods

Different immunoassay methods were used to measure isatuximab plasma concentrations in both mice and monkeys. A non-GLP ELISA method was used to quantify isatuximab in mouse plasma. For analysis of toxicokinetic profiles of isatuximab in monkey plasma, isatuximab concentrations were determined using a validated immunoassay method. An immunogenicity assay (based on polyethylene glycol precipitation and acidification with ECL immunoassay detection) was developed and validated to detect anti-isatuximab antibodies (ADA) in the GLP monkey toxicology study. A non-GLP quantitative flow cytometry assay was developed to determine CD38 receptor density (i.e. absolute number of CD38 receptors per cell) and occupancy by isatuximab on cell lines and blood lymphocyte subsets from healthy subjects.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies have been performed (see Non-clinical aspects discussion).

Repeat dose toxicity

The Applicant has conducted an exploratory (DIV1820) and a pivotal general toxicity study (TSK0154) in NHP (cynomolgus monkey).

Exploratory study

In an exploratory repeat-dose toxicity study, 2 cynomolgus monkeys (1M and 1F) were IV administered with 100 mg/kg once a week for 3 weeks. No control animals were used. Baseline values for all parameters (i.e. prior to treatment) were measured.

No isatuximab-related effects were observed. The noted changes in monocyte and eosinophil levels were not accompanied by correlating changes in clinical observations (such as reduced body weight) and not considered isatuximab specific and could relate to an immunogenic reaction against isatuximab. No statistical significance for these haematological events were determined because only two NHPs were involved in the study.

Pivotal study

A 3-week pivotal toxicity study was conducted in cynomolgus monkeys, administering 20 to 100 mg/kg isatuximab per week intravenously, starting at 26 to 29 months of age. A clinical grade batch (C1053598) and an off-the-shelf life batch (VAB-LCX1-000004) were used.

Control animals and female test animals gained body weight during the whole treatment period. A statistically significant, dose-dependent decrease in weight was observed in males after the second injection (day 8 to 15) in all dose groups.

Table 1. Mean body weight changes in the study TSK0154.

group	mean body weight (kg) at day -6	mean body weight (kg) at day 15	mean body weight (kg) change
control	2.917	3.100	+0.183
20 mg/kg/week	2.850	2.900	+0.05
50 mg/kg/week	2.667	2.650	-0.017
100 mg/kg/week	2.900	2.700	-0.2
100 mg/kg/week (VAB)	2.883	2.650	-0.233

At terminal necropsy, however, the differences in body weight were no longer apparent. Because effects on body weight were only present in males and appeared to be temporary without other clinical symptoms, and as the animals lack the isatuximab target, the finding is not regarded of toxicological relevance.

In line with the animals from the exploratory study, eosinophil counts dose-dependently increased in the treated females between the pre-test day and day 18, while the value in the control group remained stable. No statistical significance for this effect was determined. Clinically, no evidence of changes in eosinophil counts are present.

It was noted that the absolute heart weight and the heart to body weight ratio was increased in animals (especially females) at 100 mg/kg/week, without an effect on ECG parameters. Microscopically, both the control and dosed animals had mononuclear cell infiltrates in the heart, which

were considered background lesions. The finding is considered species-specific and not related to isatuximab treatment.

Therefore, under these study conditions, the dose of 100 mg/kg/week was considered to be the no-observed adverse effect level (NOAEL) with corresponding Cmax and AUC0-3d values on Week 3, respectively of 4360 µg/mL and 9670 µg.day/mL for males and 4250 µg/mL and 9290 µg.day/mL for females.

Genotoxicity

No specific studies to evaluate genotoxicity have been submitted (see discussion on non-clinical aspects).

Carcinogenicity

No specific studies to evaluate carcinogenicity were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproductive toxicity studies have been submitted (see discussion on non-clinical aspects).

The Applicant provided literature data with respect to targeting CD38 during embryofoetal development and it appears that specific reprotoxicity studies with respect to CD38 deficiency in mammals are lacking. Literature data on inhibition or knockdown of CD38 in amphibians suggest that CD38 expression may be essential for embryonic development and survival (Churamani D. et al., 2012).

Toxicokinetic data

PK parameters were evaluated in the plasma of NHP from the repeat dose toxicity study. Dose-dependent increase and decrease in plasma levels of isatuximab was present in the pivotal repeat-dose toxicity study and there was no considerable difference in dose curves between males and females.

The AUC of isatuximab was higher at week 3 compared to week 1 for each dose, indicating accumulation.

Table 2. Summary of toxicokinetic results in the pivotal study TSK0154.

Study ID	Weekly Dose (/)	Animal AUC (µg.day/ml)		Cmax (µg/ml)		Tmax (h)	
TSK0154		♂	♀	♂	♀	♂	♀
	week 1 :						
	20 mg/kg	1040/1930	959/1870	643	519	0.58	0.58
	50 mg/kg	2160/4060	2350/4490	1300	1450	0.58	0.58
	100 mg/kg	4430/8540	4560/8600	2390	2840	0.58	0.58
	100 mg/kg*	4530/8470	4120/7860	2610	2720	0.58	0.58
	week 3 :						
	20 mg/kg	1920	2040	1020	994	0.58	0.58
	50 mg/kg	4140	5540	2040	2800	0.58	0.58
	100 mg/kg	9670	9290	4360	4250	0.58	0.58
	100 mg/kg*	8640	7760	4060	4090	0.58	0.58

* batch VAB-LCX1-000004 (beyond current shelf-life)

NB: AUC week 1 = 0-3 days and 0-7 days resp.; AUC week 3 = 0-3 days

Local Tolerance

A local tolerance study was conducted in female New Zealand White rabbits of 16 weeks of age, administering them a single bolus injection of isatuximab. No local or systemic isatuximab-related effects were observed in rabbits via the different routes of administration tested.

Local tolerance was also determined in the repeat dose toxicity pivotal study in NHP. In this study, there were no compound-related macroscopic or microscopic findings at the injection sites at any dose level up to highest concentration tested of 20 mg/mL.

Immunogenicity

In the repeat-dose toxicology study in cynomolgus monkeys, animals (3 animals/sex/group) received isatuximab (C1P2F2 formulation, batch C1053598) at 20, 50 or 100 mg/kg/week by a 0.5-hour intravenous infusion once a week for 3 weeks. This study also had an additional group of monkeys who received isatuximab at 100 mg/kg/week under the same conditions as the main study animals, but using an isatuximab batch which was beyond its current shelf-life (batch VAB-LCX1-000004, approximately 28 months old).

All samples collected from animals treated with batch C1053598 (20, 50 and 100 mg/kg/week) were found to be ADA negative, while the majority of the samples from animals (4 out of 6) that received the batch VAB-LCX1-000004, which was beyond its current shelf-life, were ADA positive, with titers ranging from 160 to 320. Presence of ADAs had limited effect on the isatuximab exposure, i.e. isatuximab concentrations in ADA positive samples were slightly lower (<17%) than concentrations in the ADA negative samples.

Other toxicity studies

In vitro comparability and haemolytic potential study

The Applicant has conducted an *in vitro* study with plasma and blood from healthy donors to evaluate the clinical safety of isatuximab. Isatuxiumab appeared to be compatible with whole blood and plasma when mixed at different ratios.

2.3.5. Ecotoxicity/environmental risk assessment

No ERA studied were submitted (please see the discussion on Non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

In vitro several modes of action related to isatuximab target binding have been seen, which include CD38 enzyme inhibition, direct pro-apoptotic effect, ADCP, ADCC and CDC. A correlation to CD38 expression level and the efficacy of ADCP, ADCC, CDC and direct pro-apoptotic activity has not been established. All isatuximab modes of action differ per cell line and per patient. The applicant was asked to discuss the isatuximab modes of action mediating anti-tumour effect in patients and relation to the level of target (CD38) expression or other factors using all available data acquired during development, as well as all available literature data present up to date. The applicant noted that ADCC was the most important isatuximab-induced effector function by summarizing study IMV23-012 in which isatuximab induced ADCC appeared to occur in 15/15 cancer cell lines, showing 30-90% cell lysis at relative low effective concentrations (0.2-8 ng/mL). Isatuximab induced CDC was effective in 7/15 cell lines at ranging from 8-230 ng/mL. While the isatuximab induced apoptosis occurred in 8/15 cell lines at concentrations ranging from 2-16 ng/mL. Furthermore, the applicant summarized the results from a

study published by Moreno et al. (data not presented), testing isatuximab induced ADCC, ADCP and CDC on different MM cell lines as well as primary tumour plasma cells derived from patients. ADCC appeared effective for four MM cell lines as well as 13 patient tumour cells and it appeared that highest induction of cell death was observed for MM cells expressing high CD38 levels. ADCP and CDC occurred as well, but on a lower fraction of MM cells. ADCP was only triggered by MM cells expressing high CD38 levels and CDC occurred only in less than half of the patient samples.

The applicant concluded that ADCC was likely to be the most prominent mechanism of cell death induced by isatuximab. It occurred on CD38 low and high expressing MM cells, however was most efficient when CD38 levels were high. Though, clinically the CD38 levels appeared not to be an explanation for the variability in response.

In a xenograft tumour model a dose response activity was observed. Notwithstanding the limitations of the model: whether the use of an NHL cell line is representative for the proposed indication (MM), the model not fully simulating a systemic tumour, the extent of mediated cytotoxicity as this model lacks T and B cells, this study provides evidence for the anti-tumour effect of isatuximab towards CD38.

In addition, isatuximab has an immunomodulatory effect by stimulating the lytic capacity of NK cells. Whether this also occurs in vivo in patients has not been investigated. As described in the section on secondary pharmacology, isatuximab is able to increase the percentage of apoptotic NK-cells but does not affect the percentage of apoptotic B and T cells and monocytes. In co-culture with NK cells, isatuximab appears to indirectly polarize monocytes towards M1 monocytes probably by means of activating NK cells and the subsequent IFN-Y release by these activated NK cells. Whether this effect is to be expected in human only locally or systemically is not clear.

Applicant's investigations have shown that isatuximab increases the activity of conventional T cells, which is likely the result of the isatuximab-mediated decrease in CD38high Tregs increases T-cell clonality in MM patients in vivo and can induce T-cell responses against myeloma tumour antigens in some patients; it can be thus suggested that in addition to the Fc-mediated effector functions, isatuximab also modulates the immune system towards an anti-tumour immune response.

In vivo, a dose dependent anti-tumour effect is observed in SCID mice and in NSG mice (were ADCP, ADCC and CDC is impaired), and a synergistic effect with pomalidomide is shown, which may implicate that the pro-apoptotic effect is already quite pronounced. These studies suggest that isatuximab, irrespective of its ADCC, ADCP and CDC mechanisms, also modulates the immune system towards a more pro inflammatory anti-tumour mode by binding to CD38 on normal immune cells from peripheral blood.

It can be thus concluded that isatuximab is capable of 1) activating NK cells enhancing their lytic activity; 2) polarizing monocytes towards M1 phenotype in the presence of isatuximab stimulated NK cells; and 3) restoring the proliferation of conventional T cells inhibited by regulatory T cells (SmPC section 5.1).

No significant release of cytokines was observed after isatuximab incubation under any of the various assays and conditions used and for any of the donors tested. Occurrence of a cytokine release syndrome upon treatment with isatuximab is thus not very likely.

Most of the staining observed in tissue cross-reactivity studies is overall consistent with the known CD38 protein expression in human. Staining of non-lymphoid tissue elements (epithelial cells of the acini in prostate, endothelial cells lining the sinusoids in pituitary glands), was interpreted as evidence of cross-reactivity that may possibly indicate potential unintended target sites. Staining of Epithelial cells in the bronchi and Astrocytes in the brain were only observed in the non-GLP TCR study and not confirmed in the GLP study. These findings prompted implementation of montoring of hormone levels, pulmonary function tests and chest X-rays in a subsequent phase I trial. Regarding the staining noted

in the brain, no specific monitoring was conducted in patients, because isatuximab is unlikely to penetrate the blood-brain barrier (BBB) to any significant degree based on its large molecular size (molecular weight: about 150 000 Da) and the restrictive nature of the BBB. No signals retained from this study that would suggest isatuximab related toxicity to one of these tissues. The approach of the applicant is acknowledged and the results are reassuring (see Clinical efficacy section).

No pharmacological drug interaction studies were submitted. As the antibody is very specific making it unlikely to interfere with the pharmacological action of another drug.

Bi-weekly IV administration of isatuximab to mice or once weekly IV administration to NHP resulted in dose-dependent accumulation of isatuximab in line with its long half-life. PK parameters in repeat-dosed mice were considerably different from single-dosed mice. This is most likely the result of the presence of CD38+ tumour cells in these repeat-dosed mice, which explains the increase in isatuximab clearance (i.e. target-mediated drug disposition).

Using the population PK modelling approach with SCID mice data, a plasma concentration threshold of 128.8 µg/ml was estimated to be needed for tumour eradication. A corresponding dose in humans would be 10-20 mg/kg. However, the translation of murine data to the clinic is challenging due to limitations of the animal model used. A safe and efficacious dose has been determined in the clinical studies (see Clinical efficacy section).

From the pharmacokinetic point of view, the SCID mice with a xenograft consisting of cells from a CD38 expressing cancer cell line was the most relevant species for non-clinical efficacy testing. The chimpanzee was the most relevant model for safety studies, but was not used for ethical reasons, which is acknowledged. The used species for toxicity testing, cynomolgous monkey, was not regarded a pharmacological relevant species as the antibody does not recognise the target in this species.

In line with relevant guidelines no genotoxicity, carcinogenicity and reproductive toxicity studies were conducted (ref. ICH S6, ICH S9; SmPC section 5.3).

Based on the literature data (Churamani et al., 2012; data not presented) CD38 may be targeted during the embryofoetal development. Calcium influx and signalling are suggested to play a major role. It is also suggested that in mammals compensatory mechanism for calcium signalling might be present. This may be a reason why CD38 knockout mice survive at least for 8 months. This also may imply that early embryogenesis and foetal development in mammals is not critically dependent on CD38. As isatuximab will most likely cross the placenta in later stages of pregnancy, effects on foetal development in humans cannot be excluded. Although no transfer of monoclonal antibodies is expected in the first weeks of pregnancy, the 5 times $t_{1/2}$ calculation as advice for duration of contraception is agreed (see section 4.6 of the SmPC). Thus, a cessation period of 5 months is on the safe side and is considered the maximum period needed so that it is not likely that the foetus will be exposed to substantial isatuximab levels via the placenta.

In absence of reproductive toxicity studies and clinical experience with the use of isatuximab in pregnant women or women of childbearing potential not taking effective contraception, appropriate wording regarding use in the patients of reproductive age is included in the SmPC (see SmPC section 4.6). The Applicant did not evaluate excretion of isatuximab in milk, although excretion could be expected in colostrum (based on the general properties of IgG1 molecules, see SmPC section 4.6 and 5.3).

The local effects observed are caused by trauma due to the IV administration procedure and not due to administration of isatuximab.

No studies to evaluate antigenicity, immunotoxicity and metabolites have been conducted. The general toxic effects and the formation of metabolites and ADAs after isatuximab administration have been

described in the repeat dose toxicity study in NHP and in the Pharmacokinetic section, hence no additional studies are warranted.

The Applicant has provided a comprehensive overview of the data presented in literature with respect to the lack of CD38 expression (i.e. knockout) in all murine tissues. Additionally, studies by Hattori et al. (2017) and Zhang et al. (2014) suggest a role of CD38 in astrocyte and oligodendrocyte development (2017) and in maturation of smooth muscle cells via autophagy regulation (2014). Especially, the data with respect to nervous development may indicate toxicological potential. However, the clinical relevance of effects due to lack of CD38 expression in genetically manipulated animals is not clear. In addition, CD38 inhibition by isatuximab may be less disturbing than (almost) 100% loss of CD38 expression, especially in the CNS since isatuximab is not expected to cross the BBB.

No non-clinical studies on impurities have been performed. Based on the data presented in module 3 of the CTD, there are no quality concerns with respect to excipients and impurities. Moreover, in the non-clinical toxicity evaluation of isatuximab, concurrently with the active substance the safety of the excipients and impurities have been taken along. No additional impurity studies will be needed.

The Applicant 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.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that isatuximab alone or in combination with pomalidomide is capable of inducing anti-tumour effect on CD38 expressing Multiple myeloma. Non-clinical pharmacokinetic studies were considered adequate to support the MAA. The toxicology programme revealed no clinically relevant safety findings.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. A routine GCP inspection has been conducted for the clinical study EFC14335. In the final integrated inspection report it was concluded that despite the ICH GCP principles departure, the quality of data was not compromised and data were considered reliable in support of the initial marketing authorisation application for Sarclisa. CAPAs were agreed with the applicant and the CRO.

The applicant 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.

Table 3. Tabular overview of clinical studies.

Study	Patient population	Study Design and Indication	Treatment, schedule and sample size[a]	Status at BLA submission
Core studies in combination with pomalidomide and dexamethasone in multiple myeloma				

Study	Patient population	Study Design and Indication	Treatment, schedule and sample size[a]	Status at BLA submission
EFC14335 Pivotal Phase 3 with target combination	Patients with RRMM who have received at least 2 prior lines of anti-myeloma therapy that included at least 2 consecutives cycles of lenalidomide and a PI (bortezomib, carfilzomib or ixazomib) given alone or in combination.	A Phase 3 randomized, open-label, multicenter study comparing isatuximab in combination with pomalidomide and dexamethasone versus pomalidomide and dexamethasone in patients with refractory or relapsed/refractory MM	Experimental arm: isatuximab P2F2 (N=152): 10 mg/kg QW/Q2W, pomalidomide, and dexamethasone; Control arm: pomalidomide and dexamethasone; N=149 Randomization ratio: 1:1	Completed CSR for final PFS and interim OS analyses (cutoff 11-Oct-2018); Ongoing for final OS analysis
TCD14079 Phase 1b with target combination	Patients with RRMM who have received at least 2 previous therapies including IMiD and a PI and had progressed on or within 60 days after last therapy	A Phase 1b dose escalation and expansion (Part A only) study of isatuximab in combination with pomalidomide and dexamethasone in patients with relapsed/refractory MM	Part A: Dose escalation isatuximab P1F1 (N=23): 5 mg/kg QW/Q2W, N=8; 10 mg/kg QW/Q2W, N=9; 20 mg/kg QW/Q2W, N=6; Ongoing patients were switched to isatuximab P2F2 Part A: Expansion isatuximab P2F2 (N=22): 10 mg/kg QW/Q2W	Part A: Completed CSR (database lock 10-Nov-2017)
Supportive single agent studies in multiple myeloma or other hematological malignancies				
TED10893 Supportive Phase 1/2 with single-agent treatment or in combination with dexamethasone	Phase 1: Patients with CD38+ hematological malignancies[b] Phase 2: Patients with RRMM who have received at least 3 prior lines of therapy that included an alkylating agent, IMiD and a PI or whose disease was double refractory to an IMiD and a PI	A Phase 1/2 dose escalation and expansion safety, pharmacokinetic and efficacy study of multiple intravenous administrations of isatuximab in patients with selected CD38+ hematological malignancies	Phase 1 Dose escalation and expansion cohorts isatuximab P1F1 (N=89): ≤1 mg/kg Q2W, N=16; 3 mg/kg Q2W, N=6; 5 mg/kg Q2W, N=3; 10 mg/kg Q2W, N=26; 10 mg/kg Q2W HR[c], N=18; 20 mg/kg Q2W, N=7; 10 mg/kg QW, N=6; 20 mg/kg QW, N=7 Phase 2 Stage 1a isatuximab P1F1 (N=72): 3 mg/kg Q2W, N=23; 10 mg/kg Q2W, N=24; 10 mg/kg Q2W/Q4W, N=25; Randomization ratio: 1:1:1 Phase 2 Stage 1b isatuximab P1F1 (N=25) 20 mg/kg QW/Q2W After the study cut-off in Phase 2 Stage 1 and the start of Phase 2 Stage 2, patients in Phase 2 Stage 1 receiving P1F1 may switch to P2F2 Phase 2 Stage 2 (N=93): isatuximab P2F2 (N=63) 20 mg/kg QW/Q2W, isatuximab P2F2 (N=30) 20 mg/kg QW/Q2W and dexamethasone; Randomization ratio: 2:1	Phase 1: Completed CSR (database lock 9-Jan-2017) Phase 2 Stage 1: Completed CSR (database lock 26-Apr-2017) Phase 2 Stage 2: Interim CSR (cutoff 15-Nov-2017)
TED14154 Supportive Phase 1 with single-agent treatment	Part A: Patients with RRMM who have received at least 3 prior lines of therapy that included an IMiD and a PI or whose disease was double refractory to an IMiD and a PI	A dose-escalation/expansion (Part A only) and multi-center study to evaluate the safety, PK and efficacy of isatuximab P2F2 in patients with relapsed/refractory MM	Part A Dose escalation and expansion cohorts isatuximab: P2F2 (N=26): 10 mg/kg QW/Q2W, N=12; 20 mg/kg QW/Q2W, N=14	Part A: Completed CSR (cutoff 06-Jul-2017)

Study	Patient population	Study Design and Indication	Treatment, schedule and sample size[a]	Status at BLA submission
Supportive combination therapy studies in multiple myeloma				
TCD11863 Supportive Phase 1b with combination therapy[d]	Patients with RRMM who have had at least 2 prior anti-MM treatments	A Phase 1b dose escalation and expansion study of isatuximab in combination with lenalidomide and dexamethasone for the treatment of relapsed/refractory MM	Phase 1 Dose escalation and expansion cohorts isatuximab P1F1 (N=57): 3 mg/kg Q2W, N=4; 5 mg/kg Q2W, N=3; 10 mg/kg Q2W, N=24; 10 mg/kg QW/Q2W, N=12; 20 mg/kg QW/Q2W, N=14	Completed CSR (cutoff-26-May-2016)
TCD13983 Supportive Phase 1b with combination therapy[e]	Patients with newly diagnosed MM who are non-eligible for transplant	A 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 cohort: Dose escalation and expansion cohorts isatuximab P1F1 (N=17): 10 mg/kg, N=13; 20 mg/kg, N=4; Ongoing patients may switch to isatuximab P2F2	ICBd: Completed CSR (database lock 31-Aug-2017)

MM: Multiple myeloma, PI: Proteasome inhibitor, IMiD: Immunomodulatory drug, HR: High Risk, PK: Pharmacokinetics, PD: Pharmacodynamics, ALL: Acute lymphoblastic leukemia, LBL: Lymphoblastic lymphoma, PFS: Progression-free survival, OS: Overall survival, P1F1: Cell line 1, Process 1, Formulation 1; P2F2: Cell line 1, Process 2, Formulation 2; ICBd: Isatuximab (P1F1) in combination with cyclophosphamide, bortezomib, and dexamethasone, IBLd: Isatuximab (P2F2) in combination with bortezomib, lenalidomide, and dexamethasone, BLd: Bortezomib, lenalidomide, and dexamethasone, ICd: Isatuximab (P2F2) in combination with carfilzomib and dexamethasone, Cd: Carfilzomib and dexamethasone, mCRPC: Metastatic castrate resistant prostate cancer, NSCLC: Non-small cell lung cancer, PD-1 : Programmed cell death-1, PD-L1: Programmed cell death-ligand 1

QW: Days 1 and 8 of a 14 day cycle; Q2W: Days 1 and 15 of a 28 day cycle in all studies, except TED10893 Phase 1 (Day 1 of a 14 day cycle); Q2W/Q4W: Days 1 and 15 of a 28-day cycle (first 2 cycles) and Day 1 of a 28 day cycle in subsequent cycles; QW/Q2W: Days 1, 8, 15, and 22 of a 28-day cycle (first cycle) and Days 1 and 15 of a 28-day cycle in subsequent cycles; QW/Q3W: Days 1, 8, and 15 of a 21-day cycle (first cycle) and Day 1 of a 21-day cycle in subsequent cycles. ICBd cohort: Induction phase (Cycle 1: Isatuximab given on Days 1, 8, 15, 22, and 29 of a 42-day cycle, Cycles 2-12: Isatuximab given on Days 1 and 15 of a 28-day cycle), Maintenance phase (Following Cycle 12, isatuximab is given on Day 1 of a 28-day cycle); ICd: Isatuximab 10 mg/kg QW/Q2W.

Five patients in TED10893 had CD38+ hematological malignancies other than MM.

High risk expansion: Patients who have relapsed within 6 months of autologous transplantation; have abnormal genotype (del [17p], >3 copies of 1q21, t [4, 14], or t [14, 16]) by cytogenetics or interphase fluorescence in situ hybridization; and have a high-risk gene expression profiling signature (if available).

Isatuximab in combination with lenalidomide and dexamethasone

ICBd cohort: Isatuximab in combination with cyclophosphamide, bortezomib, and dexamethasone, IBLd cohort: Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone.

2.4.2. Pharmacokinetics

Isatuximab PK and PD has been investigated in multiple myeloma patients treated with isatuximab IV as single agent in two Phase 1/2 studies TED10893 and TED14154 Part A which provide the key information. Further, the PK and PD data of isatuximab administered in combination with pomalidomide and dexamethasone (Pd) in the target population of relapsed refractory multiple myeloma (RRMM) were obtained from Phase 1b study TCD14079 Part A and a pivotal Phase 3 study EFC14335. Additionally, PK and PD data from 2 Phase 1b studies with other combination therapies are provided in studies TCD11863 (ILd, Phase 1b) and TCD13983 (ICBd, Phase 1b).

Phase 1 studies had intensive blood sampling schedules while Phase 2/3 studies had sparse blood sampling. Although non-compartmental analysis (NCA) was used to assess the PK of isatuximab within the individual studies, popPK modelling (popPK; Study POH0503) was the primary approach to describe isatuximab's target mediated disposition with time dependency.

The proposed posology is 10 mg/kg IV in combination with pomalidomide and dexamethasone once weekly for the first 4 weeks (one cycle), followed by every 2 weeks for the following cycles. In the

clinical studies, isatuximab was administered up to a dose of 20 mg/kg, either once weekly, every 2 weeks, every two weeks for 8 weeks followed by every 4 weeks, or every week for 4 weeks followed by every 2 weeks (the latter being the proposed posology, applied in Phase 3 Study EFC14335).

All isatuximab studies used an infusion volume based on patient weight, except for Study TCD14079 part B, which uses a fixed-dilution volume of 250 mL and infusion rates in mL/hour. No PK data were provided using the fixed volume posology.

Two isatuximab formulations have been used during the clinical development program: C1P1F1 (Cell 1, Process 1, Formulation 1; hereafter referred to as isatuximab P1F1) was used in the initial clinical trials and C1P2F2 (Cell 1, Process 2, Formulation 2; hereafter referred to as isatuximab P2F2), was introduced in 2015 using the same cell line, and is the medicinal product intended for commercial use.

Absorption

Not applicable since isatuximab is administered intravenously (IV).

Absolute / Relative Bioavailability

No bioavailability studies were performed. As isatuximab is administered intravenously, bioavailability is 100%.

Bioequivalence

Table 4. Overview of drug products used in clinical studies.

Drug Product (Cell Line/Manufacturing Process/Formulation)	Isatuximab P1F1	Isatuximab P2F2
Cell Line	Cell line 1 (C1) derived from Chinese Hamster Ovary using recombinant DNA technology	Cell line 1 (C1) derived from Chinese Hamster Ovary using recombinant DNA technology
Manufacture process	P1	P2
Formulation	Concentration 5 mg/mL 10 mM L-Histidine, 10% sucrose (w/v), 0.005% polysorbate 80 (w/v), pH 6.5	Concentration 20 mg/mL 20 mM L-Histidine, 10% sucrose (w/v), 0.02% polysorbate 80 (w/v), pH 6.0
Presentation	5 mg/mL as a concentrate for solution for infusion at 100 mg/20 mL (5 mg/mL) with reference to isatuximab active entity supplied in a 25 mL Type I colorless clear glass vial.	20 mg/mL as a concentrate for solution for infusion at 500 mg/25 mL (20 mg/mL) with reference to isatuximab active entity supplied in a 30 mL Type I colorless clear glass vial.

The effect of the different formulations (P2F2 versus P1F1) on the PK of isatuximab was evaluated by population PK approach (POH0461).

The PK of isatuximab P2F2 and P1F1 were described by a 2-compartment structural kinetic model with linear elimination from the central compartment in both models, with the parameter estimates summarized in Table 8 and Table 9. For each model, exposure parameters (Cmax after the first administration [Cycle 1 Day 1], Ctrough and cumulative AUC for 1 week, 2 weeks and 4 weeks) were derived using the individual parameters. An external visual predictive checks (VPC) were generated by simulating concentration-time profiles of isatuximab in study TED14154 Part A (isatuximab P2F2) using their dosing history and the Pop PK model developed from isatuximab P1F1.

Table 5. Parameters estimates of the selected base model (separate models for TED10893 and TED14154).

	P1F1 (TED10893)			P2F2 (TED14154)		
MODEL	2 compartment linear model					
Residual error	Combined			Proportional		
Omegas	Omega Q fixed			All		
-2LL	9177.5			5620.2		
BIC	9210.2			5649.5		
Fixed effect	parameter	RSE (%)	Shrinkage (%)	parameter	RSE (%)	Shrinkage (%)
CL (L/h)	0.0126	13	2	0.0112	20	6
V_1 (L)	4.92	5	20	5.52	7	8
Q (L/h)	0.0405	13	-	0.0632	23	32
V_2 (L)	4.44	14	35	6.75	10	44
Interindividual varialbility (%)						
ω_CL	77.8	12		98.9	15	
ω_V_1	27.8	13		32.2	16	
ω_Q	-	-		87.1	20	
ω_V_2	70.6	15		34.9	27	
Residual error						
additive (µg/mL)	4.99	22		-	-	
proportional (%)	19.8	4		20.2	3	
Total No. of subject	38			26		
Observations						
Total (Average, Min-Max)	794 (20.9, 6 - 69)			522 (20.1, 9 - 53)		

Abbreviations: CL : Clearance; V_1 : central volume; RSE: Relative standard error; V_2: peripheral volume; Q : Intercompartmental clearance; ω: Interindividual variability; -: Not applicable

Table 6. Descriptive statistics of individual isatuximab P1F1 and isatuximab P2F2 exposure parameters at 20 mg/kg with geometric mean ratios (POH0461).

Parameter		Number of patients		Geometric mean		Ratio	90% CI	
		TED10893	TED14154	TED10893	TED14154		Lower	Upper
CmaxD1	µg/mL	31	14	272.4	272.8	1.00	0.85	1.18
AUC1W	µg/mL	31	14	26897.8	24785.2	0.92	0.78	1.09
CT1W	µg/mL	31	14	106.3	98.0	0.92	0.73	1.16
AUC2W	µg/mL	31	14	67839.5	62299.0	0.92	0.77	1.09
CT2W	µg/mL	31	14	183.7	174.9	0.95	0.74	1.23
AUC4W	µg/mL	30	14	188075.7	168889.5	0.90	0.74	1.10
CT4W	µg/mL	30	14	296.5	278.6	0.94	0.70	1.26

AUC: area under the plasma concentration curve; AUC1W: cumulative AUC over 1 week; AUC2W: AUC cumulative over 2 weeks; AUC4W: cumulative AUC for 4 weeks; C_{max}: maximum plasma concentration; CT1W: C_{trough} at 1 week; CT2W: C_{trough} at 2 weeks; CT4W: C_{trough} at 4 weeks; SD: standard deviation; CI: confidence interval

The population PK estimates, CL, Q, and V1 are comparable between the 2 models with the exception of V2 (larger V2 for P2F2 model). A high inter-patient variability was observed for CL (78 % [P1F1] and 99 % [P2F2]) and a moderate one for V1 (28 % [P1F1] and 32 % [P2F2]) in both models. Overall, the geometric mean ratios (P2F2 versus P1F1) ranged from 0.90 to 1.00 and all the 90% CI limits were within the 0.70 to 1.26 interval.

The analysis was performed in the target patient population (MM) using data pooled for both isatuximab P1F1 and P2F2 from single agent and combination studies (n= 476; Table 10). The effect of changing drug material (Isatuximab P2F2 versus P1F1) was tested as a covariate and drug material

was identified as a covariate influencing the volume of distribution of isatuximab (-13% decrease of the central compartment volume of distribution for isatuximab P2F2 compared to isatuximab P1F1).

Table 7. Simulated mean (%CV) post-hoc isatuximab exposure in Cycle 1 and at steady-state by isatuximab material at 10 mg/kg QW/Q2W (POH0503).

Isatuximab material (N)	Cycle 1					Steady State[b]		
	1st administration[a]			4th administration[a]				
	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{1week} (µg.h/mL)	CT4W (µg./mL)	AUC4W (µg.h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{2weeks} (µg.h/mL)
P1F1 (191)	155 (23.5)	44.1 (53.7)	12900 (33.2)	150 (54.3)	91100 (39.8)	324 (44.9)	167 (76.6)	73600 (62.0)
P2F2 (285)	183 (32.6)	50.7 (47.7)	14700 (31.3)	163 (48.6)	102000 (35.3)	362 (39.0)	177 (69.0)	78800 (54.9)

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

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

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

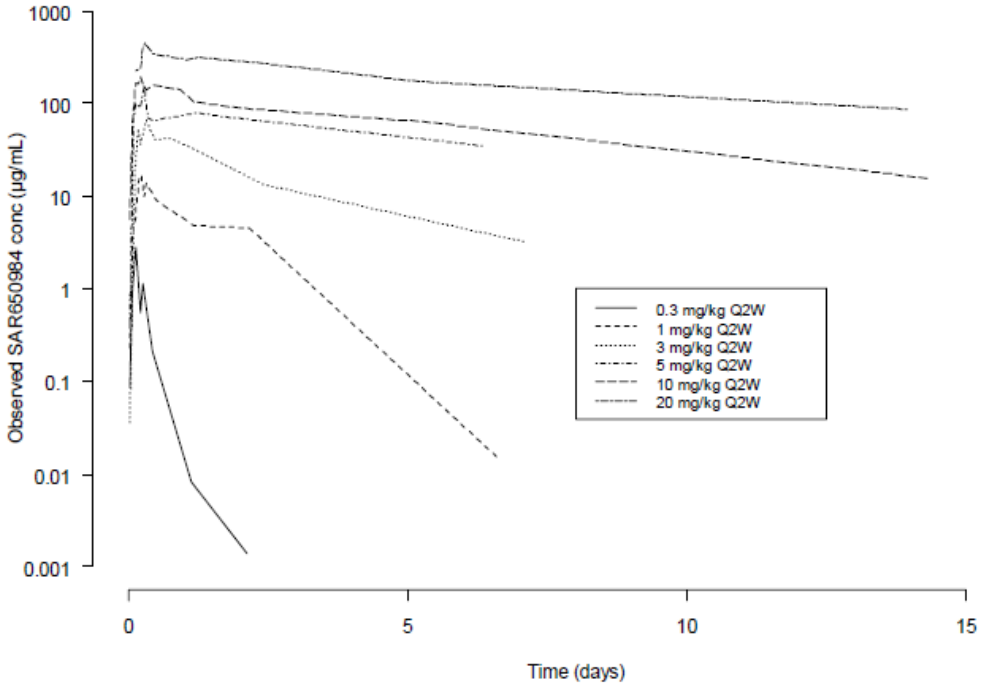
Distribution

Based on the Pop PK analysis (POH0503) performed in patients using all data pooled from single agent and combination studies (n= 476), the typical central compartment Vd of isatuximab was 5.13 L and the peripheral compartment Vd was 3.62 L, resulting in a total volume of distribution of 8.75 L .

Elimination

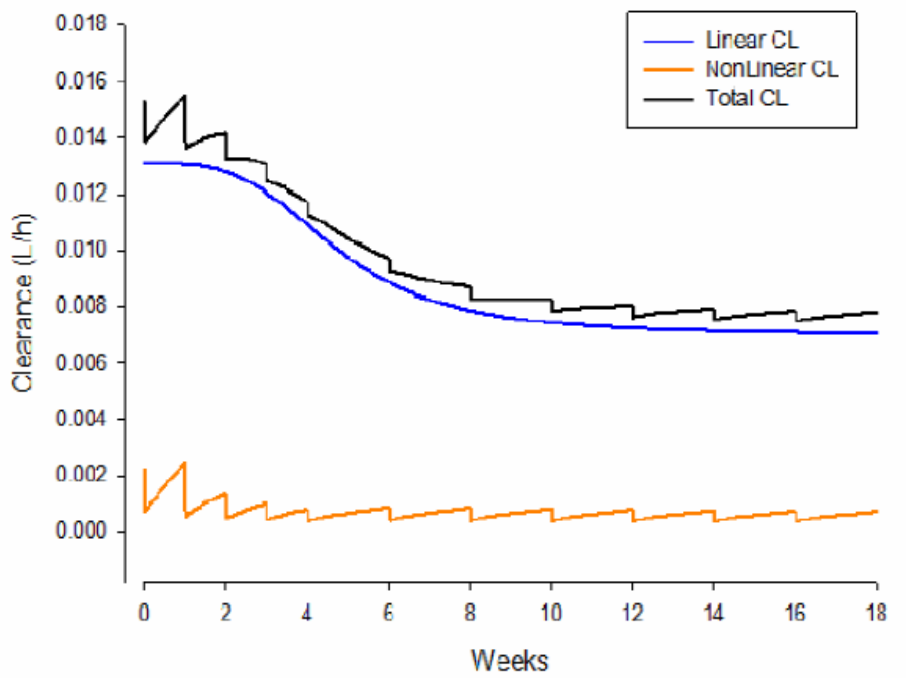
As a large protein, isatuximab is eliminated by enzymatic proteolysis into small peptides and amino acids.

Figure 2. Median isatuximab plasma concentration-time profiles following the first IV infusion of isatuximab (Phase 1TED10893).



Two parallel elimination pathways are responsible for isatuximab clearance, i.e. a nonlinear, target mediated pathway due to binding to the CD38 receptor predominating at low concentrations and a nonspecific, linear pathway predominating at higher concentrations (Fig. 5). Linear clearance is predominant over the range of plasma concentrations achieved over 10 mg/kg QW/Q2W, as it represents 90% of the total clearance at steady state. Based on popPK analysis, the linear clearance decreases by 50% from its initial value over the first 8 weeks of treatment, probably due to a lower IgG levels as well as a reduction of the inflammation obtained during treatment, a larger proportion goes through salvage pathways resulting in lower clearance. Isatuximab PK is characterized by a low plasma linear clearance at steady state of 9.55 mL/h (0.229 L/day), associated with a terminal half-life at steady-state of 28 days in a typical patient.

Figure 3. Typical linear, nonlinear, and total clearance of isatuximab over time following 10 mg/kg QW/Q2W (POH0503, base model).



No metabolism studies were conducted. Given that isatuximab is an IgG1-class antibody protein, it is expected to be degraded by non-saturable proteolytic catabolism processes into low-molecular-weight peptides and amino acids *in vivo*.

Dose proportionality and time dependencies

No apparent deviation from dose-proportionality for isatuximab exposure was noted between 5 and 20 mg/kg dose given every week for 4 weeks followed by every 2 weeks schedule (QW/Q2W) or QW. At doses lower than 5 mg/kg down to 1 mg/kg, non-proportional behaviour was noted, probably due to the different but relatively large contribution of target-mediated drug disposition to isatuximab exposure at lower doses.

Applying the posology: 10 mg/kg once weekly for 4 weeks and then once every 2 weeks, isatuximab exposure reaches steady-state after approximately 8 weeks. With this posology, as applied in the pivotal Phase 3 Study EFC14335, the mean predicted isatuximab C_{max} (CV%) and $AUC_{2\ weeks}$ at steady state (Cycle 6) when given in combination with pomalidomide/dexamethasone were 351 µg/mL (36.0%) and 72.6 mg.h/mL (51.7%), respectively.

The observed median accumulation ratios of approximately 1.8 for C_{max} and 3.1 for C_{trough} at steady-state are in line with the median overall $t_{1/2}$ of approximately 28 days and the once every 2 weeks administration schedule.

Interindividual variability for isatuximab clearance, as estimated from the popPK model POH0503, was large, i.e. 47.5%. Intraindividual variability was moderate.

Special populations

Renal impairment

The pop-PK analysis in 192 patients with mild renal impairment (60 mL/min/1.73 m2 ≤ estimated glomerular filtration rate (e-GFR) <90 mL/min/1.73 m2), 163 patients with moderate renal impairment (30 mL/min/1.73 m2≤ e-GFR < 60 mL/min/1.73 m2) and 12 patients with severe renal impairment (e-GFR <30 mL/min/1.73 m2) showed lack of effect in mild or moderate renal impairment.

Hepatic impairment. Out of the 476 patients of the population pharmacokinetic analyses, 65 patients presented with mild hepatic impairment [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate amino transferase (AST) > ULN] and 1 patient had moderate hepatic impairment (total bilirubin> 1.5 to 3 times ULN and any AST). Mild hepatic impairment had no clinically meaningful effect on the pharmacokinetics of isatuximab. The effect of moderate (total bilirubin >1.5 times to 3 times ULN and any AST) and severe hepatic impairment (total bilirubin >3 times ULN and any AST) on isatuximab pharmacokinetics is unknown.

Gender

Isatuximab PK data were obtained from 207 female and 269 male patients. The estimated effect on isatuximab exposure (C_{max}, C_{trough} and AUC) was limited, and therefore no dose adjustments are necessary based on gender.

Race

The popPK analysis consisted of data from 377 patients with Caucasian (79%) background, 25 Asian (5%), 18 Black (4%), and 33 other race (7%). No relevant difference in isatuximab exposure (C_{max}, C_{trough}, AUC) was observed among patients.

Weight

With the proposed weight-based dosing, steady-state exposure in patients with a higher body weight is increased compared to that in patients with lower body weight.

Age

In the popPK analyses, age was not a statistically significant covariate for isatuximab PK. Clinical studies included 476 subjects aged from 36 to 85 years old, of which 70 (14.7%) were >75 years of age.

Table 8. Number of elderly patients by age group and by PK trials included in the population PK analysis (Study POH0503).

PK Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
TED10893 phase 1 (N=73 pts)	27/73	5/73	0/73
TED10893 phase 2 stage 1 (N=95 pts)	29/95	7/95	1/95
TED10893 phase 2 stage 2 (N=90 pts)	31/90	15/90	0/90
TED14154 Part A (N=26 pts)	9/26	5/26	0/26
TCD14079 Part A (N=44 pts)	19/44	7/44	0/44
EFC14335 (N=148 pts)	65/148	30/148	0/148
TOTAL (N=476 pts)	180/476	69/476	1/476

Pharmacokinetic interaction studies

Effect of interacting drugs on isatuximab

Given that isatuximab is an IgG1-class antibody protein, it is catabolized into amino acids by general protein degradation process and is unlikely to be interacting with the metabolic enzymes of low-molecular-weight medicines used in combination. Further, metabolic enzymes, transporters, and protein binding, factors generally involved in interactions with low-molecular-weight medicines, are not considered to play a role in the PK of isatuximab. The absence of DDIs was confirmed by inter-study comparisons which showed that isatuximab exposures in combination studies were comparable to those observed in the single agent study TED0893, suggesting that these combinations (including Ld, Pd, and CBd) have no influence on the pharmacokinetics of isatuximab. In addition, an intra-study comparison showed no effect of dexamethasone on the pharmacokinetics of isatuximab.

Effects of isatuximab on interacting drugs

Given that isatuximab is an IgG1-class antibody protein, it is unlikely to affect the metabolic enzymes of low-molecular-weight drugs used in chemotherapy. Based on comparison with literature data, isatuximab had no impact on the pharmacokinetics of pomalidomide, lenalidomide, and cyclophosphamide. Potential risks of DDI caused by isatuximab due to the alteration of cytokine levels, especially IL-6, which has been shown to impact drug metabolizing enzymes such as CYP enzymes in humans, were considered by the Applicant. Transient elevation of cytokines, such as IL-6 and IFNγ, have been noted upon treatment with isatuximab; however, these transient elevations are expected to have a limited effect on CYP activity.

2.4.3. Pharmacodynamics

Mechanism of action

Pharmacodynamic modulation was investigated through CD38 receptor occupancy in the multiple myeloma plasma cells, and by changes in the immune cell subsets in the peripheral blood and T-cell clonality after isatuximab treatment.

The decrease of peripheral NK cells and CD19+ B-cells was seen in patients treated with isatuximab as a single agent or in combined treatments. $CD4^+$ T-cells and Tregs (CD3+, CD4+, CD25+, CD127-) were decreased in studies TED10893 (single agent) and TCD13983 (ICBd). The pharmacodynamic effects of isatuximab in multiple myeloma patients support its immunomodulatory mechanism of action. In addition to its effector functions, isatuximab induced T-cell response by clonal expansion of the T-cell receptor repertoire indicating an adaptive immune response.

Primary pharmacology

CD38 receptor occupancy

The CD38 receptor occupancy (RO) of multiple myeloma plasma cells was measured after treatment in bone marrow aspirates from patients from Phase 1/2 studies. When data obtained from all single agent studies at one month after treatment were combined, the median CD38 RO values increased from 12.8% to ~80% over the wide dose range of 1 mg/kg Q2W to 20 mg/kg Q2W. Over a narrow range of 10 to 20 mg/kg QW the CD38 RO values ranged from 79.4 to 84.1% (data from TED10893 Phase 1, TED10893 Phase 2 Stage 1, TED14154 single agent studies and TCD11863 combination study with lenalidomide/dexamethasone).

CD38 receptor density

The CD38 receptor density (RD) of multiple myeloma plasma cells was measured at baseline in bone marrow aspirates from 198 patients from Phase 1/2 studies (TED10893 Phase 1 and Phase 2 Stage 1, TED14154 Part A, TCD11863, TCD14079 and TCD13893 ICBd). CD38 receptor was abundant in plasma cells of most of the patients with multiple myeloma as expected. When all the single agent studies were combined (TED10893 Phase 1 and Phase 2 Stage 1 and TED14154 Part A), the median value was overall similar between 10 and 20 mg/kg QW/Q2W dose levels (150,068 versus 157,672 respectively) and between responders and non-responder patients (median value of 160,679.5 versus 141,904.5 respectively). No association between CD38 receptor density and clinical efficacy based on ORR was found after multivariate analysis with data from studies TED10893 Phase 1 and Phase 2 Stage 1. CD38 RD was similar in responders versus non-responder patients in all the studies (TED10893 Phase 1 and Phase 2 Stage 1,TED14154 Part A, TCD11863, TCD14079 and TCD13893 ICBd).

Soluble CD38

The level of soluble CD38 was measured at baseline from 184 patients from Phase I/II studies treated at doses above or equal to 3 mg/kg (TED10893 Phase 2 Stage 1, TED14154 Part A, TCD14079 Part A, TCD13983 IBCd). The level of soluble CD38 was quite low (0.10 to 7.2 ng/mL) and far below the plasma concentration of isatuximab (C_{trough} >100 µg/mL) and therefore would unlikely impact isatuximab pharmacokinetics. The level of soluble CD38 at Cycle 1 and Cycle 3 was not associated with parameters of clinical response. The level of soluble CD38 decreased at Cycle 3 compared to Cycle 1 in study TED10893, whereas it slightly increased in the 2 combination studies.

CD38 mRNA expression

CD38 mRNA levels (normalized values) were similar at screening between responders and non-responders and for all or ABD isoforms in all the studies (TED10893 Phase 2 Stage 1, TCD14079 part A, TCD13983 IBCd). Differences between responders and non-responders observed may be due to the low number of samples and the high standard deviations (Table 12 from 2.7.2 document, 3.3.4).

Table 12. Differences between responders and non-responders in CD38 mRNA isoforms.

CD38 mRNA isoforms		TED10893 Phase 2 Stage 1		TCD14079 part A				TCD13983 IBCd
		Screening		Screening		EOT		Screening
		NR	R	NR	R	NR	R	All
ALL	Median	22.50	34.20	23.30	34.45	11.47		10.24
	Min:Max	2.7 to 107.0	9.9 to 85.7	2.3 to 244.7	8.1 to 88.4	4.2 to 18.7		3.9 to 46.7
	Patient number	53	15	13	17	2	0	10
ABD	Median	14.20	21.90	21.77	32.56	8.64		7.04
	Min:Max	1.4 to 73.8	5.0 to 53.7	1.9 to 192.9	7.6 to 70.0	3.0 to 14.3		2.8 to 39.4
	Patient number	53	15	13	17	2	0	10

BL: baseline; R: responders (at least with PR); NR: non-responders

Phenotyping of immune cells

The median change in immune blood cells values observed at Day 1 of Cycle 3 compared to Day 1 of Cycle 1 for each type of immune cells for responders (with at least Partial Response) and non-responders was analysed in studies TED10893 Phase 2 Stage 1 and TCD14079 Part A. Only data for the all treated population were provided for TCD13983 study due to the very low number of not-responder patients (N=1). The decrease of NK cells and of CD19+ B-cells was consistently seen in patients treated with isatuximab as a single agent or in combined treatments.

$CD4^+$ T-cells and T_{regs} were decreased in studies TED10893 (single agent) and TCD13983 (ICBd). T_{regs} were also slightly decreased in the responder population of studies TCD14079 Part A (IPd). $CD3^+$ T-cells were decreased in study TCD13983 (ICBd) only.

Secondary pharmacology

Immunogenicity

Immunogenicity is assessed in all clinical studies of isatuximab. Among the 6 completed studies (EFC14335 (IPd arm only), TCD14079 Part A, TED10893, TED14154 Part A, TCD11863, and TCD13983 ICBd), a total of 14 patients exhibited a positive response in the ADA assay in at least one patient sample. Among them, one patient was positive at baseline only (before the first administration); this patient was classified as transient, non-treatment induced positive ADA. The incidence of positive ADA response across studies was therefore 2.3% (13 of 564) with a median titer of 10 (maximum titer of 320 with the majority ≤80). Most of these responses were transient, with only 2 out of the 13 treatment-induced ADA positive patients showing persistent ADA kinetics with a median time to first onset of 1 month. No impact of the dose or of schedule of administration was observed on the incidence of ADA positive response. In addition, ADA positive response was observed irrespective whether isatuximab was applied as single agent (N=8) or given in combination with Ld (N=4) or Pd (N=1). The change from isatuximab P1F1 to P2F2 did not increase the incidence of ADA positive

response (ie, 1 treatment induced ADA positive patient with isatuximab P2F2 versus 12 treatment induced ADA positive patient with isatuximab P1F1).

There was no confirmed positive ADA response in the pivotal Phase 3 study EFC14335 for the IPd combination, and hence, no neutralizing ADA assessment was done.

Overall, the presence of treatment-emergent ADAs did not appear to have an effect on isatuximab concentrations when it is assessed at individual patient level (ie, individual concentration-time profile) nor on individual PK estimate (linear CL) and on the population PK parameter estimates of the models before and after withdrawal of the concentrations of positive ADA samples.

Exposure-response analysis for QTc with single agent therapy (studyTED10893 Phase 1)

The ECG parameters considered for the PK/PD ECG analyses were corrected QT interval by Fredericia (QTcF), heart rate, pulse rate and QRS, based on Holter digital extract, unless otherwise specified. The QTcF was considered as the most relevant pharmacologic parameter. The relationship between baseline adjusted QTcF/Heart rate/Pulse rate/QRS changes and isatuximab plasma concentrations was assessed using a linear mixed effects model on Day 1, Cycle 1 with data from 81 patients from study TED10893 Phase 1 using the overall concentrations from mid infusion to 24 hours. Patients treated with isatuximab at doses ranging from 0.3 to 20 mg/kg QW or Q2W were included in the analysis. The simulated C_{max} at steady state of 148 patients from the pivotal Phase 3 Study EFC14335, assuming they all received 10 mg/kg QW/Q2W were in the range of those observed following the first administration of isatuximab and used to predict the different PD outcomes.

The slope of the concentration-QT relationship was small (-0.003), representing a 0.3 msec QTcF decrease per 100 µg/mL increase in isatuximab concentration indicating no apparent effect on QTcF change from baseline. For heart rate, the confidence interval of the slope of concentrations (0.023) did not include 0. This represents a 2.3 bpm increase per 100 µg/mL increase in isatuximab concentration. Potentially clinically significant abnormalities (PCSAs) in heart rate were generally isolated events, and were not considered clinically significant by the investigators, except for one case of sinus tachycardia which was associated with IRs in a patient who went on to receive 14 cycles of treatment. No PK/PD relationship was observed between isatuximab plasma concentrations and pulse rate or QRS.

Genetic differences in PD response

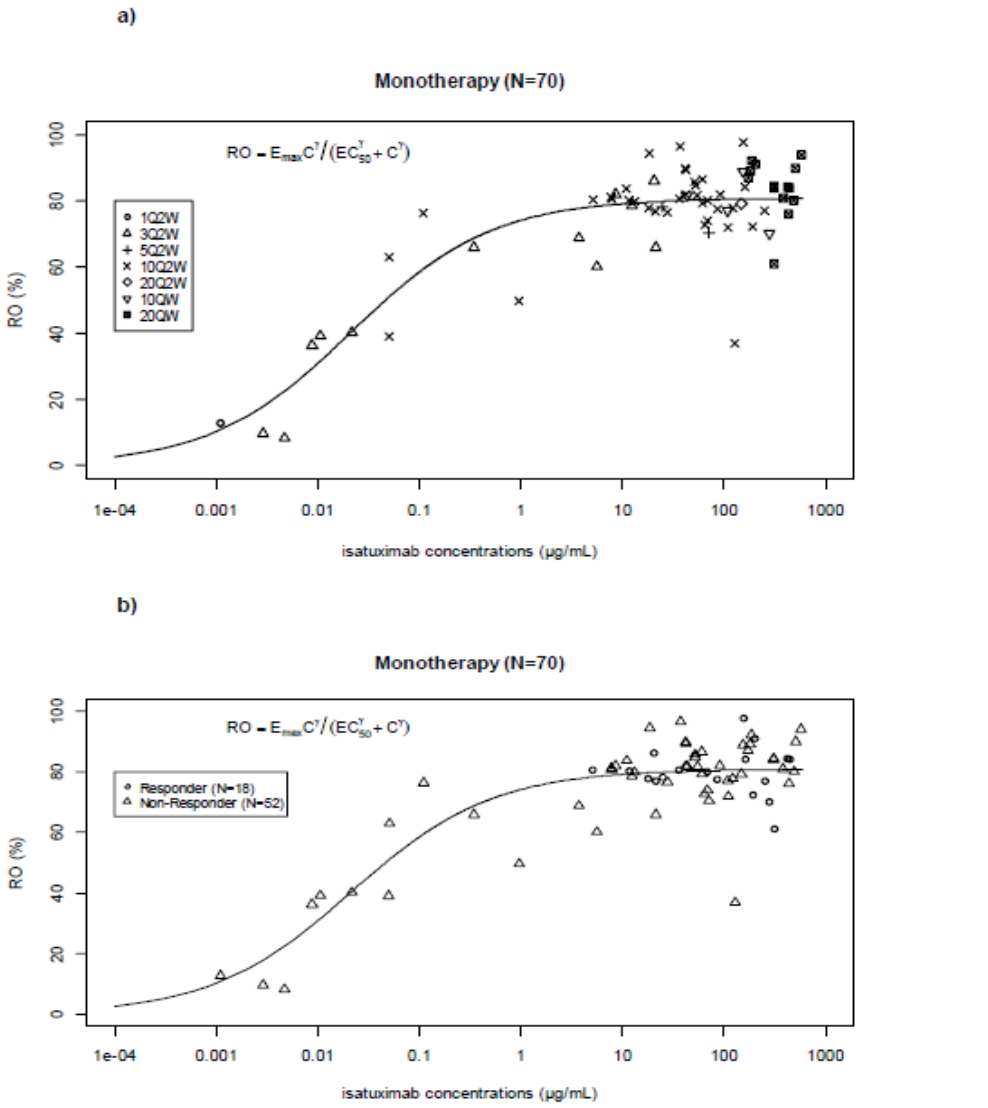
F158V bi-allelic polymorphism of FCGR3A gene was analyzed in blood samples from 481 patients in all studies (TED10893 Phase 1 and Phase 2 Stage 1, TCD14079, TCD11863, TCD13983 and EFC14335). FCGR3A polymorphism was not associated with ORR, PFS or OS. Genes coding for KIR killer cell Ig-like receptors and their HLA ligands were not associated with parameters of clinical response in Phase 1/2 studies.

PK/PD

PK/PD evaluations were based on modelling using data obtained from three primary settings: isatuximab as a single agent, or in combination with either pomalidomide/dexamethasone or lenalidomide/dexamethasone.

An exploratory analysis between isatuximab plasma concentration and CD38 receptor occupancy at one month showed that 99% of plateau for occupancy (being 80%) was reached over the wide dose range of 1 mg/kg Q2W to 20 mg/kg Q2W and for plasma concentrations of approximately 31 µg/mL as mentioned in the Primary pharmacology section above (Fig.5). Over a narrow range of 10 to 20 mg/kg QW the CD38 RO values ranged from 79.4 to 84.1% (data from TED10893 Phase 1, TED10893 Phase 2 Stage 1, TED14154 single agent studies and TCD11863 combination study with lenalidomide/ dexamethasone).

Figure 4. Relationship between Receptor Occupancy and isatuximab plasma concentrations by a) dose schedule and b) responder status.



Parameter (RSE%) : E_{max}: 80.8% (2%), EC_{50}: 0.0214 (32%) µg/mL, γ= 0.0214 (22%), constant residual error: 9.91 (8%)
EC_{50}: half maximal effective concentration; E_{max}: maximum effect, γ: coefficient of sigmoidicity; QW: every week; Q2W: every 2 weeks;
RO: receptor occupancy

Exposure Response - Efficacy

Design: Exposure-efficacy analysis with ORR and PFS as efficacy endpoints was conducted with PK/PD data from Study EFC14335 alone (two arms with IPd vs pomalidomide/dexamethasone).

The Pop PK model (Report POH503) was used to provide for each patient its individual PK parameters from which predicted exposure parameters were derived, C_{trough} concentration at week 1 (CT1W), at week 4 (CT4W), cumulative AUC over 1 or 4 weeks (AUC1W or AUC4W), C_{max} of the first administration at Cycle 1 or Cycle 2 (C_{max}D1C1 or C_{max}D1C2), maximum value of C_{max} (MaxC_{max}).

ORR defined the proportion of patients achieving a stringent complete response (5sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) as best overall response (BOR).

PFS defined as the time from the date of randomization to the first documented data of progressive disease or death due to any cause.

First, demographic, disease and baseline characteristics potentially influential of the efficacy endpoints (ORR or PFS) in the absence of isatuximab administration were screened based on control arm population only. Using Cox regression model (PFS) or logistic regression model (ORR), a univariate analysis was conducted. In case of more than 2 covariates associated with p-values <0.10, a stepwise procedure including those covariates followed the univariate analysis. The final set of covariates was used to identify the best PK predictor and link function (linear, log-linear, E_{max}) with PFS or ORR in comparing these covariate adjusted models using AIC criteria, based on the whole population. The exposure value of Pd arm was set to 0. Then, once the PK predictor and link function were identified, univariate analysis was conducted to assess the effect of each covariate adjusted on the PK effect. Those covariates significant at the 0.10 level were used in the multivariate analysis. The multivariate analyses performed with the best PK predictor and stepwise inclusion and deletion of covariates using a significance level of 10% for variable entry and of 5% for removal at each step.

ORR

Results: Data from n= 297 patients, with 149/148 patients for Pd/ IPd arm in EFC14335.

Two exploratory analysis were performed to find influential covariates and to explore the correlation between PK exposure metrics and clinical response to isatuximab. Based on Table 13 after logistic regression with stepwise selection of covariates, baseline bone marrow plasma cells by category (<50% vs > 50%) was the only covariate that remained significant (First row AIC of 184.567).

Table 9. Estimates of covariate effects in Pd control arm.

Variable	Label	DF	p-value	N-Used	AIC	AUC
PLSGR3	Baseline Plasma Cells in Bone Marrow <50 vs. >=50	1	0.0082	144	184.567	0.61
TSDIAGYR	Time Since Diagnosis (Years) to Rand	1	0.0084	149	191.605	0.62
SERISSTG	Revised ISS Stage at Study Entry	2	0.0181	149	190.105	0.62
TSDIAGYGR	Time Since Diagnosis <=5 vs. >5 years	1	0.0222	149	193.846	0.60
PLSGR0	Baseline Plasma Cells in Bone Marrow <5 or >=50 vs. >=5 - <50	1	0.0254	144	187.196	0.60
PLSGR4	Baseline Plasma Cells in Bone Marrow <5, 5 - <50 and >=50	2	0.0285	144	186.446	0.62
PLSCEBL	Baseline Plasma Cells in Bone Marrow (%)	1	0.0349	144	187.616	0.59
GFRGR2	Baseline e-GFR <60, 60-<90 and >=90	2	0.0404	141	185.993	0.62
CAREBL	Baseline Chromosomal Aberration Risk Estimated	2	0.0411	149	193.696	0.61
ALPBL	Baseline ALP (IU/L)	1	0.0583	149	194.749	0.58
B2MGR2	Baseline Beta-2 Microglobulin <3.5 vs. >=3.5	1	0.0627	146	191.800	0.58
PLSGR2	Baseline Plasma Cells in Bone Marrow <5, 5 - <20 , 20-<50 and >=50	3	0.0650	144	188.340	0.62
GFREBL	Baseline e-GFR (mL/min/1.73m)	1	0.0710	141	187.153	0.62
ALBGR1	Baseline Albumin <35 vs. >=35	1	0.0876	149	196.068	0.57

PGM=PRODOPS/SAR650984/OVERALL/DREG_POH0648/REPORT/PGM/pk_0648_univ_logistic_efc_t.sas
OUT=REPORT/OUTPUT/pk_0648_univ_logistic_efc_t_i.rtf (04APR2019 1:12)

Among the different PK exposure parameters tested, according to the applicant CT4W was found to be the best predictor (p <0.001) of ORR (Table 14). Indeed, as shown in Figure 7 where ORR increase as CT4W increase.

A time dependent linear clearance was identified for isatuximab (Report POH0503) with a linear decreasing over time. This time dependency of the CL could be an evidence of a relationship between

linear kinetics and disease status evolution. At week 4, no statistical difference was observed between responders and non-responders with median CL of 0.0107 L/h and 0.0121 L/h respectively. Therefore CT4W is likely to be less confounded by disease status than a steady state related exposure variable and was then considered as an acceptable metric for an exposure response analysis.

Table 10. Estimate of different PK exposure parameter effect: univariate analysis for exposure-response model for ORR adjusted on bone marrow plasma cell groups.

Model	PK or Emax Estimate	PK or Emax p-value	Log(EC50)	Std log(EC50)	N used	AIC	AUC
LogCmaxD1C2	0.2136	<.0001			279	357.65	0.6942
Emax_CmaxD1C2	1.2356	<.0001	-8.6810	2622.00	279	359.5	0.6925
CmaxD1C2	0.0032	<.0001			279	361.37	0.6990
CT4W	0.0073	<.0001			291	372.19	0.6949
LogCT4W	0.2491	<.0001			291	372.31	0.6944
Emax_CT4W	2.7515	0.3601	5.1958	2.12	291	373.56	0.7009
AUC4W	0	<.0001			291	375.1	0.6897
LogAUC4W	0.0979	<.0001			291	376.26	0.6886
LogMaxCmax	0.1916	<.0001			291	376.53	0.6863
Emax_AUC4W	3.5165	0.6102	12.2030	3.03	291	376.86	0.6899
LogAUC1W	0.1137	<.0001			291	377.11	0.6771
LogCmaxD1C1	0.2036	<.0001			291	377.87	0.6735
Emax_MaxCmax	1.812	0.2147	5.3033	2.07	291	378.26	0.6818
MaxCmax	0.003	<.0001			291	378.42	0.6865
CT1W	0.0176	<.0001			291	378.71	0.6865
Emax_CmaxD1C1	1.0932	<.0001	-11.3200	2611.00	291	378.92	0.6735
Emax_AUC1W	1.0933	<.0001	-6.3230	1634.20	291	378.92	0.6820
LogCT1W	0.2623	<.0001			291	379.06	0.6784
AUC1W	0.0001	<.0001			291	380.03	0.6762
Emax_CT1W	3.6927	0.6931	4.9459	3.69	291	380.57	0.6843
CmaxD1C1	0.0039	0.0012			291	385.69	0.6563

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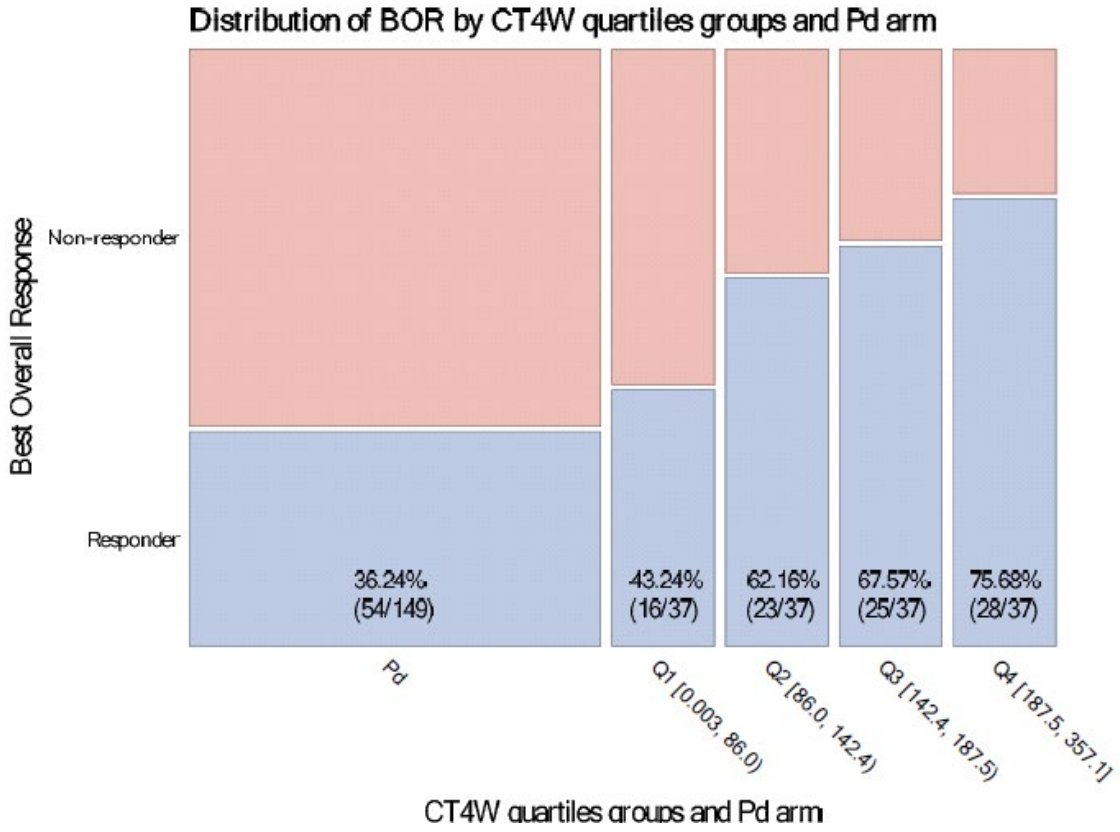
Figure 5. Distribution of Responder/Non responder by CT4W quartiles.



Base model

Table 15 presents the parameter estimates for the linear model (logit function) and Table 16 the observed vs model predicted ORR with CT4W as a descriptor. A good agreement is observed between predicted and observed ORR probability.

Table 11. Parameter estimates for the Base linear model with only CT4W

Parameter	Estimate	Standard Error	p-value	95% Confidence Limits
Intercept	-0.5590	0.1547	0.0003	(-0.8623, -0.2557)
CT4W	0.00784	0.00152	<.0001	(0.0049, 0.0108)

PGM=PRODOPS/SAR650984/OVERALL/DREG_POH0648/REPORT/PGM/pk_0648_orr_est_ct4w_t.sas
OUT=REPORT/OUTPUT/pk_0648_orr_est_ct4w_t_i.rtf (03APR2019 13:58)

Table 12. Observed vs model-predicted ORR probability from the logistic regression model with only CT4W.

	Response Rate (%)	N	Observed Rate (95%CI)	Predicted
Median	Patients with 0<CT4W< Median(CT4W)	74	52.70 (40.75, 64.43)	51.57
	Patients with CT4W>= Median(CT4W)	74	71.62 (59.95, 81.50)	72.48
Q1	Patients with 0<CT4W< Q1(CT4W)	37	43.24 (27.10, 60.51)	44.64
	Patients with CT4W>= Q1(CT4W)	111	68.47 (58.96, 76.96)	67.82
Q3	Patients with 0<CT4W< Q3(CT4W)	111	57.66 (47.92, 66.98)	56.88
	Patients with CT4W>= Q3(CT4W)	37	75.68 (58.80, 88.23)	77.46
Control	Pd arm	149	36.24 (28.53, 44.51)	36.38
	IPd arm	148	62.16 (53.83, 70.00)	62.02

PGM=PRODOPS/SAR650984/OVERALL/DREG_POH0648/REPORT/PGM/pk_0648_orr_observe_predict_isaonly_t.sas OUT=REPORT/OUTPUT/pk_0648_orr_observe_predict_isaonly_t_i.rtf (04APR2019 0:58)

Final model

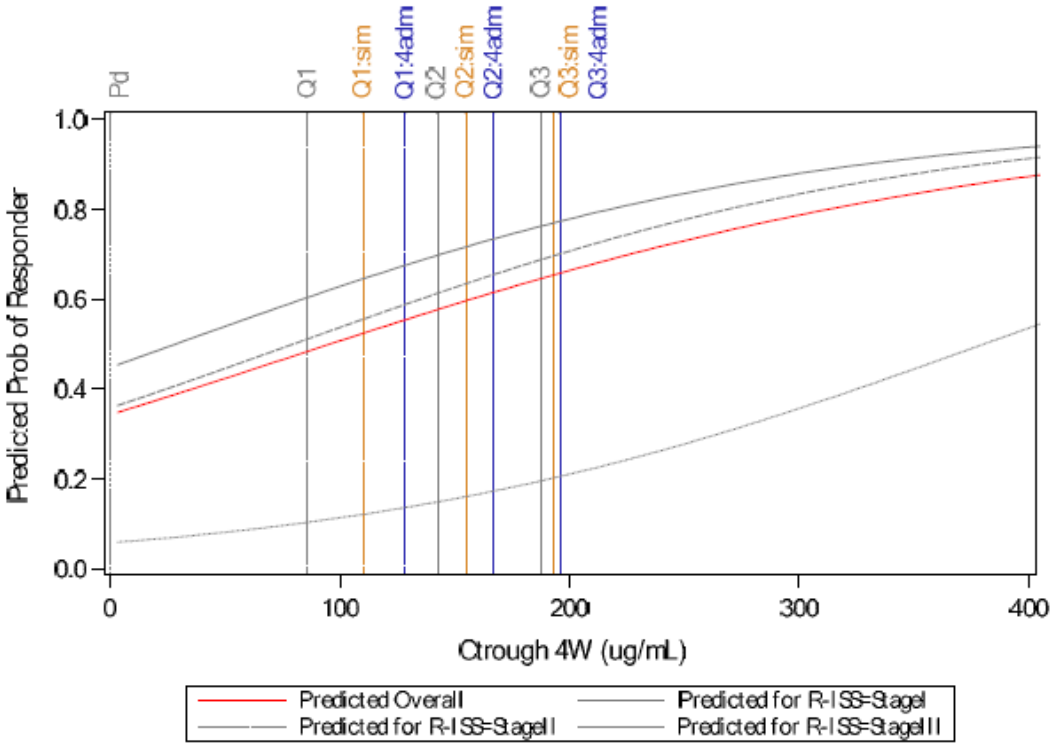
The covariates that were found to be significantly associated with ORR in the univariate analyses were integrated in the exposure-response model using a stepwise inclusion/deletion approach. Final PD parameter estimates are provided in Table 17. The final model included CT4W, time since diagnosis and R-ISS score and an interaction between these two covariates.

Table 13. Final logistic regression model for isatuximab exposure-response relationships for ORR.

Parameter		Estimate	Standard Error	p-value	95% Confidence Limits
Intercept		-4.8840	1.3899	0.0004	(-7.6081, -2.1599)
CT4W		0.00732	0.00159	<.0001	(0.0042, 0.0104)
TSDIAGYR		0.4968	0.1859	0.0075	(0.1325, 0.8612)
SERISSTG	Stage I	4.1139	1.4776	0.0054	(1.2179, 7.0099)
SERISSTG	Stage II	3.8971	1.4160	0.0059	(1.1219, 6.6723)
TSDIAGYR*SERISSTG	Stage I	-0.3636	0.2045	0.0754	(-0.7644, 0.0373)
TSDIAGYR*SERISSTG	Stage II	-0.4011	0.1912	0.0359	(-0.7758, -0.0264)

Figure 8 presents the exposure-response relationship model by expected probability of being responder for the whole population (solid red line) and by R-ISS stage (grey line) according to each quartile of CT4W and simulated CT4W assuming they all received 10 mg/kg QW for 4 weeks.

Figure 6. Model-predicted probability of ORR by R-ISS stage, time since diagnosis set to median value.



PFS

Results

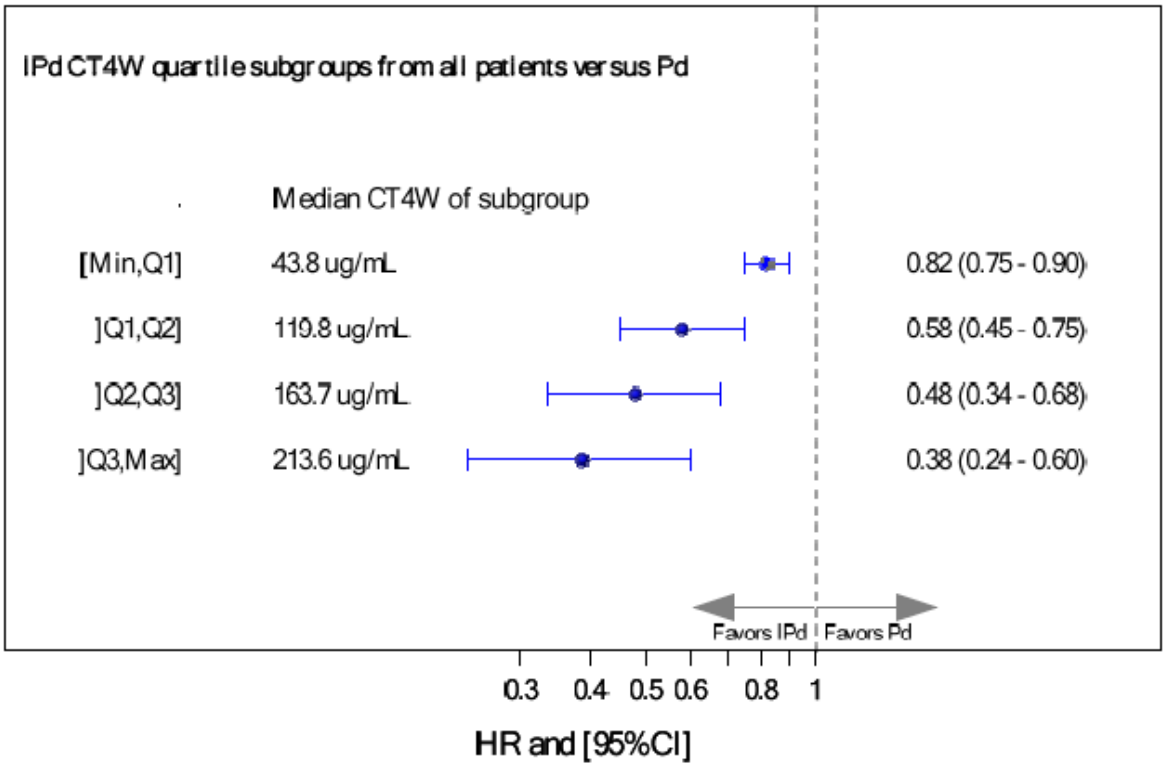
The final model was constructed using the same methodology as for ORR, following first an exploratory analysis, then the development of a base model and a search of covariates of interest. CT4W concentration were split in two groups instead of 4 groups (based on quartiles).

Table 14. Parameter estimates from the Weibull parametric hazard model for isatuximab ER relationship with PFS.

Parameter	Estimate	p-value
$Log(\lambda_0)$	3.9593	<.0001
θ	0.003745	<.0001
β_1	-0.6271	0.0043
β_2	-0.4412	0.0004
β_3	0.04460	0.0023
α (shape parameter)	1.2209	<.0001

The PFS HR associated with CT4W showed that patients in all isatuximab exposure quartiles have positive treatment effect (HR<1). The treatment effect is more pronounced in 2nd quartile (HR 0.58), 3rd quartile (HR 0.48) and 4th quartile (HR 0.38) than in patients in the lower quartile of exposure as shown in Figure 9.

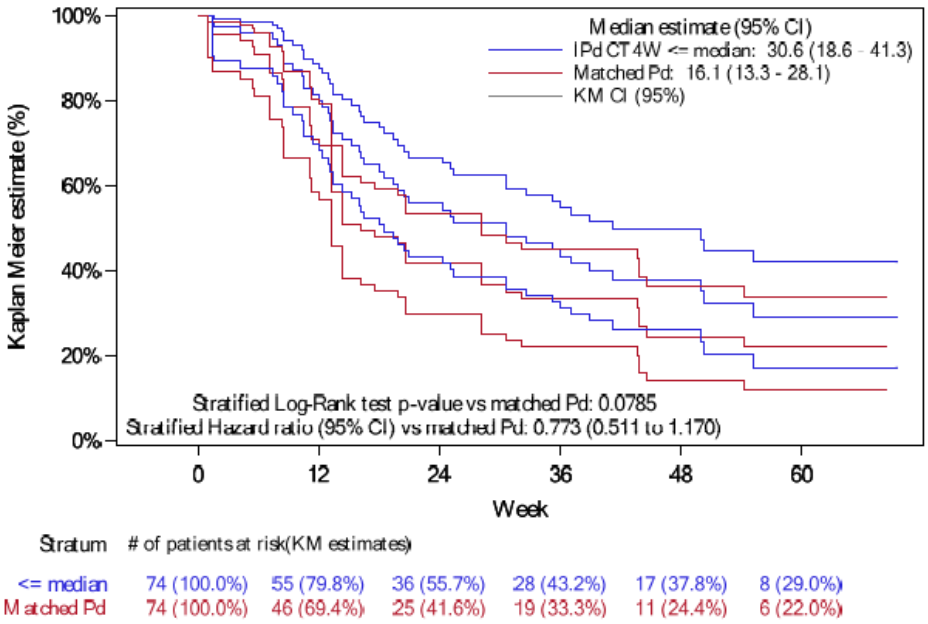
Figure 7. Forest plot of HR associated with CT4W of PFS at the median, 5th and 95th percentiles by CT4W quartiles.



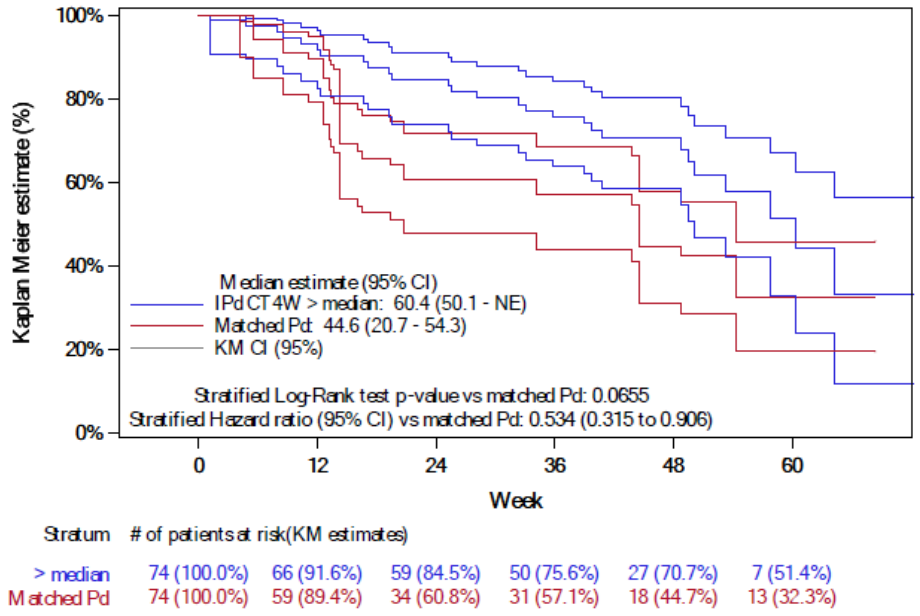
Furthermore, patients with isatuximab in the two lowest and the two highest quartiles (ie, ≤ or > median C_{trough} at 4 weeks) showed 14.5 and 15.8 weeks increase in median PFS compared to matched active control as shown in Figure 10 which results in a HR of 0.773 and 0.534 for the two lower CT4W (≤ median C_{trough} at 4 weeks) and higher CT4W (>median C_{trough} at 4 weeks) groups, respectively.

Figure 8. Kaplan-Meier survival curves with Pomalidomide control arm matched to (a) first and second quartiles 5Q1 and Q2) group and (b) third and fourth quartiles (Q3 and Q4) group.

a)



b)



ER-Safety

Design: Exposure-safety analysis used pooled data from Studies TCD14079 Part A and EFC14335. Safety endpoints consisted of IRs, heamatological toxicities, infection or respiratory events. The Pop PK model (Report POH503) was used to provide for each patients its individual PK exposure parameter. For the purpose, C_{max}D1C1, C1TW and AUC1W were explored for IRs because the majority of IRs occurred after the first dose, while for the other safety endpoint all the derived PK exposure parameters were used.

First, exploratory analyses were conducted using PK exposure parameters and safety endpoints of interest with the incidence rates of AEs summarized according to quartiles of the exposure metrics, and corresponding 95% CI. Analyses were performed for the overall population (Safety PK/PD population), for the Phase 3 study EFC14335 and subgroup analysis (Ig MM type). Univariate and multivariate analysis using logistic regressions were to be performed based on the findings from these exploratory analyses. Exposure parameters estimated after the first administration were explored for IRs because the majority of IRs occurred after the first dose, while PK exposure parameters after repeated administrations were investigated for the other safety endpoints.

Results: There was no apparent relationship between an increase of isatuximab C_{max},c1d1 and IRs, nor between an increase in C_{max},c1d1 or Cpost-infusion,max and an increase in the incidence of the examined AEs of interest including, thrombocytopenia, neutropenia, lymphopenia, respiratory events, cardiac arrhythmia, cardiac and nervous system disorders based on the pooled safety PK/PD population or on data from study EFC14335 alone. When comparing to the pomalidomide control arm (EFC14335), there was a trend of higher neutropenia, and cardiac arrhythmias and disorders in the isatuximab/pomalidomide arm, but with no difference between the quartiles of isatuximab exposure for neutropenia and a trend to less cardiac events in the highest exposure quartile.

In addition, there was a trend toward decreasing rate of Grade ≥3 anemia as the drug exposure increased, with patients in the low-exposure quartile of Q1 having the highest incidence. A slightly lower event rate of Grade ≥3 infections was observed in patients in the high-exposure quartiles (Q3 and Q4) than in patients in the low-exposure quartiles (Q1 and Q2). A lower incidence of IRs was observed for IgG patients compared to the non-IgG MM patients.

Overall, comparable results were observed for the other PK metrics (AUC and C_{trough}) tested at any time point and for the subgroup analysis (IgG and non-IgG MM type patients).

Immunogenicity

ADA

The incidence of treatment-emergent ADA is low (2.3%). The presence of treatment-emergent ADA did not appear to have an effect on isatuximab concentrations.

Influence of disease characteristics on isatuximab pharmacokinetics

IgG and non-IgG Myeloma type patients.

The Ig MM type (IgG versus non-IgG) was shown to affect isatuximab pharmacokinetics. The typical linear clearance at steady state was 2.1-fold higher in IgG patients compared to non-IgG patients due to the competition of IgG and isatuximab for recycling through FcRn. The magnitude of change in linear clearance with repeated dosing was comparable between IgG and non-IgG patients but occurred slower in IgG patients compared to non-IgG patients (typical after 6.3 and 2.5 weeks, respectively).

High and low β2 microglobulin patients.

The level of β2 microglobulin appears to affect the isatuximab pharmacokinetics with a 30% difference in exposure between high (>5.5 mg/L) and low (<3.5 mg/L) β2 microglobulin.

2.4.4. Discussion on clinical pharmacology

During the development plan, two different sources of isatuximab were used, from the same cell line, i.e., Product 1/Formulation 1 (P1F1) and Product 2/formulation 2 (P2F2). P2F2 will be the commercial formulation, and this formulation has been used in the pivotal Study EFC14335. Based on popPK

analyses, no relevant difference was noted between P1F1 and P2F2 isatuximab, whereas also the exposure-response curves obtained for P1F1 and P2F2 are comparable. Therefore, the PK data obtained with either of these isatuximab formulations can be used in support of the current application.

All isatuximab studies used an infusion volume based on patient weight, except for Study TCD14079 part B, which uses a fixed dilution volume of 250 mL and infusion rates in mL/hour. No PK data were provided using the fixed volume posology, which is the finally proposed regimen in the SmPC. Overall, the Aplicant demonstrated, based on popPK simulations, that the change of the duration of infusion by using a fixed 250ml volume as compared to the applied weight-based infusion volume has minimal to no impact on isatuximab PK. Therefore, no effect on efficacy or safety is expected, and the use of a fixed volume infusion is expected to yield comparable efficacy and safety as that observed in studies applying a weight-based infusion volume. The final analysis as per statistical analysis plan (including efficacy endpoints) for study TCD14079 part B requested by the CHMP did not reveal differences in efficacy and safety. The fixed volume infusion is considered acceptable (See Efficacy and Safety sections).

The volume of distribution of 8.75 L, estimated based on the final popPK model, suggests that isatuximab is primary distributed in the vascular systems with some limited extravascular tissue distribution, consistent with what is known for other IgG1 class antibodies. At steady-state, isatuximab PK is characterized by a low plasma linear clearance of 0.00955 L/h (0.229 L/day), associated with a terminal half-life of 28 days in a typical patient. In the non-IgG subpopulation (in fact representing 'normal' IgG1 conditions), $t_{1/2}$ appears to be approximately 45 days. The Applicant states that steady-state is reached later in IgG MM patients as compared to non-IgG MM patients. This finding is explained by the fact that, although the $t_{1/2}$ at steady state is shorter in IgG MM patients (26 days) than in non-IgG MM patients (45 days) due to a higher linear CL, the time to achieve steady state is longer in IgG MM patients as it takes longer for the CL (and the half-life) to stabilize (in 6 vs 12 weeks).

With respect to popPK analyses, overall, the developed model is considered adequate to describe the PK characteristics of isatuximab.

With respect to patients with hepatic impairment, it is agreed with the Applicant that from the popPK study POH0503 no conclusion can be drawn regarding the isatuximab PK in patients with moderate (and severe) hepatic impairment. Considering the fact that isatuximab is an antibody, a warning on the lack of PK data in patients with moderate or severe hepatic impairment is considered not needed, and the mentioning of the absence of PK data only as a fact in sections 4.2 and 5.2 of the SmPC is agreed.

The pop-PK analysis in 192 patients with mild to severe renal impairment showed no effect on isatuximab exposure and no need for dose adjustment (See SmPC sections 4.2, 5.2).

With the proposed weight-based dosing, exposure in patients with a higher body weight is somewhat higher than that in patients with lower body weight. The difference in C_{trough} at 4 weeks (CT4W) between patients <50 kg and patients >100 kg is a factor of 2 (92.8 µg/mL vs 186 µg/mL). However, the clinical response observed in low weight patients was in line with the overall response observed. Further, based on Exposure-Response analysis, the lower than average exposure obtained in low weight patients is still in the category for which efficacy can be expected. Vice versa, no differences with respect to safety were noted in high weight patients having increased exposure as compared to average. Based on this discussion, it is agreed that no modification of the dose in low- or high weight patients is necessary.

No clinical/PK data were available in patients older than 85 years, and therefore, no valid dosing recommendations for patients older than 85 years could be proposed. This is adequately addressed by the Applicant with a warning in the SmPC.

The obligation to submit the results of studies with Sarclisa in paediatric patients from 28 days to less than 18 years of age has been deferred (SmPC section 5.1).

In line with information on the dose-proportionality described earlier the pharmacokinetic behaviour of isatuximab demonstrated target-mediated drug disposition which was evident, especially in individual patients, at doses below 5 mg/kg. Above this dose, specifically at doses of 10 mg/kg QW, 20 mg/kg Q2W and QW, target-mediated drug disposition was no longer evident, indicative of saturation of the target for these doses/regimens. Of note, all of the above-mentioned dosing regimens result in trough concentrations at or above that required for 99% of the plateau for CD38 receptor occupancy in a majority of patients.

For exposure-efficacy and exposure-safety analyses, PK exposure metrics of isatuximab were predicted from the final Pop PK model (Report POH503) and consisted of C_{trough} concentration at week 1 (CT1W), at week 4 (CT4W), cumulative AUC over 1 or 4 weeks (AUC1W or AUC4W), Cmax of the first administration at Cycle 1 or Cycle 2 (C_{max}D1C1 or C_{max}D1C2), maximum value of C_{max} (MaxC_{max}). In view of the CHMP, the relatively high ETA-shrinkage observed on all PK parameters from 22 to 95% vs 11.9 to 72%, hindered drawing valid conclusions using the predicted individual PK parameters derived from the final Pop PK model. Consequently, the Applicant has provided as requested the additional ER-ORR, ER-PFS and ER-safety analyses with observed CT4W as input instead of predicted CT4W, showing similar results.

A clear PK/PD relationship for the impact of isatuximab on serum M-protein was evident but had different characteristics dependent on the therapeutic setting (single agent versus combination setting). In the single agent setting, in patients with measurable serum M-protein, isatuximab produced a dose- and concentration-dependent reduction in serum M-protein with the deepest response at doses of 20 mg/kg QW/Q2W. In addition, the use of a once-weekly loading dose for 4 weeks to reach an efficacious concentration range more rapidly (by saturating the target-mediated clearance pathway) produced greater reduction in M-protein than regimens that did not include a loading dose period. Prolonging the loading period from 4 to 8 weeks did not provide further benefits on serum M-protein reduction. In the combination setting with pomalidomide/dexamethasone, the overall reduction in serum M-protein was greater than for isatuximab alone and a substantial increase in response to M-protein was not evident at doses above 10 mg/kg QW/Q2W. Finally, similar to the PK/PD relationship described above for serum M protein, a clear PK/PD relationship for the impact of isatuximab on ORR was seen, and the characteristics were different dependent on the therapeutic setting. In the combination setting (pomalidomide/dexamethasone), the ORR was greater than for isatuximab alone at or above a dose of 10 mg/kg. The probability of success to reach the targeted ORR was high with 10 mg/kg QW/Q2W for IPd with no substantial additional clinical benefit above this dose.

Although the Ig MM type (IgG versus non IgG) was shown to affect isatuximab pharmacokinetics, with typical linear clearance at steady state 2.1 fold higher in IgG patients compared to non IgG patients (see also above), exposure-effect investigations did not identify Ig MM type as a covariate for efficacy, and in addition, in the pivotal Phase 3 trial EFC14335 the PFS in IgG and non-IgG patients was comparable. Therefore, it is agreed that the impact of Ig MM type (IgG versus non-IgG) on isatuximab exposure does not appear to be clinically significant.

Although the level of β2 microglobulin appears to affect the isatuximab pharmacokinetics, the 30% difference in exposure between high (>5.5 mg/L) and low (<3.5 mg/L) β2 microglobulin does not translate into a clinically relevant difference.

Isatuximab binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). To avoid potential problems with RBC transfusion, patients being treated with Sarclisa should have blood type and screen tests performed prior to the first infusion. Phenotyping may be considered prior to starting Sarclisa treatment as per local practice. If

treatment with Sarclisa has already started, the blood bank should be informed. Patients should be monitored for theoretical risk of haemolysis. If an emergency transfusion is required, non- cross-matched ABO/Rh-compatible RBCs can be given as per local blood bank practices. There is currently no available information with regards to how long the interference with the indirect Coombs test may persist after the last infusion of Sarclisa. Based on the half-life of isatuximab, it is anticipated that isatuximab mediated positive indirect Coombs test may persist for approximately 6 months after the last infusion (SmPC section 4.4).

Isatuximab is an IgG kappa monoclonal antibody that could be detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein. Twenty-two patients in the isatuximab regimen arm who met Very Good Partial Response (VGPR) criteria with only residual immunofixation-positivity were tested for interference. Serum samples from these patients were tested by mass spectrometry to separate isatuximab signal from the myeloma M-protein signal (SmPC section 4.4).

In conclusion, with respect to the 10 mg/kg QW/Q2W dosing regimen, provided PK/PD data on receptor occupancy, saturation of the target as indicated by lack of target mediated drug disposition, isatuximab dose/concentration relationships for serum M-protein and ORR supported for the 10 mg/kg QW/Q2W dose regimen for isatuximab with IPd chosen for the pivotal Phase 3 study EFC14335.

2.4.5. Conclusions on clinical pharmacology

Overall, isatuximab PK has been sufficiently evaluated.

With respect to the 10 mg/kg QW/Q2W dosing regimen, PK/PD data provided on receptor occupancy, saturation of the target as indicated by lack of target mediated drug disposition, isatuximab dose/concentration relationships for serum M-protein and ORR provided support for the 10 mg/kg QW/Q2W dose regimen for isatuximab with IPd chosen for the pivotal Phase 3 study EFC14335.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The proposed isatuximab dosing regimen of 10 mg/kg IV in combination with pomalidomide and dexamethasone in patients with R/R MM has been selected based on the results of Part A from Phase 1b study TCD14079, a multicenter, open label, non-comparative, 3 + 3 dose escalation study of isatuximab followed by an expansion cohort at the selected dose, together with the PK/PD modelling (see also PK/PD sections of this report).

In study TCD14079 part A isatuximab was administered every week (QW) during Cycle 1 and every 2 weeks (Q2W) thereafter at the three dose levels 5 mg/kg (n=8), 10 mg/kg (n=9; including expansion phase: n=31) or 20 mg/kg (n=6). Pomalidomide 4 mg was taken orally from D1 to D21 of each 28 day-cycle. Dexamethasone 40 mg (or 20 mg for patients of 75 years or older) was administered either orally or by IV infusion before isatuximab infusion.

The median number of cycles was 10, with a median duration of exposure of 41.7 weeks.

Among the 3 evaluated dose levels 5-10-20 mg/kg, the maximum tolerated dose (MTD) was not reached. As no MTD was reached in the dose escalation cohort in Study 14079, isatuximab RD of 10 mg/kg QWx4, followed by 10 mg/kg Q2W was chosen based on PK/PD modelling and simulations using data from Studies TED14154, TED10893, TCD14079 and TCD11863.

Fixed volume infusion

Based on an interim analysis of part B of study TCD14079, performed in the US only, a fixed volume infusion is proposed for commercial use. All other isatuximab studies use an infusion volume based on patient weight, while TCD14079 part B uses a fixed dilution volume of 250 mL and infusion rates in mL/hour as follows:

- For 1st infusion, the starting infusion rate was 25 mL/hour, which corresponds to a lower infusion rate (40 to 120 mg/hour for patients with weight ranging from 40 to 120 kg) than the initial infusion rate used in weight-based infusions (175 mg/hour).
- For 2nd infusion, the starting infusion rate was 50 mL/hour, which corresponds to a lower infusion rate (80 mg/h for patients with weight of 40 kg), similar infusion rate (175 mg/hour for patients with a weight of 87.5 kg), or higher infusion rate (240 mg/hour for patients with a weight of 120 kg) than the initial infusion rate used in weight-based infusions (175 mg/hour).
- For 3rd and subsequent infusions, the fixed infusion rate of 200 mL/hour, corresponds to a higher infusion rate (320 to 960 mg/hour for patients with weight ranging from 40 to 120 kg) than the initial infusion rate used in weight-based infusions (175 mg/hour).

The change in infusion volume does not impact the actual isatuximab dose in mg/kg. The premedication protocol is the same as in the pivotal EFC14335 study. The study population consisted of patients with RRMM, who had received at least 2 previous therapies including lenalidomide and proteasome inhibitor and have demonstrated disease progression on or after completion of the last therapy.

The primary endpoint of the single arm study was the incidence of Grade ≥3 infusion reaction (IRR) during the first six infusions. Secondary endpoints were duration of infusion, AEs, immunogenicity, and efficacy (ORR, CBR, duration of response). Approximately 40-44 patients were needed for evaluation,

based on the incidence of Grade ≥3 IRRs of 2.2% (4/186) with a 95% confidence interval (CI) of 0.6% - 5.5% as per isatuximab investigator brochure (edition 8). With a total of 40 patients, the fixed infusion volume of isatuximab would be considered not feasible if the lower bound of the 95% CI is >5.5%; i.e., if ≥6 patients have grade ≥3 IRR. The evaluable population for IRR assessment was defined as patients receiving at least six planned infusions of isatuximab, unless drop out early due to a grade ≥3 IR within the first six infusions of isatuximab administration. All analyses were descriptive and no efficacy results were provided in this interim report.

A total of 47 patients were enrolled from 11 study sites based in the US. Final cut-off data was 30 Oct 2019. Twenty-two patients (46.8%) were still receiving study treatment at the cut-off date. The median age of patients was 65 years (range 45 to 85 years). Most patients (45 or 95.7%) had an ECOG performance status of 0 or 1, except 2 patients (4.3%) who had an ECOG PS of 2. The majority (74.5%) of patients had an ISS staging of I or II at study entry. The median number of prior treatment lines was 3 (min-max: 1-8) with all patients previously treated with a proteasome inhibitor and an immunomodulatory drug and 83.0% of patients being previously treated with an alkylating agent. Twenty-three (48.9%) and 7 (14.9%) patients had received prior pomalidomide and prior daratumumab (anti-CD38 monoclonal antibody), respectively.

The median number of cycles administered were 9 (range: 1-19). The median duration of infusion decreased from 3.70 hours during the first infusion to 1.85 hours during the second infusion, and to 1.25 hours for ≥3 infusions when the infusion was administered at the fixed infusion rate of 200 mL/hour.

Efficacy was observed in 47 patients who received isatuximab administered via a fixed infusion volume in combination with pomalidomide and dexamethasone, with an ORR of 53.2% (95% CI: 38.1% to 67.9%), and median PFS and OS not yet reached at a median duration of 9.9 months follow-up. The 12-month probability of PFS was 55.7%, and the 12-month probability of OS was 70.6%. Of the 7 patients with prior exposure to daratumumab, there was 1 PR and 2 MRs for an ORR of 14.3% and a CBR of 42.9%; the ORR in the 40 patients without prior exposure to daratumumab was 60.0%. The median duration of response and the 25th percentile have not been reached.

2.5.2. Main study

Study EFC14335 – ICARIA

Phase 3 trial EFC14335/ICARIA is a randomized, open-label, multicenter study comparing isatuximab + pomalidomide and dexamethasone (IPd) with pomalidomide and dexamethasone alone (Pd) in patients with relapsed/refractory (R/R) multiple myeloma (MM).

Methods

Study Participants

Key inclusion criteria

- Age ≥18 years.
- Patients had to have a documented diagnosis of MM with evidence of measurable disease.
    - Serum M protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis and/or
    - Urine M protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis

- Patients had to have received at least 2 prior lines of anti-myeloma therapy, which included at least 2 consecutives cycles of lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) given alone or in combination.

  Note: An induction treatment followed by autologous stem cell transplant (ASCT) and consolidation/maintenance was considered as one line of treatment.

- Patients had to have failed treatment with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination, defined by any of the following (failure to lenalidomide and a proteasome inhibitor may have occurred at any line of therapy):
  - Progression had occurred while on or within 60 days from end of the treatment with lenalidomide and/or a proteasome inhibitor
  - In case of previous response ≥PR to lenalidomide and/or a proteasome inhibitor, patient had progressed within 6 months after discontinuation of the treatment
  - Patients who had developed intolerable toxicity after a minimum of 2 consecutive cycles of a regimen containing lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination.
- Patients had to have progressed on or within 60 days after end of the previous therapy before study entry, i.e., refractory to the last line of treatment. This patient population included the following two categories:
  - Refractory disease: patients who were refractory to all previous lines of treatment but had achieved at least a minimal response (MR) in one previous line.
  - Relapsed and refractory disease: patients who were relapsed from at least one previous line of treatment and refractory to the last line of treatment. Patients could have been refractory to other previous line/lines of treatment.

    Note: Patients had to have achieved a MR or better to at least one of the previous lines of treatment (i.e., primary refractory disease was not eligible).

<u>Key exclusion criteria</u>

- Primary refractory MM defined as: patients who had never achieved at least a MR with any treatment during the disease course.
- Free light chain (FLC) measurable disease only.
- Patient with prior anti-CD38 monoclonal antibody treatment with progression on or within 60 days after end of anti-CD38 monoclonal antibody treatment or failure to achieve at least MR to treatment (i.e., refractory to anti-CD38).
- Prior therapy with pomalidomide.
- Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone.
- Prior allogenic hematopoietic stem cell (HSC) transplant with active graft versus host disease (GvHD) any grade and/or were under immunosuppressive treatment within the last 2 months.
- Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty was not considered a major procedure), radiotherapy.

- Patient who had received any other investigational drugs or prohibited therapy for this study within 28 days or 5 half-lives from randomization, whichever was longer.
- Eastern Cooperative Oncology Group (ECOG) status >2.
- Platelets <75 000 cells/µL if <50% of bone marrow nucleated cells were plasma cells and, <30 000 cells/µL if ≥50% of bone marrow nucleated cells were plasma cells. Platelet transfusion was not allowed within 3 days before the screening hematological test.
- Absolute neutrophil count (ANC) <1000 µ/L (1 x 109/L). The use of granulocyte colony stimulating factor (G-CSF) was not allowed to reach this level.
- Creatinine clearance <30 mL/min; Total bilirubin >2 x upper limit of normal (ULN); Corrected serum calcium >14 mg/dL (>3.5 mmol/L); Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN.
- Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy >Grade 1.
- Hypersensitivity to IMiDs (thalidomide or lenalidomide) defined as any hypersensitivity reaction leading to stop IMiDs within the 2 first cycles or reaction, which does meet intolerance definition. Hypersensitivity to dexamethasone, sucrose histidine (as base and hydrochloride salt) and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents.
- Significant cardiac dysfunction; myocardial infarction within 12 months; unstable, poorly controlled angina pectoris.
- Diagnosed or treated for another malignancy within 3 years prior to randomization with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low risk prostate cancer after curative therapy.
- Concomitant plasma cell leukaemia.
- Daily requirement for corticosteroids (equivalent to ≥10 mg/day of prednisone) for more than 7 days (except for inhalation corticosteroids).
- Any severe acute or chronic medical condition which would have impaired the ability of the patient to participate in the study or interfered with interpretation of study results (e.g., systemic infection unless specific anti-infective therapy was employed) or patient was unable to comply with the study procedures.

Treatments

IPd arm

The patients randomized in the IPd arm were to receive the following treatments:

- Dexamethasone 40 mg (or 20 mg if the patient was ≥75 years old) PO (the preferred route) or IV (if PO route could not be used) administered on Days 1, 8, 15 and 22. (A single administration used as premedication for isatuximab treatment as well as study treatment.)
- Isatuximab 10 mg/kg IV administered 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 infusion reactions (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 the absence of IAR after 1 hour of infusion, the rate was increased by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

- Pomalidomide 4 mg PO was taken on Days 1 to 21 of each 28-day cycle.

Pd arm

The patients randomized in the Pd arm were to receive dexamethasone and pomalidomide according to the same dosing regimen as administered in the IPd arm.

Dose modification

Isatuximab dose reductions were not permitted. A patient could have had a dose omitted within a cycle if toxicity occurred and the patient did not recover by the day of planned infusion/administration.

Dose reductions or interruption for pomalidomide and low-dose dexamethasone and/or cycle delay (i.e., delay of all study treatments) were permitted in case of toxicity. Once a dose of pomalidomide or dexamethasone was decreased, intra-patient dose re-escalation back to the previous dose level was not permitted.

If one of the study treatments was prematurely permanently discontinued, then other drug(s) could be continued until disease progression or unacceptable toxicity or patient's wish to discontinue study treatment.

Treatment duration and response assessment

If a patient was clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, the patient could remain on treatment until disease progression, unacceptable AEs, patient wish, or any other reason.

Objectives

Primary objective

To demonstrate the benefit of IPd in the prolongation of *progression free survival (PFS)* as compared to Pd in patients with R/R MM.

Key secondary objectives

- To evaluate the objective response rate (ORR) as per International Myeloma Working Group (IMWG) criteria in each arm.
- To compare overall survival (OS) between the 2 arms.

Other secondary objectives

- To evaluate the time to progression (TTP) in each arm.
- To evaluate the PFS in high risk cytogenetic population defined as patients carrying del(17p), t(4;14), t(14;16) in each arm.
- To evaluate the duration of response (DOR) in each arm.
- To evaluate safety in both treatment arms.
- To determine the PK profile of isatuximab in combination with pomalidomide.
- To evaluate the immunogenicity of isatuximab.
- To assess disease-specific and a generic health-related quality of life (HRQL), disease and treatment-related symptoms, health state utility and health status.

Exploratory objectives

- To explore the relationship between immune genetic determinants and efficacy endpoints.
- To explore PK and pharmacodynamic (PDy) relationships.
- To explore the minimal residual disease (MRD) rate in both treatment arms.

Outcomes/endpoints

Primary endpoint

PFS, defined as the time from the date of randomization to the first documented date of progressive disease or death due to any cause before the analysis cut-off, whichever came first. An independent response committee (IRC) determined disease response including progression status per IMWG criteria.

Key secondary endpoints

ORR, defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), as best overall response (BOR), assessed by IRC using the IMWG criteria. Additional analyses included ORR by investigator, best overall response (BOR, IRC based), clinical benefit rate (MR or better), VGPR rate (VGPR or better).

OS, defined as the time from the date of randomization to date of death from any cause.

Sample size

The sample size calculation was based on the primary efficacy endpoint (PFS). The following assumptions were used:

- Pd arm had a median PFS of 4.0 months.
- IPd arm had 40% risk reduction in hazard rate in comparison to Pd arm. The targeted hazard ratio (HR) was 0.60, which corresponded to an improvement in the true median PFS time from 4 months to 6.67 months.
- A log-rank test at a 1-sided 2.5% significance level.

Based on the above assumptions, a total of 162 PFS events were needed to achieve a 90% power for the study.

The OS objective also supported the sample size calculation using the following assumptions:

- Pd arm had a median OS of 13.0.
- IPd had a 31.5% risk reduction in hazard rate in comparison to Pd arm. The targeted HR was 0.685 and this was expected to correspond to a difference of 6 months in median OS between the control arm and the experimental arm.
- A log-rank test at a 1-sided 2.5% significance level.
- An interim analysis for OS was planned at the time of primary analysis of PFS, which was estimated (at the time of protocol development) to occur when about 36% of the OS events were observed. An O'Brien and Fleming α-spending function was used to obtain the nominal significance levels for the interim (according to the actual number of events) and final analyses of survival.

Based on the above assumptions, a total of 220 death events would achieve 80% power for the study. Approximately 300 patients (150 in each arm) were expected to be adequate to achieve the targeted number of events for both PFS and OS.

Randomisation

All eligible patients were randomly assigned to one of the 2 treatment groups (either IPd arm or Pd arm) in a 1:1 ratio using an IRT. Randomization was stratified according to age (<75 versus ≥75 years) and number of previous lines of therapy (2 or 3 versus more than 3), based on data provided by the Investigator.

Blinding (masking)

This was an open-label study. A centralized randomization system (IRT) was used to prevent the Investigator from knowing a patient's treatment assignment in advance. The disease response assessments were evaluated based on radiological and central laboratory assessments by the Independent Review Committee (IRC), which was blinded to treatment group allocation.

Statistical methods

The primary population for the efficacy analysis was the intent-to-treat (ITT) population, including all randomized patients with a signed informed consent.

Hypothesis testing to evaluate the duration of FPS between the two treatment arms was performed using the stratified log-rank test procedure, using a 1-sided 0.025 alpha level. The stratification factors were the same used to stratify the randomization: age and number of previous lines of therapy. The cut-off date for the analysis of PFS was the actual date when 162 events (first occurrence of either disease progression or death due to any cause) were observed. At the time of final PFS analysis, the critical value for the Wald test on PFS HR would be 0.734.

Sensitivity analyses of PFS were performed at a 1 sided 0.025 alpha level:

- PFS analysis based on IRC, without censoring for further anti-myeloma treatment
- PFS analysis using Investigator assessment of response, based on local laboratory M protein analyses and local radiologic assessments. Symptomatic deteriorations were not considered PFS events.
- PFS analysis using Investigator's disease assessment, similar to sensitivity analysis 2, but including symptomatic deterioration (clinical progression with no progression on imaging or M protein per investigator) as an event.
- PFS analysis based on IRC, where initiation of further anti-myeloma treatment was considered an event.
- Analysis based on scheduled assessment dates instead of actual assessment dates and late PFS censored (analysis done if lack of adherence to the protocol-defined schedule of disease assessments between the treatment groups has been detected)

Subgroup analyses were planned in the following categories: age, number of previous lines of therapy, gender, race, region of the world (geographical and regulatory), ECOG PS at baseline, ISS staging at diagnosis, R-ISS at study entry, cytogenetic abnormality, MM type at diagnosis, baseline creatinine clearance, refractory to PI, refractory to lenalidomide. For each predefined demographic/baseline factor, PFS was analysed using a Cox proportional hazards model with terms for the factor, treatment and their interaction. The test of the interaction was performed at the 10% alpha level.

Evaluation of confounding factors: A multivariate Cox proportional hazards model was used to identify prognostic factors among the demographic and baseline characteristics factors using a stepwise selection procedure with a 15% significance level for removing effects.

Multiplicity: At the one and final analysis of PFS, ORR and OS were tested hierarchically, multiplicity among this interim OS analysis and the final OS analysis was handled via group-sequential testing.

No interim analysis was planned for PFS. However, an interim analysis for OS was planned to occur at the time of the final analysis of PFS (once 162 PFS events have been observed), at approximately the 36% information fraction for OS.

The final OS analysis will take place after at least 220 deaths have been observed. This is projected to occur approximately 51 months after the first patient is randomized. The nominal significance level will be determined by an O'Brien and Fleming alpha spending function. It would be of 0.0249 for 220 events (corresponding to a HR of 0.767).

No update of PFS or ORR as per IRC will be provided at the time of final OS analysis.

Results

Participant flow

A total of 387 patients were screened and 307 patients were randomized to the study (ITT population), 154 in the IPd arm and 153 in the Pd arm.

Six of the 307 randomized patients (4 patients in the Pd arm and 2 patients in the IPd arm) did not receive study treatment due to: AE in 3 patients (pre-existing thrombocytopenia in 2 patients and hyperviscosity in 1 patient); PD in 1 patient; consent withdrawal by 1 patient; and woman of childbearing potential (WOCBP) unwilling to prevent pregnancy or to be tested for pregnancy in 1 patient.

At the data cut off date of 22 November 2018, a total of 100 patients are still on treatment:
65 patients (42.2%) in the IPd arm and 35 (22.9%) in the Pd arm.

Table 15. Participants flow in study EFC14335/ICARIA.

	Pd (N=153)	IPd (N=154)
Treated but not randomized	0	0
Randomized and not treated	4 (2.6)	2 (1.3)
Randomized and treated	149 (97.4)	152 (98.7)
Patients still on treatment	35 (22.9)	65 (42.2)
Patients with definitive treatment discontinuation	114 (74.5)	87 (56.5)
Reason for definitive treatment discontinuation		
Adverse event	19 (12.4)	11 (7.1)
Progressive disease	88 (57.5)	66 (42.9)
Poor compliance to protocol	0	1 (0.6)
Withdrawal by subject	6 (3.9)	5 (3.2)
Other	1 (0.7)	4 (2.6)
Reason for treatment withdrawal by subject		
Adverse event	1 (0.7)	0
Study procedure	0	0
Other	5 (3.3)	5 (3.2)
Status at the cutoff date[a]		
Alive	97 (63.4)	111 (72.1)
Death	56 (36.6)	43 (27.9)
Time from last contact to the cutoff date[b]		
<= 2 weeks	0	0
> 2 weeks and <= 4 weeks	0	1 (0.6)
> 4 weeks and <= 8 weeks	0	0
> 8 weeks	7 (4.6)	4 (2.6)

a Cut-off date for overall survival (11OCT2018)

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 or of the last ongoing study drug.

Note: Percentages are calculated using the number of patients randomized as denominator. Patients treated but not randomized are tabulated according to treatment actually received (as treated)

Recruitment

Patients were enrolled between 10 January 2017 and 1 February 2018. The cut-off date for efficacy analysis was 22 November 2018.

Conduct of the study

The original study protocol (dated 4 Aug 2016) underwent 3 global and 2 country-specific amendments, one for the UK that was introduced before inclusion of any patients in the UK and one for Japan; key changes are summarized below.

Amendment 1 (dated 1 Nov 2016, all countries)

- ECG assessments added at Cycle 2 Day 1 (pre-dose) and at end of treatment.
- Specified 2 options for assessment of bone disease: skeletal survey and low-dose whole body CT-scan.

- Clarified that prior treatment with lenalidomide and a proteasome inhibitor could be alone or in combination.
- Clarified that dexamethasone was not permitted within 14 days of study entry.
- IMWG criteria were updated to most recent guidance.
- Patients who discontinued without PD were to continue in the follow-up even if they initiated other anti myeloma treatment.
- Second primary malignancy was added as an AESI.
- The definition of renal dysfunction was updated from a creatinine clearance of <45 mL/min to <30 mL/min.
- Added possibility to modify ADA sampling based on updated information on isatuximab immunogenicity.

Amendment 2 (dated 24 Feb 2017, UK only – added to amendment 3a for all countries)

- Added exclusion criterion 32: Any severe acute or chronic medical condition which could impair the ability of the patient to participate to the study or interfere with interpretation of study results (e.g., systemic infection unless anti-infective therapy is employed) or patient unable to comply with the study procedures.

Amendment 3a (dated 18 May 2017, all countries)

- Exclusion criterion 3 modified to specify patients who received prior anti-CD 38 monoclonal antibody had to have achieved at least MR in addition to not having PD on or within 60 days of last dose.
- IRC no longer needed to assess patients for extramedullary disease at baseline to determine whether they required radiologic follow-up.
- Added that patients who did not have IRs with first 4 administrations of isatuximab could have the premedication requirement reconsidered at the Investigator's discretion.
- Number of OS events to be observed before interim analysis was updated because enrollment window was reduced.
- Clarification of Investigator decision to continue study treatment based on local laboratory results.

Amendment 3 (dated 13 Sep 2018, Japan only)

- Added text to specify that for Japanese patients, the IRC review will continue after the cut-off for the primary analysis until at least 7 PFS events in the Japanese population are reported.
- Added an Appendix with details of country specific requirements for Japan as per the new template requirements.

Amendment 4 (dated 25 Oct 2018, all countries)

- Clarified in Schedule of Assessments that minimal residual disease assessment had to be performed in case of CR at end of treatment EOT, i.e. 30 days after last study treatment administration and post treatment follow-up period, i.e. 60±5 days and every 3 months (±7 days) after last study treatment administration.
- The following additional guidance on neutropenia monitoring was added: if Grade 4 neutropenia, assess absolute neutrophil count every 2-3 days until ANC ≥0.5 x 109/L and at least weekly thereafter until ANC ≥1.0 x 109/L.
- Clarified full dose of study treatment was to be maintained as planned within cycle for Grade 4 thrombocytopenia events.

- Added description about precautions and consideration of risk-benefit ratio while using dexamethasone with CYP3A inhibitors.

Protocol deviations

Inclusion/exclusion criteria: Major deviations reported in more than 1 patient included: enrolment when progression occurred ≥60 days after the end of the last line immediately before informed consent form signature (3 and 4 patients in the IPd and Pd arms, respectively) and ANC <900/µL (2 patients in the Pd arm). One patient in the IPd arm had prior exposure to pomalidomide.

Randomization: Major deviations related to randomization procedures occurred in 16 patients (10.4%) in the Ipd arm and 14 patients (9.2%) of the Pd arm. This only included patients randomized to the wrong strata.

Other: Few patients had other critical or major deviations and most were related to assessments/procedures (3.9% and 3.3% in the IPd and Pd arms, respectively).

For the outcome of the GCP inspection see above.

Baseline data

Baseline demographic characteristics

Table 16. Demographic characteristics – ITT population.

	Pd (N=153)	IPd (N=154)	All (N=307)
Age (years)			
Number	153	154	307
Mean (SD)	65.2 (9.5)	66.6 (9.1)	65.9 (9.3)
Median	66.0	68.0	67.0
Min ; Max	41 ; 86	36 ; 83	36 ; 86
Age group (years) [n(%)]			
Number	153	154	307
<65	70 (45.8)	54 (35.1)	124 (40.4)
[65-75[	54 (35.3)	68 (44.2)	122 (39.7)
≥75	29 (19.0)	32 (20.8)	61 (19.9)
Gender [n(%)]			
Number	153	154	307
Female	83 (54.2)	65 (42.2)	148 (48.2)
Male	70 (45.8)	89 (57.8)	159 (51.8)
Race [n(%)]			
Number	153	154	307
White	126 (82.4)	118 (76.6)	244 (79.5)
Black or African American	3 (2.0)	1 (0.6)	4 (1.3)
Asian	15 (9.8)	21 (13.6)	36 (11.7)
Native Hawaiian or other Pacific Island	1 (0.7)	2 (1.3)	3 (1.0)
Missing/Not reported	8 (5.2)	12 (7.8)	20 (6.5)
Ethnicity [n(%)]			
Number	153	154	307
Hispanic or Latino	3 (2.0)	4 (2.6)	7 (2.3)
Not Hispanic or Latino	134 (87.6)	130 (84.4)	264 (86.0)
Unknown	2 (1.3)	2 (1.3)	4 (1.3)
Not Reported	14 (9.2)	18 (11.7)	32 (10.4)
ECOG performance status [n(%)]			
Number	153	154	307
0	69 (45.1)	55 (35.7)	124 (40.4)
1	68 (44.4)	83 (53.9)	151 (49.2)
2	16 (10.5)	16 (10.4)	32 (10.4)
Geographical region[a] [n(%)]			
Number	153	154	307
Western Europe	76 (49.7)	55 (35.7)	131 (42.7)
Eastern Europe	20 (13.1)	28 (18.2)	48 (15.6)
North America	5 (3.3)	7 (4.5)	12 (3.9)
Asia	15 (9.8)	21 (13.6)	36 (11.7)
Other Countries	37 (24.2)	43 (27.9)	80 (26.1)
Regulatory region[b] [n(%)]			
Number	153	154	307
Western Countries	97 (63.4)	77 (50.0)	174 (56.7)
Other Countries	56 (36.6)	77 (50.0)	133 (43.3)

a Other countries=Australia, New Zealand, Turkey and Russia.

b Other countries=Czech Republic, Hungary, Poland, Slovakia, Japan, Korea, Republic of Taiwan (Province of China), Turkey and Russia

Disease characteristics

Table 17. Summary of disease characteristics at initial diagnosis – ITT population.

	Pd (N=153)	IPd (N=154)	All (N=307)
Initial diagnosis [n(%)]			
Number	153	154	307
Multiple Myeloma	153 (100)	154 (100)	307 (100)
Time from initial diagnosis of MM to randomization (years)			
Number	153	154	307
Mean (SD)	5.29 (3.69)	5.23 (3.24)	5.26 (3.46)
Median	4.09	4.46	4.23
Min ; Max	0.5 ; 20.5	0.6 ; 18.4	0.5 ; 20.5
MM subtype at initial diagnosis [n(%)]			
Number	153	154	307
Ig G	100 (65.4)	102 (66.2)	202 (65.8)
Ig A	41 (26.8)	34 (22.1)	75 (24.4)
Ig M	0	2 (1.3)	2 (0.7)
Ig D	0	0	0
Ig E	0	0	0
Kappa light chain only	7 (4.6)	8 (5.2)	15 (4.9)
Lambda Light chain only	4 (2.6)	7 (4.5)	11 (3.6)
Unknown/undetected	1 (0.7)	1 (0.6)	2 (0.7)
Biclonal status at inital diagnosis [n(%)]			
Number	153	154	307
Yes	3 (2.0)	1 (0.6)	4 (1.3)
No	150 (98.0)	153 (99.4)	303 (98.7)
ISS stage at initial diagnosis [n(%)]			
Number	153	154	307
Stage I	41 (26.8)	36 (23.4)	77 (25.1)
Stage II	48 (31.4)	49 (31.8)	97 (31.6)
Stage III	44 (28.8)	42 (27.3)	86 (28.0)
Unknown	20 (13.1)	27 (17.5)	47 (15.3)

Ig: Immunogloblin, MM : Multiple Myeloma, ISS: International staging system

Table 18. Summary of disease characteristics at study entry – ITT population.

	Pd (N=153)	IPd (N=154)	All (N=307)
MM subtype at study entry[a] [n(%)]			
Number	153	154	307
Ig G	101 (66.0)	104 (67.5)	205 (66.8)
Ig A	41 (26.8)	33 (21.4)	74 (24.1)
Ig M	0	2 (1.3)	2 (0.7)
Ig D	0	0	0
Ig E	0	0	0
Kappa light chain only	7 (4.6)	8 (5.2)	15 (4.9)
Lambda light chain only	4 (2.6)	7 (4.5)	11 (3.6)
Biclonal status at study entry[a] [n(%)]			
Number	153	154	307
Yes	2 (1.3)	1 (0.6)	3 (1.0)
Beta 2-microglobulin (mg/L)			
Number	150	151	301
Mean (SD)	5.71 (6.72)	4.68 (3.84)	5.19 (5.49)
Median	3.75	3.40	3.60
Min ; Max	0.7 ; 54.7	0.4 ; 27.0	0.4 ; 54.7
Beta 2-microglobulin (mg/L) [n(%)]			
Number	150	151	301
< 3.5	65 (43.3)	77 (51.0)	142 (47.2)
≥ 3.5 and <5.5	42 (28.0)	40 (26.5)	82 (27.2)
≥ 5.5	43 (28.7)	34 (22.5)	77 (25.6)
Albumin (g/L)			
Number	153	154	307
Mean (SD)	36.93 (5.49)	36.81 (5.36)	36.87 (5.42)
Median	37.90	37.00	37.50
Min ; Max	16.5 ; 50.0	16.0 ; 48.7	16.0 ; 50.0
Albumin (g/L) [n(%)]			
Number	153	154	307
< 35	48 (31.4)	52 (33.8)	100 (32.6)
≥ 35	105 (68.6)	102 (66.2)	207 (67.4)
Serum LDH [n(%)]			
Number	153	154	307
≤ ULN	102 (66.7)	106 (68.8)	208 (67.8)
> ULN	51 (33.3)	48 (31.2)	99 (32.2)
ISS stage at study entry [n(%)]			
Number	153	154	307
Stage I	51 (33.3)	64 (41.6)	115 (37.5)
Stage II	56 (36.6)	53 (34.4)	109 (35.5)
Stage III	43 (28.1)	34 (22.1)	77 (25.1)
Unknown	3 (2.0)	3 (1.9)	6 (2.0)
R-ISS stage at study entry [n(%)]			
Number	153	154	307
Stage I	31 (20.3)	39 (25.3)	70 (22.8)
Stage II	98 (64.1)	99 (64.3)	197 (64.2)
Stage III	24 (15.7)	16 (10.4)	40 (13.0)
Unknown	0	0	0

Table 19. Summary of disease characteristics at study entry – ITT population (continued).

	Pd (N=153)	IPd (N=154)	All (N=307)
Refractory status			
Number	153	154	307
Relapsed and refractory[b]	153 (100)	154 (100)	307 (100)
Primary refractory	0	0	0
Relapsed	0	0	0

a as per eCRF

b excluding primary refractory

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/EFC14335/CIR/REPORT/PGM/dem_dischar_ent_t.sas
OUT=REPORT/OUTPUT/dem_dischar_ent_r_t_i.rtf (20FEB2019 11:58)

Other disease characteristics

Approximately 97% of patients in both treatment arms had measurable paraprotein at baseline, primarily serum M-protein (~68%) or serum M-protein and urine M-protein (~18%). A median of 27% BM plasma cells was reported at baseline, and ~8% of patients had soft tissue plasmacytoma (per IRC) at baseline in both arms. Bone lesions were detected in almost 68% of patients per IRC, with 33% of patients having more than 10 lesions. One third of the population (36.2%) entered the study with renal impairment (creatinine clearance [MDRD] <60 mL/min/1.73 m^2), with slightly more patients in the IPd arm (38.7% vs. 33.8% Pd arm).

Cytogenetics

More patients in the control arm had high risk cytogenetic abnormalities (23.5% Pd, vs. 15.6% in the Ipd arm), most frequently being del (17) [9.1% vs. 15%] and t(4;14) [7.8% vs. 9.2%].

Prior anti-cancer therapy

All patients had received at least 2 prior lines of treatment including prior lenalidomide and PI. The median number of prior lines was 3 (range 2 to 11), with 34.9% of patients having received 4 or more prior lines of treatment.

All patients received lenalidomide and a PI; 92.5% were refractory to lenalidomide, 75.9% to PI, and 72.6% to both. Nearly all patients (98.0%) were refractory to their last regimen and all patients (100%) were considered relapsed and refractory. Over half of patients (56.4%) had received a prior stem cell transplant, and 16.0% had received a double stem cell transplant.

Subsequent anti-myeloma treatment

Additional systemic therapy post-study was administered in 39% of patients in the IPd arm and 54% of patients in the Pd arm. Daratumumab was administered in 6 patients (4%) of the IPd arm vs. 45 (29%) of patients in the Pd arm.

Numbers analysed

All 307 randomized patients (n=154 IPd arm vs. n=153 Pd arm) were included in the intent-to-treat (ITT) population, which was the primary population for all efficacy parameters.

The AT/Safety population consisted of 301 patients: 152 patients in the Ipd arm, and 149 in the Pd arm.

Outcomes and estimation

Primary endpoint – PFS

The PFS analysis cut-off date was 11 October 2018, at which time a total of 162 PFS events (according to IRC) were reported. This was also the cut-off date for all other efficacy analyses.

The addition of isatuximab to pomalidomide and low dose dexamethasone led to a statistically significant increase in PFS, as assessed by an IRC. Median PFS improved from 6.47 months in the Pd arm to 11.53 months in the IPd arm, with a HR of 0.596 (95% CI 0.436, 0.814; p=0.001) (Table 24; Figure 11).

Table 20. PFS by IRC – ITT population.

	Pd (N=153)	IPd (N=154)
Number (%) of events	89 (58.2)	73 (47.4)
Number (%) of patients censored	64 (41.8)	81 (52.6)
Kaplan-Meier estimates of PFS in months		
25% quantile (95% CI)	2.76 (1.971 to 3.055)	4.27 (3.088 to 5.848)
Median (95% CI)	6.47 (4.468 to 8.279)	11.53 (8.936 to 13.897)
75% quantile (95% CI)	NC (10.382 to NC)	NC (14.784 to NC)
Stratified[a] Log-Rank test p-value[b]		
vs Pd	-	0.0010
Stratified[a] Hazard ratio (95% CI)		
vs Pd	-	0.596 (0.436 to 0.814)
PFS probability (95% CI)[c]		
2 Months	0.801 (0.723 to 0.859)	0.910 (0.850 to 0.947)
4 Months	0.617 (0.529 to 0.694)	0.760 (0.681 to 0.822)
6 Months	0.506 (0.417 to 0.588)	0.665 (0.580 to 0.737)
8 Months	0.432 (0.345 to 0.516)	0.620 (0.534 to 0.695)
10 Months	0.369 (0.284 to 0.453)	0.547 (0.459 to 0.627)
12 Months	0.296 (0.213 to 0.384)	0.476 (0.380 to 0.566)
14 Months	0.259 (0.174 to 0.351)	0.387 (0.277 to 0.495)
16 Months	0.259 (0.174 to 0.351)	0.310 (0.186 to 0.443)
Number of patients at risk[c]		
2 Months	105	129
4 Months	80	106
6 Months	63	89
8 Months	51	81
10 Months	33	52
12 Months	17	30
14 Months	5	14
16 Months	0	1

PFS: Progression-free survival, CI: Confidence interval, HR: Hazard ratio, IRC: Independent Response Committee

Cut-off date: 11OCT2018 Median follow-up time = 11.60 months. HR<1 favors IPd arm

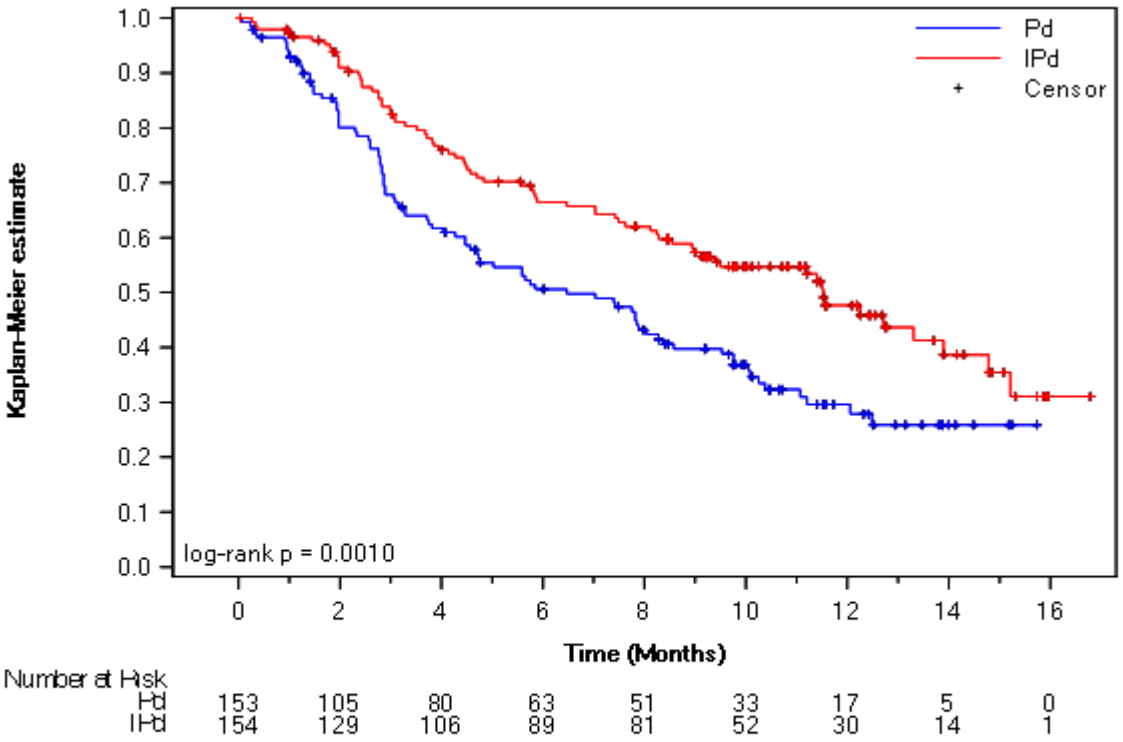
CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley

a Stratified on age (<75 years versus >=75 years) and Number of previous lines of therapy (2 or 3 versus > 3) according to IRT

b One-sided significance level is 0.025

c Estimated using the Kaplan-Meier method

Figure 9. PFS by IRC – Kaplan Meier curves by treatment group – ITT population.



Cutoff date = 11OCT2018
Median follow-up time = 11.60 months
PFS: Progression-free survival, IRC: Independent Response Committee
Logrank p value: Stratified on age (<75 years versus >=75 years) and number of previous lines of therapy (2 or 3 versus > 3) according to IRT. One-sided significance level is 0.025.

Sensitivity analyses

The results of sensitivity analyses performed are presented below.

Table 21. PFS - Summary of sensitivity analyses.

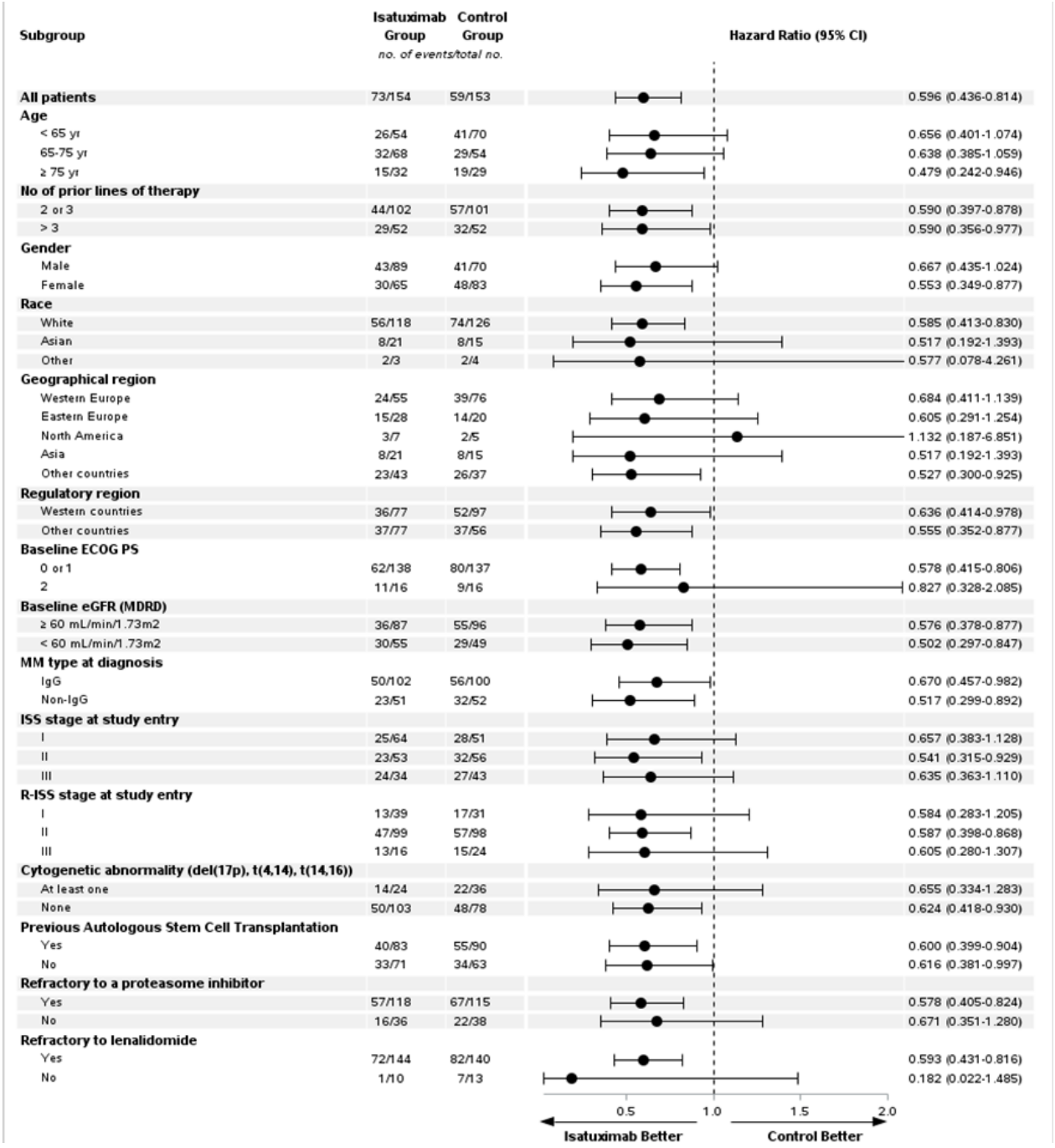
	Pd		IPd			
	N(%) of Events	Median (Months) (95% CI)	N(%) of Events	Median (Months) (95% CI)	Hazard Ratio (95% CI) vs Pd	P-value[a]
Main analysis: PFS as per IRC, stratified by stratification factors as entered in the IRT	89 (58.2)	6.47 (4.468 to 8.279)	73 (47.4)	11.53 (8.936 to 13.897)	0.596 (0.436 to 0.814)	0.0010
PFS as per IRC, stratified by stratification factors as entered in the eCRF	89 (58.2)	6.47 (4.468 to 8.279)	73 (47.4)	11.53 (8.936 to 13.897)	0.568 (0.414 to 0.779)	0.0004
PFS #1: PFS as per IRC without censoring for further anti-myeloma treatment	105 (68.6)	5.85 (4.468 to 7.819)	82 (53.2)	11.20 (8.246 to 13.306)	0.599 (0.447 to 0.801)	0.0005
PFS #2: PFS as per investigator (ignoring symptomatic deterioration)	96 (62.7)	6.54 (4.468 to 7.885)	76 (49.4)	11.14 (7.491 to 14.784)	0.602 (0.444 to 0.816)	0.0009
PFS #3: PFS as per investigator including symptomatic deterioration as an event	103 (67.3)	5.59 (4.041 to 7.491)	78 (50.6)	11.14 (7.425 to 14.784)	0.580 (0.431 to 0.780)	0.0003
PFS #4: PFS as per IRC including initiation of further anti-myeloma treatment as an event	114 (74.5)	4.60 (3.055 to 5.848)	90 (58.4)	8.97 (7.228 to 11.565)	0.591 (0.447 to 0.781)	0.0002

CI: Confidence interval
Cutoff date = 11OCT2018
a One-sided significance level is 0.025

Subgroup analyses

Subgroup analyses of PFS are presented below.

Figure 10. PFS: Summary of subgroup analyses in Study EFC14335.



PFS multivariate analysis

A multivariate analysis of PFS adjusted for demographic and baseline characteristics is presented below.

Table 22. PFS primary analysis by IRC - multivariate analysis – ITT population.

Prognostic factors	Hazard ratio (95% CI)	P-value
Treatment: IPd vs Pd	0.484 (0.334 to 0.702)	0.0001
Number of previous lines of therapy (as per IRT): >3 vs (2 or 3)	1.445 (0.990 to 2.109)	0.0564
Race: Asian vs White	0.583 (0.308 to 1.104)	0.0975
Race: Other vs White	15.200 (3.445 to 67.059)	0.0003
Region (regulatory): Other countries vs Western countries	1.464 (0.993 to 2.158)	0.0545
Baseline ECOG PS: 2 vs (0 or 1)	1.627 (0.938 to 2.824)	0.0835
R-ISS staging at study entry: II vs I	1.731 (1.077 to 2.782)	0.0235
R-ISS staging at study entry: III vs I	4.457 (2.471 to 8.040)	<0.0001
Refractory to lenalidomide: Yes vs No	3.946 (1.239 to 12.565)	0.0202

Final Cox regression model determined by a stepwise selection method with a 15% significance level for entering effects and a 15% significance level for removing effects

Key secondary endpoints

Overall response rate (ORR)

Table 23. Summary of ORR by IRC – ITT population.

	Pd (N=153)	IPd (N=154)
Best Overall Response [n(%)]		
Stringent complete response	1 (0.7)	0
Complete response	2 (1.3)	7 (4.5)
Very good partial response	10 (6.5)	42 (27.3)
Biochemical CR but with missing bone marrow[a]	2 (1.3)	9 (5.8)
Near-CR[b]	5 (3.3)	24 (15.6)
Partial response	41 (26.8)	44 (28.6)
Minimal response	17 (11.1)	10 (6.5)
Stable disease	45 (29.4)	33 (21.4)
Non Progressive Disease	3 (2.0)	4 (2.6)
Progressive disease	14 (9.2)	6 (3.9)
Unconfirmed progressive disease	4 (2.6)	1 (0.6)
Not evaluable/Not assessed	16 (10.5)	7 (4.5)
Overall Response		
Responders (sCR, CR, VGPR or PR)	54 (35.3)	93 (60.4)
95% CI[c]	0.2775 to 0.4342	0.5220 to 0.6817
Stratified Cochran-Mantel-Haenszel test p-value[d] vs Pd		<0.0001
VGPR or better	13 (8.5)	49 (31.8)
95% CI[c]	0.0460 to 0.1409	0.2455 to 0.3980
Stratified Cochran-Mantel-Haenszel test p-value[d] vs Pd		<0.0001
Clinical benefit		
Responders (MR or better)	71 (46.4)	103 (66.9)
95% CI[c]	0.3832 to 0.5464	0.5885 to 0.7425

CI: Confidence interval, IRC: Independent Response Committee, 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 Age (<75 years versus >=75 years) and Number of previous lines (2 or 3 versus >3) according to IRT. 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.

The ORR results for the prespecified subgroups were generally in line with the ORR in the ITT population.

Overall survival (OS)

At the time of the primary analysis for PFS, an interim analysis for OS was performed. The OS data was still immature with 99 events (information fraction 45%), and median OS had not been reached in either arm. The median follow-up time was 11.6 months.

Although no significant difference in OS was observed at this interim analysis, results suggested a trend in favour of the IPd arm with a HR of 0.687 (95% CI 0.461, 1.023, p=0.0631;). The probability of surviving 12 months in IPd was 72% compared to 63% in Pd.

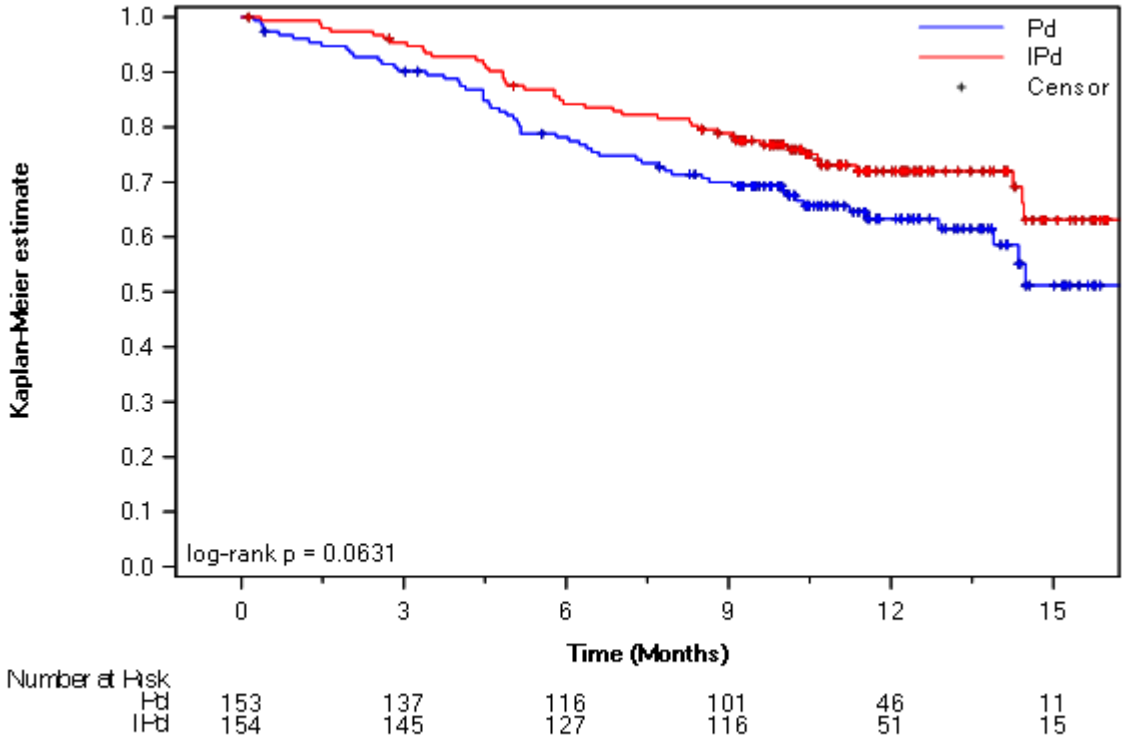
Table 24. OS by treatment group – ITT population.

	Pd (N=153)	IPd (N=154)
Number (%) of deaths	56 (36.6)	43 (27.9)
Number (%) of patients censored	97 (63.4)	111 (72.1)
Kaplan-Meier estimates of OS in months		
25% quantile (95% CI)	6.60 (5.027 to 10.086)	10.64 (7.688 to 14.456)
Median (95% CI)	NC (13.897 to NC)	NC (NC to NC)
75% quantile (95% CI)	NC (NC to NC)	NC (NC to NC)
Stratified[a] Log-Rank test p-value[b]		
vs Pd	-	0.0631
Stratified[a] Hazard ratio (95% CI)		
vs Pd	-	0.687 (0.461 to 1.023)
Survival probability (95% CI)[c]		
3 Months	0.901 (0.842 to 0.939)	0.954 (0.906 to 0.978)
6 Months	0.781 (0.706 to 0.839)	0.842 (0.774 to 0.891)
9 Months	0.700 (0.619 to 0.767)	0.789 (0.715 to 0.846)
12 Months	0.633 (0.545 to 0.709)	0.720 (0.636 to 0.787)
15 Months	0.512 (0.376 to 0.632)	0.631 (0.504 to 0.733)
Number of patients at risk[c]		
3 Months	137	145
6 Months	116	127
9 Months	101	116
12 Months	46	51
15 Months	11	15

OS: Overall survival, CI: Confidence interval, HR: Hazard ratio
Cut-off date: 11OCT2018 Median follow-up time = 11.60 months. HR<1 favors IPd arm
CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley

a Stratified on age (<75 years versus >=75 years) and Number of previous lines of therapy (2 or 3 versus > 3) according to IRT
b One-sided significance level is set to 0.0008 using the O'Brien-Fleming alpha spending function.
c Estimated using the Kaplan-Meier method

Figure 11. OS Kaplan Meier curves by treatment group – ITT population.



Cutoff date = 11OCT2018

Logrank p value: Stratified on age (<75 years versus >=75 years) and number of previous lines of therapy (2 or 3 versus > 3) according to IRT. One-sided significance level is set to 0.0008 using the O'Brien-Fleming alpha spending function.

Table 25. Other secondary endpoints (IPd vs. Pd).

	IPd	Pd	Comment
Time to progression (TTP)	12.71 months (95% CI 11.20-15.211)	7.75 months (95% CI 5.027-9.758).	
Duration of response (DOR)	13.27 months [10.612 to NC]	11.07 months [8.542 to NC]	
Time to first response	1.94 months (95% CI: 1.31 to 2.00)	3.02 months (95% CI: 2.83 to 5.06)	
Time to best response (TTBR)	4.30 months (95% CI 2.891, 5.125)	5.06 months (95% CI 3.778, 7.885)	
Time to next treatment (TTNT)	NR (range 12.123, NR)	9.10 months (range 6.374, 12.255)	HR 0.538, 95% CI 0.382, 0.758, p =0.0003
Patient reported outcomes (PRO: EORTC QLQ-C30,			No clinically important differences

QLQ-MY20 and EQ-5D-5L (health state utility values, HSUV; and VAS).			between treatment arms
ECOG Performance status score (PS)			Improvements in ECOG PS were generally similar in the IPd and Pd arms but a trend towards slightly less frequent deterioration was observed for the IPd arm.

Exploratory analyses

Minimal residual disease (MRD; evaluable in 14 patients IPd arm vs. 2 patients Pd arm): 10 patients in the IPd arm were MRD negative at 10^{-4} (6.5%), 8 patients were MRD negative at 10^{-5} (5.2%), and 2 patients were MRD negative at 10^{-6} (1.3%). In the Pd arm, neither of the 2 patients were MRD negative by any sensitivity level.

Renal impairment/response: trend toward less deterioration in renal function in the IPd arm, as well as increase in complete renal response (CRenal; 71.9% vs. 38.1% of patients improved in creatinine clearance from <50 mL at baseline to ≥60 mL at ≥1 postbaseline assessment). In almost half of the patients in both arms, the CRenal duration was ≥60 days.

M-protein interference: To evaluate whether isatuximab had interfered with M protein quantification, the IRC identified a subcategory of VGPR patients in whom criteria for CR were met except for residual immunofixation positivity (historic near-CR category). Serum samples from these patients were tested by mass spectrometry. After separation of isatuximab signal from the myeloma M protein signal, in 11 out of 22 investigated patients, there was no residual myeloma M protein detectable at the sensitivity level of the immunofixation test (25 mg/dL); 10 of the 11 patients were IgG subtype at baseline and 1 was undetectable.

Summary of main study

The following table summarises 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 26. Summary of Efficacy for trial EFC14335.

Title: A Phase 3 randomized, open-label, multicentre study comparing isatuximab (SAR650984) in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma.	
Study identifier	EFC14335
Design	Prospective, multicentre, multinational, randomized, open-label, parallel group design.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		22 months (Jan 2017 – Nov 2018; ongoing) N/A N/A
Hypothesis	Superiority		
Treatments groups	IPd (n=154)		- *Isatuximab*: 10 mg/kg IV QW for 4 weeks on Days 1, 8, 15, and 22 of Cycle 1; Q2W on Days 1 and 15 of each subsequent cycle. - *Pomalidomide*: 4 mg capsule on Days 1 to 21 of a 28-day cycle. - *Dexamethasone*: 40 mg (or 20 mg if ≥75 years) on Days 1,8,15 and 28 of a 28-day cycle, IV or tablet. Treatment continued until PD, unacceptable toxicity, patient wish or other reason.
	Pd (n=153)		- *Pomalidomide* - *Dexamethasone* Both with similar dosing regimen as compared to Ipd treatment group.
Endpoints and definitions	Primary endpoint	PFS (by IRC)	Time from the date of randomization to the first documented date of progressive disease or death due to any cause before the analysis cut-off, whichever came first.
	Key secondary endpoints	ORR	Proportion of patients with sCR, CR, VGPR, and PR, as best overall response, assessed by IRC using the IMWG criteria.
		OS	Time from the date of randomization to date of death from any cause.
Database lock	Primary analysis: 22 November 2018; OS follow up ongoing		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) Efficacy data cut-off: 22 November 2018		
Descriptive statistics and estimate variability	Treatment group	IPd	Pd
	Number of subjects	n=154	n=153
	PFS (median)	**11.53 months**	**6.47 months**
	95% CI	8.936 - 13.897	4.468 – 8.279

	ORR (%)	**60.4%**	**35.3%**
	95% CI	0.5220 – 0.6817	0.2775 – 0.4342
	OS (median) *Interim analysis*	**NR**	**NR**
Effect estimate per comparison	Primary endpoint **PFS**	Comparison groups	IPd vs. Pd
		Hazard ratio (HR)	0.596
		95% CI	0.436, 0.814
		P-value	p=0.001
	Key secondary endpoint **OS**	Comparison groups	IPd vs. Pd
		Hazard ratio (HR)	0.687
		95% CI	0.461, 1.023
		P-value	p=0.0631
Notes	The primary comparison for PFS was IRC based on the ITT set, with a stratified log rank test at the 1-sided 0.025 alpha level, adjusted for the stratification factors age (<75 versus ≥75 years) and number of previous lines of therapy (2 or 3 versus more than 3). In the primary PFS analysis, patients were censored in case of further anti-myeloma treatment.		
Abbreviations	*BOR: Best Overall Response, CI: Confidence Interval, CR: Complete Response, IRC: Independent Response Committee, ITT: intent to treat, ORR: Overall Response Rate, OS: Overall Survival, PD: Progressive Disease, PFS: Progression Free Survival, PR: Partial Response, PRO: Patient Reported Outcome, sCR: stringent Complete Response, VGPR: very good partial response.*		

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

Efficacy data from Study EFC14335 was not pooled with data from other supportive studies.

Clinical studies in special populations

Elderly: Subgroup analysis for the primary endpoint were provided in patients <65, 65-75 and ≥75 years of age (Table 31,Table 32, Table 33).

Table 27. Kaplan-Meyer estimates of progression free survival by age – Study EFC14335.

	EFC14335							
	Pd (N=153)				IPd 10 mg/kg (N=154)			
	<65 (N=70)	65 to 74 (N=54)	75 to 84 (N=26)	≥85 (N=3)	<65 (N=54)	65 to 74 (N=68)	75 to 84 (N=32)	≥85 (N=0)
Number (%) of events	41 (58.6)	29 (53.7)	18 (69.2)	1 (33.3)	26 (48.1)	32 (47.1)	15 (46.9)	
Number (%) of patients censored	29 (41.4)	25 (46.3)	8 (30.8)	2 (66.7)	28 (51.9)	36 (52.9)	17 (53.1)	
Kaplan-Meier estimates of PFS in months								
25% quantile (95% CI)	2.30 (1.478; 3.055)	2.89 (2.333; 5.585)	1.94 (0.066; 3.088)	3.81 (3.811; NC)	3.81 (2.398; 4.830)	5.82 (3.285; 8.246)	3.09 (2.366; 8.969)	
Median (95% CI)	5.03 (3.285; 8.279)	8.57 (4.567; 12.057)	4.47 (1.938; 7.754)	NC (3.811; NC)	11.53 (4.567; 14.784)	11.56 (8.279; NC)	11.40 (4.435; NC)	
75% quantile (95% CI)	NC (8.378; NC)	12.48 (10.251; NC)	9.76 (5.585; NC)	NC (3.811; NC)	14.78 (13.306; NC)	NC (15.211; NC)	NC (12.255; NC)	
PFS probability (95% CI)[a]								
2 Months	0.756 (0.628; 0.845)	0.897 (0.771; 0.956)	0.693 (0.461; 0.841)	1.000 (1.000; 1.000)	0.881 (0.754; 0.945)	0.921 (0.821; 0.966)	0.934 (0.761; 0.983)	
4 Months	0.588 (0.454; 0.700)	0.710 (0.559; 0.817)	0.508 (0.289; 0.692)	0.500 (0.006; 0.910)	0.715 (0.566; 0.820)	0.810 (0.690; 0.887)	0.727 (0.527; 0.853)	
6 Months	0.464 (0.333; 0.584)	0.623 (0.470; 0.743)	0.370 (0.178; 0.563)	0.500 (0.006; 0.910)	0.605 (0.452; 0.727)	0.715 (0.586; 0.810)	0.657 (0.457; 0.799)	
8 Months	0.392 (0.268; 0.515)	0.552 (0.398; 0.681)	0.277 (0.114; 0.469)	0.500 (0.006; 0.910)	0.558 (0.405; 0.687)	0.667 (0.537; 0.769)	0.621 (0.420; 0.770)	
10 Months	0.338 (0.220; 0.460)	0.464 (0.309; 0.606)	0.231 (0.084; 0.420)	0.500 (0.006; 0.910)	0.558 (0.405; 0.687)	0.549 (0.417; 0.663)	0.540 (0.341; 0.704)	
12 Months	0.290 (0.175; 0.414)	0.348 (0.195; 0.506)	0.173 (0.049; 0.361)	0.500 (0.006; 0.910)	0.465 (0.294; 0.620)	0.486 (0.344; 0.614)	0.480 (0.275; 0.659)	
14 Months	0.290 (0.175; 0.414)	0.209 (0.067; 0.403)	0.173 (0.049; 0.361)	0.500 (0.006; 0.910)	0.279 (0.092; 0.506)	0.446 (0.296; 0.585)	0.384 (0.166; 0.601)	
16 Months	0.290 (0.175; 0.414)	0.209 (0.067; 0.403)	0.173 (0.049; 0.361)	0.500 (0.006; 0.910)	0.186 (0.037; 0.424)	0.334 (0.136; 0.547)	0.384 (0.166; 0.601)	
18 Months	0.290 (0.175; 0.414)	0.209 (0.067; 0.403)	0.173 (0.049; 0.361)	0.500 (0.006; 0.910)	0.186 (0.037; 0.424)	0.334 (0.136; 0.547)	0.384 (0.166; 0.601)	
20 Months	0.290 (0.175; 0.414)	0.209 (0.067; 0.403)	0.173 (0.049; 0.361)	0.500 (0.006; 0.910)	0.186 (0.037; 0.424)	0.334 (0.136; 0.547)	0.384 (0.166; 0.601)	

Table 28. Best overall response and overall response by age – Study EFC14335.

	EFC14335							
	Pd (N=153)				IPd 10 mg/kg (N=154)			
	<65 (N=70)	65 to 74 (N=54)	75 to 84 (N=26)	≥85 (N=3)	<65 (N=54)	65 to 74 (N=68)	75 to 84 (N=32)	≥85 (N=0)
Best overall response [n(%)]								
Stringent complete response (sCR)	1 (1.5)	0	0	0	0	0	0	0
Complete response (CR)	2 (3.0)	0	0	0	3 (5.6)	3 (4.6)	1 (3.1)	0
Very good partial response (VGPR)	3 (4.5)	7 (14.6)	0	0	14 (25.9)	19 (29.2)	9 (28.1)	0
Partial response (PR)	18 (27.3)	14 (29.2)	8 (33.3)	1 (33.3)	15 (27.8)	22 (33.8)	7 (21.9)	0
Minimal response (MR)	8 (12.1)	7 (14.6)	2 (8.3)	0	1 (1.9)	5 (7.7)	4 (12.5)	0
Stable disease (SD)	23 (34.8)	12 (25.0)	8 (33.3)	2 (66.7)	13 (24.1)	11 (16.9)	9 (28.1)	0
Progressive disease (PD)	5 (7.6)	4 (8.3)	5 (20.8)	0	4 (7.4)	1 (1.5)	1 (3.1)	0
Unconfirmed progressive disease (PDu)	4 (6.1)	0	0	0	1 (1.9)	0	0	0
Not evaluable (NE)	1 (1.5)	2 (4.2)	1 (4.2)	0	2 (3.7)	2 (3.1)	0	0
Overall response rate [n(%)]								
Responder (≥PR)	24 (34.3)	21 (38.9)	8 (30.8)	1 (33.3)	32 (59.3)	44 (64.7)	17 (53.1)	0
95% CI[a]	23.3, 46.6	25.9, 53.1	14.3, 51.8	0.8, 90.6	45.0, 72.4	52.2, 75.9	34.7, 70.9	
VGPR or better rate [n(%)]								
Responder (≥VGPR)	6 (9.1)	7 (14.6)	0	0	17 (31.5)	22 (33.8)	10 (31.3)	0
95% CI[a]	3.4, 18.7	6.1, 27.8			19.5, 45.6	22.6, 46.6	16.1, 50.0	

Note: For EFC14355, response is based on independent review committee assessment and percentages are calculated using the number of patients in the ITT population as the denominator.

[a] Estimated by Clopper-Pearson exact method

CI: Confidence interval Pd: pomalidomide and dexamethasone Ipd: isatuximab in combination with pomalidomide and dexamethasone

Table 29. ***Kaplan-Meyer estimates of overall survival by age – Study EFC14335.***

	EFC14335							
	Pd (N=153)				IPd 10 mg/kg (N=154)			
	<65 (N=70)	65 to 74 (N=54)	75 to 84 (N=26)	≥85 (N=3)	<65 (N=54)	65 to 74 (N=68)	75 to 84 (N=32)	≥85 (N=0)
Number (%) of events	24 (34.3)	17 (31.5)	14 (53.8)	1 (33.3)	17 (31.5)	18 (26.5)	8 (25.0)	
Number (%) of patients censored	46 (65.7)	37 (68.5)	12 (46.2)	2 (66.7)	37 (68.5)	50 (73.5)	24 (75.0)	
Kaplan-Meier estimates of OS in months								
25% quantile (95% CI)	7.39 (4.468 ; 11.565)	10.09 (4.600 ; 14.489)	4.47 (0.690 ; 5.125)	10.25 (10.251 ; NC)	8.44 (4.830 ; NC)	10.71 (6.867 ; NC)	10.38 (3.351 ; NC)	
Median (95% CI)	NC (11.565 ; NC)	14.49 (14.357 ; NC)	8.30 (4.764 ; NC)	NC (10.251 ; NC)	NC (14.259 ; NC)	NC (14.456 ; NC)	NC (NC ; NC)	
75% quantile (95% CI)	NC (NC ; NC)	NC (14.489 ; NC)	NC (NC ; NC)	NC (10.251 ; NC)	NC (NC ; NC)	NC (NC ; NC)	NC (NC ; NC)	
OS probability (95% CI)[a]								
2 Months	0.957 (0.872 ; 0.986)	0.944 (0.838 ; 0.982)	0.885 (0.684 ; 0.961)	1.000 (1.000 ; 1.000)	0.981 (0.876 ; 0.997)	0.955 (0.868 ; 0.985)	1.000 (1.000 ; 1.000)	
4 Months	0.898 (0.798 ; 0.950)	0.907 (0.792 ; 0.960)	0.808 (0.598 ; 0.915)	1.000 (1.000 ; 1.000)	0.926 (0.815 ; 0.972)	0.955 (0.868 ; 0.985)	0.873 (0.696 ; 0.950)	
6 Months	0.795 (0.678 ; 0.873)	0.851 (0.723 ; 0.922)	0.577 (0.368 ; 0.739)	1.000 (1.000 ; 1.000)	0.833 (0.703 ; 0.909)	0.866 (0.758 ; 0.928)	0.808 (0.622 ; 0.909)	
8 Months	0.735 (0.613 ; 0.824)	0.775 (0.638 ; 0.866)	0.500 (0.299 ; 0.672)	1.000 (1.000 ; 1.000)	0.776 (0.639 ; 0.866)	0.851 (0.740 ; 0.917)	0.808 (0.622 ; 0.909)	
10 Months	0.720 (0.596 ; 0.811)	0.756 (0.617 ; 0.850)	0.462 (0.266 ; 0.636)	1.000 (1.000 ; 1.000)	0.738 (0.598 ; 0.836)	0.788 (0.668 ; 0.869)	0.776 (0.586 ; 0.886)	
12 Months	0.630 (0.491 ; 0.741)	0.729 (0.583 ; 0.831)	0.462 (0.266 ; 0.636)	0.500 (0.006 ; 0.910)	0.677 (0.521 ; 0.791)	0.747 (0.619 ; 0.838)	0.735 (0.537 ; 0.859)	
14 Months	0.560 (0.375 ; 0.710)	0.677 (0.501 ; 0.802)	0.462 (0.266 ; 0.636)	0.500 (0.006 ; 0.910)	0.677 (0.521 ; 0.791)	0.747 (0.619 ; 0.838)	0.735 (0.537 ; 0.859)	
16 Months	0.560 (0.375 ; 0.710)	0.464 (0.196 ; 0.696)	0.462 (0.266 ; 0.636)	0.500 (0.006 ; 0.910)	0.592 (0.374 ; 0.756)	0.632 (0.435 ; 0.777)	0.735 (0.537 ; 0.859)	
18 Months	0.560 (0.375 ; 0.710)	0.464 (0.196 ; 0.696)	0.462 (0.266 ; 0.636)	0.500 (0.006 ; 0.910)	0.592 (0.374 ; 0.756)	0.632 (0.435 ; 0.777)	0.735 (0.537 ; 0.859)	
20 Months	0.560 (0.375 ; 0.710)	0.464 (0.196 ; 0.696)	0.462 (0.266 ; 0.636)	0.500 (0.006 ; 0.910)	0.592 (0.374 ; 0.756)	0.632 (0.435 ; 0.777)	0.735 (0.537 ; 0.859)	

Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone
Note: For EEFC14355, percentages are calculated using the number of patients in the age group as the denominator
OS: Overall survival, CI: Confidence interval.
CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley
[a]Estimated using the Kaplan-Meier method.
NC: not calculable.

Hepatic/renal impairment: No formal studies of isatuximab in patients with hepatic impairment have been conducted.

Paediatric patients: There is no data available in children and adolescents below 18 years of age.

Pregnancy and lactation: No formal clinical studies have been performed with isatuximab in pregnant or lactating women. No pregnancies were reported in the pivotal study.

Supportive studies

Study TCD 14079, Part A

Main supportive efficacy data is derived from dose escalation and expansion Phase 1b Study TCD14079, Part A. The study design and results are discussed in the section Dose response study above.

Patients with prior anti-CD38 treatment

Study TCD14079 Part B is a Phase 1 study of isatuximab in combination with pomalidomide and dexamethasone with similar inclusion/exclusion criteria to Study EFC14335, except that this trial allowed enrolment of patients refractory to prior anti-CD38 therapy and refractory to pomalidomide. The trial enrolled 7/47 (15%) patients previously exposed and refractory to daratumumab.

Table 30. Best overall response, overall response rate and clinical benefit rate - Patients who received Daratumumab as prior therapy in Study TCD14079 Part B.

	Isatuximab (dose level and schedule) + pomalidomide/dexamethasone
	10 mg/kg QW/Q2W (N=7)
Overall Response Rate (⩾PR)	1 (14.3%)
95% CI[a]	(0.4% to 57.9%)
- Partial response (PR)	1 (14.3%)
Stable disease (SD)	5 (71.4%)
Not evaluable	1 (14.3%)
Clinical benefit rate (⩾MR)	1 (14.3%)
95% CI[a]	(0.4% to 57.9%)

a estimated by Clopper-Pearson Exact method
PGM=PRODOPS/SAR650984/TCD14079B/DRSR/REPORT/PGM/eff_oresp_s_t.sas OUT=REPORT/OUTPUT/eff_oresp_dara_s_t_i.rtf (02OCT2019 - 17:51)

In **Study TED14154** Part B, a total of 32 patients with relapsed and refractory multiple myeloma were enrolled, all of whom were previously exposed to daratumumab (either as monotherapy or in combination with other anti-myeloma drugs). Patients received isatuximab 20 mg/kg weekly for the first 4-week cycle and then every other week.

Inclusion criterion 2 of the study was: patients must have received at least 3 cycles of daratumumab treatment with at least 6 weeks from the last treatment with daratumumab to the first study treatment, or at least 2 cycles of daratumumab treatment in case another therapy was given between daratumumab and isatuximab with at least 12 weeks from the last treatment with daratumumab to the first study treatment.

The median number of prior lines of therapy was 7 (range 2-14). All patients were refractory to their last line of treatment before they enrolled in the trial, and the median duration of treatment in the previous line of therapy was 4.52 months. A total of 59% of patients received daratumumab-based regimen as last prior treatment. The median time from the last dose of daratumumab to the first dose of isatuximab was 13 weeks and 43% of patients received daratumumab within the last 3 months before study treatment. All patients were refractory to daratumumab (progressed on or within 60 days after last daratumumab dose). More than half of these patients had received daratumumab in combination with other agents, and 46.9% of patients received daratumumab as monotherapy.

Among the 31 patients evaluable for efficacy, 1 partial response and 17 patients reported stable disease. The remaining patients had progressive disease as their best overall response. Follow up time was short (median follow up of 1.6 months), the median progression free survival was 1.6 months (95% CI) and the median overall survival 10.7 months.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study EFC14335/ICARIA is a randomized, open-label, multicentre phase 3 trial comparing isatuximab + pomalidomide and dexamethasone (IPd) with pomalidomide and dexamethasone alone (Pd) in patients with relapsed/refractory (R/R) multiple myeloma (MM).

In line with scientific advice provided by the CHMP in 2016, the use of Pd as control arm is considered acceptable, as it represents one of the available treatment options for the proposed target population. The planned add-on design (IPd versus Pd) allows for isolation of any potential effect of isatuximab on efficacy and safety. At the time the study was initiated daratumumab plus Pd was not approved in any region of the world, which therefore precluded conducting the trial with daratumumab as active comparator.

Study EFC14335 included adult patients with R/R MM that had received at least 2 prior lines of anti-myeloma therapy, which included at least 2 consecutive cycles of lenalidomide and a proteasome inhibitor (PI) given alone or in combination. Patients had to have failed treatment with lenalidomide and a PI, and had to have progressed on or within 60 days after end of the previous therapy before study entry. Patients with primary refractory disease, free light chain disease only, refractory to an anti-CD38 antibody or previously exposed to pomalidomide were excluded from the trial as well as those with inadequate renal, hepatic and bone marrow (BM) function.

Inclusion of a relevant proportion of elderly patients and of patients with low ECOG performance status, and more than half of the patients included in Europe, are indications that the study population was representative for the targeted R/R MM population.

Imbalances in (R-)ISS stage at study entry, as well as high risk cytogenetic abnormalities are in favour of the IPd arm. The frequency of ISS stage I at study entry was lower in the Pd arm (41.6% IPd vs. 33.3% Pd). ISS stage III was observed less frequently in the IPd arm (22.1% vs. 28.1% Pd). A similar imbalance was observed for the R-ISS stage at study entry. As a correlation has been reported between ISS stage at diagnosis and survival (e.g. reported median OS of 62 months for ISS stage I, 44 months for ISS stage II and 29 months for ISS stage III), it is uncertain whether this difference could have impacted the study results. The higher frequency of high-risk cytogenetic abnormalities in the control arm (15.6% IPd vs. 23.5% Pd) adds to this uncertainty. On the other hand imbalances in other prognostic factors such as age and ECOG PS between the two treatment arms suggest a more favourable prognosis for the Pd arm. Despite the stratification for age (<75 years versus ≥75 years) and similar median age in both treatment arms, less patients <65 years of age were included in the IPd arm (35.1% vs. 45.8% in the Pd arm), and more patients between 65 and 75 (44.2% vs. 35.3%). Most patients had ECOG performance status 0 or 1. More patients in the IPd arm had ECOG 1 (53.9% IPd vs. 44.4% Pd), and less patients ECOG 0 (35.7% vs. 45.1%). Overall, it seems unlikely that the imbalances in prognostic factors would have influenced observed efficacy results.

The proposed isatuximab dose in combination with pomalidomide and dexamethasone is acceptable. As no MTD was reached in dose escalation Study 14079, isatuximab 10 mg/kg QWx4, followed by 10 mg/kg Q2W was chosen for the pivotal Phase 3 study based on PK/PD modelling and simulations. The dosing regimen applied in the Pd (control) arm is in line with the regimen employed in the pivotal study supporting registration of pomalidomide with dexamethasone. The study treatment duration is acceptable. In line with comparable treatments in this later line of R/R MM, treatment could be continued until disease progression, unacceptable AEs, patient wish, or any other reason.

Patients received as premedication acetaminophen, ranitidine and diphenhydramine prior to isatuximab infusion to reduce the risk and severity of infusion reactions (IRs) commonly observed with monoclonal antibodies.

The selection of PFS as primary endpoint of the pivotal study and key secondary endpoints, ORR and OS, are acceptable. All recent phase 3 trials in MM have used PFS as primary endpoint, e.g. leading to the approval of elotuzumab and daratumumab in the relapsed and refractory setting. Clinically relevant PFS effects should be substantiated by supportive secondary endpoints – see also recommendation below.

The 'ITT analysis set' is a true intention-to-treat analysis set, but the primary analysis censors for subsequent therapy. Therefore, it does not estimate the treatment-policy estimand as recommended in CHMP/27994/2008 Rev. 1 (i.e., the effect of starting with IPd instead of Pd regardless of any intercurrent event such as start of new therapy). Sensitivity analysis 1 does that and is therefore the preferred primary analysis as recommended by CHMP/27994/2008 Rev. 1.

Being a human IgG kappa monoclonal antibody, isatuximab (similarly to what was observed with daratumumab) can be detected by serum protein electrophoresis (SPE) as well as immunofixation (IFE) assays, both of which are used for clinical monitoring of endogenous M-protein. the potential consequences of the interference with M-protein detection might have for the relapse assessment in the pivotal study was discussed, however, taking into account the definition of progressive disease by IMWG criteria, it was concluded that the impact of this interference on the assessment of progression would be limited, as the maximum concentration of isatuximab contributed to a very small extent (e.g. 0.0347 g/dL) to the total immunoglobulin concentration. Therefore, the isatuximab concentration alone is not sufficient to reach criteria for progressive disease and result in false positive results.

Despite occurrences of protocol deviations, a routine GCP inspection of the study EFC14335 concluded that there was no impairment of the quality or reliability of the study data. The inspection team considered that, the CRO and applicant should implement robust preventive measures in future applications.

Efficacy data and additional analyses

The primary endpoint was met. The pivotal study showed a statistically significant improvement in IRC based PFS with addition of isatuximab to Pd. The HR was 0.596 (95% CI 0.436, 0.814; p=0.001), and median PFS increased by 5.06 months (11.53 IPd vs. 6.47 months Pd). A total of 162 PFS events was reported at the time of data cut-off, similar to the number of PFS events defined in the study protocol. The observed treatment effect (HR 0.596) is consistent with the protocol-specified hypothesis on PFS (HR 0.6), although both treatment arms performed better than anticipated (predicted median PFS was 6.67 vs. 4 months) which can possibly be ascribed to differences in patient population between trials, i.e. EFC14335 patient population received numerically fewer prior treatments, had fewer patients with baseline ECOG PS $\geq$2, and received less thalidomide and more new generation medicinal products compared to patients in the pomalidomide pivotal study MM 003, as well as better management of pomalidomide toxicity.

Results of the primary PFS analysis were supported by 5 sensitivity analyses, showing hazard ratios ranging from 0.568 to 0.602. This included the CHMP SA recommended PFS analysis and investigator based PFS analysis. The fact that all PFS subgroup HRs were in the range of 0.50-0.70 or more favourable and that the multivariate analyses showed a statistically significant and favourable effect is reassuring.

The observed difference is supported by key secondary endpoints and a trend in OS benefit. The key secondary endpoint, ORR based on IRC assessment, significantly improved with the addition of

isatuximab to Pd compared to Pd in the ITT population (60.4% vs. 35.3%, respectively). The depth of response (VGPR or better, 31.8% vs. 8.5%) and clinical benefit rate significantly increased as well (66.9% vs. 46.5%).

Interim analysis of the key secondary endpoint, OS, supports the primary endpoint. Although no statistically significant difference has been observed between treatment arms, a trend in favour of the IPd arm was observed, with a HR of 0.687 (95% CI 0.461, 1.023, p=0.0631). Final analysis of OS is expected by first quarter of 2021 once the planned number of events will be reached (220 death events). Final OS analysis will be submitted in line with the CHMP recommendation, the analysis will include subgroup analyses by best response to previous therapy and by refractoriness to lenalidomide, PI inhibitors or both.

A substantial part of the study population received additional systemic therapy post-study: 39% of patients in the IPd arm and 54% of patients in the Pd arm. Daratumumab was administered in 6 patients (4%) of the IPd arm vs. 45 (29%) of patients in the Pd arm. OS in Pd patients that switched to daratumumab subsequent therapy was better than for those Pd patients that did not switch. Therefore, the ITT OS analysis would be biased in favour of the Pd arm, but in fact it was still numerically in favour of IPd and close to statistical significance. This strongly suggests that the effect in absence of daratumumab subsequent therapy would be in favour of IPd. This observation is also supported by the IPCW analysis (addressing the effect as if no daratumumab had been given in the control arm) that was numerically positive for IPd as well, i.e. the stratified HR was 0.708 [0.451 to 1.111] which is consistent with the ITT-estimate of 0.687 [0.461 to 1.023].

Preliminary analyses comparing IPd vs. Pd with subsequent daratumumab suggest a possible negative effect for IPd (data not shown). However, these patient groups are pre-selected (probably selection of the 'best' Pd patients able to continue with daratumumab vs. all IPd patients (including patients with worse prognosis). Updated post-study treatment data will be provided at the time of the final OS analysis.

The other secondary endpoints time to progression (TTP: 12.71 months, 95% CI 11.20, 15.211 IPd vs.7.75 months; 95% CI 5.027, 9.758 Pd) and time to next treatment (TTNT: NR, 95% CI 12.123 IPd vs. 9.10 months 95% CI 6.374, 12.255 Pd; p-value=0.0003) supported the primary endpoint. Mature data on time to next treatment will be available in the first quarter of 2021. Although the secondary endpoints DOR, median time to first IRC determined response (TT1R), and time to best response (TTBR) were not statistically significant different between the two treatment arms, a trend in favour of isatuximab was observed for all three endpoints. Based on the limited available data and the exploratory nature of the analysis it is not possible to draw conclusions with regard to minimal residual disease (MRD).

The results of the PRO measures appear to indicate no significant improvement of QoL by addition of isatuximab to Pd, but also no deterioration of QoL/cancer related symptoms. However, results should be interpreted with caution due to the open-label design of the study and the missing data due to non-response.

A trend toward less deterioration in renal function in the IPd arm, as well as increase in complete renal response (CRenal; 71.9% vs. 38.1% of patients improved in creatinine clearance from <50 mL at baseline to ≥60 mL at ≥1 postbaseline assessment) was observed. In almost half of the patients in both arms, the CRenal duration was ≥60 days. These results support the primary endpoint, and are considered important for the target population with renal impairment as common clinical feature of end organ damage in MM. However, results should be interpreted with caution due to the likely exploratory nature of this endpoint.

In conclusion, the clinical benefit of isatuximab (Sarclisa), an antibody targeting CD38, 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 has been adequately demonstrated. In line with the enrolment criteria of pivotal Phase 3 study EFC14335/ ICARIA, patients were relapsed and refractory, >18 years of age, and no patients with primary refractory disease were included, this is reflected in section 5.1 of the SmPC.

The posology regimen based on a fixed volume infusion following results of an interim analysis of part B of study TCD14079 proposed in section 4.2 of the SmPC is supported by the efficacy data from the same study.

Efficacy of isatuximab after daratumumab treatment is unknown, since only 1 patient was included in the pivotal trial who had previously received daratumumab treatment. Results of the currently ongoing Study TCD14079 part B (a Phase 1b study in combi with pomalidomide dexamethasone in RR MM) and TED14154 Part B (single arm monotherapy dose escalation study in adult RRMM patients) that allowed enrolment of patients previously exposed to daratumumab, suggest that isatuximab has some activity in that population. Interpretation of the data is difficult due to the limited amount of subjects, variations in inclusion/exclusion of the study population between both studies, and the single arm design, therefore there is insufficient data available to conclude on the efficacy of isatuximab in patients previously treated with daratumumab. This is reflected in the SmPC.

2.5.4. Conclusions on the clinical efficacy

The clinical benefit of adding isatuximab to pomalidomide and dexamethasone is demonstrated in relapsed and refractory multiple myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

In line with a recommendation of the CHMP the Applicant will provide:

- the final safety and OS analysis, including subgroup analyses by best response to previous therapy and by refractoriness to lenalidomide, PI inhibitors or both, from study EFC14335.

2.6. Clinical safety

Clinical safety data have been presented for 6 clinical studies: the pivotal Phase 3 trial EFC14335 and 5 supportive studies (please see section *Pharmacokinetics*). In these 6 studies, a total of 576 patients were treated with isatuximab. Safety data were reported in 4 data pools, of which safety data from the pivotal Phase 3 trial as included in pool 1 is considered most important:

- **Data Pool 1**: Consisting of the core isatuximab, pomalidomide and dexamethasone combination studies in line with the requested indication (n=197). The main population is provided by the pivotal study EFC14335 (n=152). The remaining patients were treated in the TCD14079 study of which 22 were administered 10 mg/kg isatuximab (22 in the expansion phase with P2F2, the other patients in the escalation phase with P1F1).

The Applicant submitted also the other 3 safety data pools including supportive monotherapy studies (Pool 2), supportive combination therapy studies with other regimens than Pd (Pool 3) and data from the 6 studies together (Pool 4):

- **Data Pool 2**: Contains supportive single-agent isatuximab studies (n=305). 48 patients received isatuximab <10 mg/kg, 111 isatuximab 10 mg/kg, 116 isatuximab 20 mg/kg without dexamethasone, and 30 isatuximab 20 mg/kg with dexamethasone. This pool can be used to evaluate toxicity specific for the anti-CD38 MoA of isatuximab and to assess additional toxicity of combining isatuximab with Pd

(comparison with Pool 1). The included patients differed from newly diagnosed to RRMM with different lines of prior therapy.

- **Data Pool 3**: In this pool supportive studies of isatuximab in combination with other regimens are described. This pool is less relevant for this Application due to the combination with another backbone therapy (lenalidomide (n=57; ILd) or bortezomib/cyclophosphamide (n=17); ICBd) and the small number of patients (n=74). The bortezomib study was in newly diagnosed MM patients not eligible for transplant.
- **Data Pool 4**: This Pool is a combination of the former 3 Pools and entails all patients exposed to isatuximab (n=576).

The dossier cut-off date for inclusion of clinical safety data was 15 November 2018, in line with the efficacy data cut off.

Of note, the clinical development of isatuximab was originally initiated with a concentrate for solution for infusion at 5 mg/mL (C1P1F1; cell 1, process 1, formulation 1, hereafter referred to as isatuximab P1F1). It was subsequently continued with a concentrate for solution for infusion of 20 mg/mL (C1P2F2; cell 1, process 2, formulation 2, hereafter referred to as isatuximab P2F2). Isatuximab P2F2 is the formulation intended for commercial use and was used in the pivotal Phase 3 study EFC14335 (See also Clinical Pharmacology section).

In the completed studies a weight-based infusion volume was used, except for the ongoing TCD14079 part B study in which a fixed infusion volume was used. The Applicant is applying for the fixed infusion volume method .

Patient exposure

Disposition of subjects and patients

The safety population in Data Pool 1 included 149 patients and 152 patients in the Pd and IPd groups of study EFC14335, 183 patients in group pooled IPd 10 mg/kg, and 197 patients in group pooled All IPd doses (Table 35).

Table 31. Disposition of patients - Data Pool 1 - safety population.

	EFC14335		Pooled	
n (%)	**Pd (N=149)**	**IPd 10 mg/kg (N=152)**	**IPd(10 mg/kg) (N=183)**	**All IPd dose (N=197)**
Enrolled and treated patients	149 (100)	152 (100)	183 (100)	197 (100)
Ongoing treatment	35 (23.5)	65 (42.8)	81 (44.3)	84 (42.6)
Main reasons for definitive treatment discontinuation				
Adverse event	19 (12.8)	11 (7.2)	13 (7.1)	13 (6.6)
Progressive disease	88 (59.1)	66 (43.4)	75 (41.0)	84 (42.6)
Poor compliance to protocol	0	1 (0.7)	1 (0.5)	1 (0.5)
Withdrawal by subject	6 (4.0)	5 (3.3)	5 (2.7)	5 (2.5)
Other reason	1 (0.7)	4 (2.6)	8 (4.4)	10 (5.1)
Main reasons for premature treatment discontinuation of isatuximab				
Adverse event	0	4 (2.6)	4 (2.2)	4 (2.0)
Other reason	0	0	0	0

n (%)	EFC14335		Pooled	
	Pd (N=149)	IPd 10 mg/kg (N=152)	IPd(10 mg/kg) (N=183)	All IPd dose (N=197)
Main reasons for premature treatment discontinuation of dexamethasone				
Adverse event	3 (2.0)	2 (1.3)	2 (1.1)	2 (1.0)
Other reason	0	0	0	0
Main reasons for premature treatment discontinuation of pomalidomide				
Adverse event	0	8 (5.3)	8 (4.4)	8 (4.1)
Other reason	0	0	0	0

Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone

Extent of exposure

Data Pool 1: Core isatuximab and pomalidomide combination studies

The extent of overall treatment exposure in study EFC14335 was greater in group IPd compared to group Pd in terms of the median number of cycles started (10 versus 6, respectively) and the median duration of exposure (41 versus 24 weeks).

Comparing groups IPd and Pd, respectively, in Study EFC14335, more patients in group IPd had a cycle delay (57.9% versus 43.0%) and a cycle delay of >7 days (34.9% versus 17.4%). The percent of cycles delayed was 13.1% versus 10.9%.

The extent of isatuximab exposure was similar among the 3 IPd groups in Pool 1. The median number of cycles started with isatuximab (10) and the median duration of isatuximab exposure (about 41 weeks), were similar to that described for the overall extent of exposure. The median RDI was approximately 92% in all three groups. The percent of patients having at least 6, 12, 18, or >24 months of isatuximab exposure in group EFC14335 IPd 10 mg/kg was 101 (66.4%), 36 (23.7%), 0, and 0, respectively.

Comparing the IPd and Pd groups from study EFC14335, pomalidomide exposure was greater in the IPd group, in terms of the median number of cycles started (10 versus 6) and the median duration of pomalidomide exposure (40.36 versus 24.00 weeks). The RDI of pomalidomide, however, was greater in group Pd (85.14% versus 93.33%). Comparing the IPd and Pd groups in study EFC14335, more patients in group IPd had a pomalidomide dose omitted (82.9% versus 63.1%) or reduced (42.8% versus 24.2%).

Dexamethasone exposure was similar for EFC14335 IPd was greater than in group EFC14335 Pd in terms of the median number of cycles started per patient (10 vs 6, respectively) and the median duration of dexamethasone exposure (40.86 vs 24.00 weeks). However, the RDI was greater in group Pd (87.76% vs 96.32%, respectively).

A similar extent of exposure was reported for the pooled IPd 10 mg/kg, and pooled All IPd doses patient groups.

Adverse events

Common adverse events

Overview of AEs

Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serous during the treatment period, which is defined as the time from first dose of study treatments administration to the last dose of study treatments +30 days.

An overview of the TEAEs in Data Pool 1 is presented below. Comparing the IPd and Pd groups in study EFC14335, the incidence of TEAEs was higher in the IPd group for treatment-related TEAEs (90.8% versus 79.9%, respectively), Grade ≥3 TEAEs (86.8% versus 70.5%), and serious TEAEs (61.8% versus 53.7%). When serious TEAEs were adjusted for the longer duration of exposure in the IPd arm compared to the Pd arm in study EFC14335, the incidence rate in patient years was similar in the IPd and Pd arms (1.36 and 1.30 incidence rate per patient year in the IPd and Pd arms, respectively). The incidence of TEAEs with a fatal outcome during the treatment period was 7.2% versus 8.7%, respectively, and TEAEs leading to definitive treatment discontinuation was 7.2% versus 12.8%. In the IPd arm 1 treatment-related fatal TEAE was reported; in the Pd arm 2.

Table 32. Overview of treatment-emergent adverse events - Data Pool 1 - safety population.

N(%)	EFC14335		Pooled[a]	
	Pd (N=149)	IPd 10 mg/kg (N=152)	IPd(10 mg/kg) (N=183)	All IPd doses[b] (N=197)
Patients with any TEAE (any grade)	146 (98.0)	151 (99.3)	182 (99.5)	196 (99.5)
Patients with any treatment-related TEAE (any grade)	119 (79.9)	138 (90.8)	169 (92.3)	183 (92.9)
Patients with any TEAE of grade ≥ 3	105 (70.5)	132 (86.8)	158 (86.3)	171 (86.8)
Patients with any treatment-related TEAE of grade ≥ 3	71 (47.7)	109 (71.7)	132 (72.1)	143 (72.6)
Patients with any TEAE of grade 3-4	103 (69.1)	129 (84.9)	155 (84.7)	168 (85.3)
Patients with any AESI	1 (0.7)	10 (6.6)	25 (13.7)	31 (15.7)
Patients with any AESI of grade ≥ 3	0	8 (5.3)	10 (5.5)	13 (6.6)
Patients with any IR (excluding symptoms)	0	58 (38.2)	72 (39.3)	77 (39.1)
Patients with any IR of grade ≥ 3 (excluding symptoms)	0	4 (2.6)	5 (2.7)	5 (2.5)
Patients with any serious TEAE	80 (53.7)	94 (61.8)	111 (60.7)	120 (60.9)
Patients with any serious treatment-related TEAE	24 (16.1)	54 (35.5)	62 (33.9)	67 (34.0)
Patients with any TEAE with fatal outcome during the treatment period	13 (8.7)	11 (7.2)	15 (8.2)	16 (8.1)
Patients with any treatment-related TEAE with fatal outcome during the treatment period	2 (1.3)	1 (0.7)	1 (0.5)	1 (0.5)
Patients with any TEAE leading to definitive discontinuation	19 (12.8)	11 (7.2)	13 (7.1)	13 (6.6)
Patients with any TEAE leading to premature discontinuation of isatuximab	0	4 (2.6)	4 (2.2)	4 (2.0)
Patients with any TEAE leading to premature discontinuation of pomalidomide	0	8 (5.3)	8 (4.4)	8 (4.1)
Patients with any TEAE leading to premature discontinuation of dexamethasone	2 (1.3)	2 (1.3)	3 (1.6)	3 (1.5)

Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone

Data Pool 1: EFC14335 and TCD14079 Part A

5, 10, and 20 mg/kg QW/Q2W isatuximab

Treatment-related AEs

In groups IPd and Pd in study EFC14335, the incidence of treatment-related TEAEs (in ≥10% of patients) which were ≥5% greater in group IPd included neutropenia (42.8 vs 32.2%), infusion related

reaction (36.2 vs 0.0%), upper respiratory tract infection (9.9 vs 4.4%), febrile neutropenia (10.5 vs 2.0%), and bronchitis (8.6 vs 2.0%). The treatment-related Grade ≥3 TEAEs (in ≥5% of patients) with an incidence ≥5% greater in group IPd were neutropenia (42.1 vs 30.9%) and febrile neutropenia (10.5 vs 2.0%). There were no treatment-related TEAEs (All grade in ≥10% of patients or Grade ≥3 in ≥5% of patients) with an incidence ≥5% greater in group Pd compared to group IPd.

The incidence of treatment-related TEAEs was similar among the two pooled IPd groups and the IPd group in study EFC14335.

Most frequent AEs

The most frequent TEAEs (All grades and Grade ≥3) in Data Pool 1 are presented below.

Table 33. Number (%) of patients with TEAEs with an incidence >= 5% (all grades) or >= 2% (grades >= 3) by PT - Data Pool 1 - Safety population.

	EFC14335				Pooled[a]			
	Pd (N=149)		IPd 10 mg/kg (N=152)		IPd(10 mg/kg) (N=183)		All IPd doses[b](N=197)	
Preferred Term [n(%)]	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any event	146 (98.0)	105 (70.5)	151 (99.3)	132 (86.8)	182 (99.5)	158 (86.3)	196 (99.5)	171 (86.8)
Neutropenia	50 (33.6)	48 (32.2)	71 (46.7)	70 (46.1)	91 (49.7)	90 (49.2)	101 (51.3)	100 (50.8)
Infusion related reaction	2 (1.3)	0	56 (36.8)	4 (2.6)	70 (38.3)	5 (2.7)	75 (38.1)	5 (2.5)
Upper respiratory tract infection	26 (17.4)	1 (0.7)	43 (28.3)	5 (3.3)	55 (30.1)	5 (2.7)	62 (31.5)	5 (2.5)
Diarrhoea	29 (19.5)	1 (0.7)	39 (25.7)	3 (2.0)	50 (27.3)	4 (2.2)	55 (27.9)	4 (2.0)
Fatigue	32 (21.5)	0	26 (17.1)	6 (3.9)	44 (24.0)	7 (3.8)	54 (27.4)	9 (4.6)
Pneumonia	26 (17.4)	23 (15.4)	31 (20.4)	25 (16.4)	39 (21.3)	32 (17.5)	41 (20.8)	33 (16.8)
Bronchitis	13 (8.7)	1 (0.7)	36 (23.7)	5 (3.3)	39 (21.3)	5 (2.7)	40 (20.3)	6 (3.0)
Constipation	26 (17.4)	0	24 (15.8)	0	34 (18.6)	0	40 (20.3)	0
Dyspnoea	15 (10.1)	2 (1.3)	23 (15.1)	6 (3.9)	33 (18.0)	7 (3.8)	39 (19.8)	9 (4.6)
Nausea	14 (9.4)	0	23 (15.1)	0	29 (15.8)	0	34 (17.3)	0
Back pain	22 (14.8)	2 (1.3)	25 (16.4)	3 (2.0)	32 (17.5)	4 (2.2)	33 (16.8)	4 (2.0)
Pyrexia	21 (14.1)	2 (1.3)	22 (14.5)	2 (1.3)	27 (14.8)	3 (1.6)	32 (16.2)	3 (1.5)
Headache	8 (5.4)	0	15 (9.9)	0	23 (12.6)	0	29 (14.7)	0
Cough	11 (7.4)	1 (0.7)	14 (9.2)	0	23 (12.6)	0	27 (13.7)	0
Insomnia	12 (8.1)	1 (0.7)	13 (8.6)	1 (0.7)	24 (13.1)	2 (1.1)	26 (13.2)	2 (1.0)
Vomiting	5 (3.4)	0	18 (11.8)	2 (1.3)	21 (11.5)	2 (1.1)	25 (12.7)	2 (1.0)
Oedema peripheral	16 (10.7)	0	20 (13.2)	1 (0.7)	22 (12.0)	1 (0.5)	24 (12.2)	1 (0.5)
Thrombocytopenia	18 (12.1)	18 (12.1)	19 (12.5)	18 (11.8)	21 (11.5)	20 (10.9)	24 (12.2)	22 (11.2)
Arthralgia	13 (8.7)	1 (0.7)	16 (10.5)	4 (2.6)	20 (10.9)	5 (2.7)	23 (11.7)	6 (3.0)
Asthenia	27 (18.1)	4 (2.7)	23 (15.1)	5 (3.3)	23 (12.6)	5 (2.7)	23 (11.7)	5 (2.5)
Muscle spasms	15 (10.1)	0	14 (9.2)	0	19 (10.4)	0	23 (11.7)	0
Urinary tract infection	14 (9.4)	2 (1.3)	15 (9.9)	7 (4.6)	21 (11.5)	9 (4.9)	23 (11.7)	10 (5.1)
Tremor	6 (4.0)	0	12 (7.9)	3 (2.0)	18 (9.8)	3 (1.6)	20 (10.2)	3 (1.5)
Dizziness	4 (2.7)	0	8 (5.3)	0	13 (7.1)	0	19 (9.6)	1 (0.5)
Nasopharyngitis	7 (4.7)	0	14 (9.2)	0	16 (8.7)	0	19 (9.6)	0
Bone pain	8 (5.4)	2 (1.3)	12 (7.9)	1 (0.7)	15 (8.2)	2 (1.1)	18 (9.1)	2 (1.0)
Febrile neutropenia	3 (2.0)	3 (2.0)	18 (11.8)	18 (11.8)	18 (9.8)	18 (9.8)	18 (9.1)	18 (9.1)
Decreased appetite	7 (4.7)	1 (0.7)	15 (9.9)	2 (1.3)	17 (9.3)	2 (1.1)	17 (8.6)	2 (1.0)
Pain in extremity	4 (2.7)	0	7 (4.6)	0	14 (7.7)	1 (0.5)	17 (8.6)	2 (1.0)
Peripheral sensory neuropathy	9 (6.0)	0	11 (7.2)	1 (0.7)	13 (7.1)	2 (1.1)	17 (8.6)	2 (1.0)
Fall	8 (5.4)	1 (0.7)	8 (5.3)	0	12 (6.6)	1 (0.5)	14 (7.1)	2 (1.0)
Muscular weakness	7 (4.7)	0	11 (7.2)	1 (0.7)	14 (7.7)	3 (1.6)	14 (7.1)	3 (1.5)

	EFC14335				Pooled[a]			
	Pd (N=149)		IPd 10 mg/kg (N=152)		IPd(10 mg/kg) (N=183)		All IPd doses[b](N=197)	
Preferred Term [n(%)]	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Musculoskeletal chest pain	7 (4.7)	0	13 (8.6)	0	14 (7.7)	0	14 (7.1)	0
Myalgia	5 (3.4)	0	10 (6.6)	0	12 (6.6)	0	14 (7.1)	0
Disease progression	8 (5.4)	8 (5.4)	8 (5.3)	8 (5.3)	12 (6.6)	12 (6.6)	13 (6.6)	13 (6.6)
Hypertension	8 (5.4)	3 (2.0)	7 (4.6)	2 (1.3)	11 (6.0)	4 (2.2)	13 (6.6)	4 (2.0)
Musculoskeletal pain	5 (3.4)	0	7 (4.6)	0	11 (6.0)	1 (0.5)	12 (6.1)	1 (0.5)
Pathological fracture	8 (5.4)	3 (2.0)	9 (5.9)	3 (2.0)	12 (6.6)	5 (2.7)	12 (6.1)	5 (2.5)
Stomatitis	4 (2.7)	0	10 (6.6)	1 (0.7)	11 (6.0)	1 (0.5)	12 (6.1)	1 (0.5)
Abdominal pain	4 (2.7)	0	7 (4.6)	0	9 (4.9)	0	11 (5.6)	0
Influenza	8 (5.4)	1 (0.7)	9 (5.9)	4 (2.6)	11 (6.0)	5 (2.7)	11 (5.6)	5 (2.5)
Oropharyngeal pain	3 (2.0)	0	8 (5.3)	0	9 (4.9)	0	11 (5.6)	0
Rash	8 (5.4)	0	5 (3.3)	0	7 (3.8)	0	11 (5.6)	0
Traumatic fracture	1 (0.7)	0	5 (3.3)	2 (1.3)	8 (4.4)	3 (1.6)	11 (5.6)	5 (2.5)
Weight decreased	2 (1.3)	0	10 (6.6)	0	10 (5.5)	0	11 (5.6)	0
Anaemia	2 (1.3)	1 (0.7)	6 (3.9)	5 (3.3)	9 (4.9)	6 (3.3)	10 (5.1)	7 (3.6)
Hyperglycaemia	1 (0.7)	0	5 (3.3)	4 (2.6)	9 (4.9)	5 (2.7)	10 (5.1)	5 (2.5)
Hyperhidrosis	4 (2.7)	0	5 (3.3)	0	10 (5.5)	0	10 (5.1)	0
Productive cough	2 (1.3)	0	7 (4.6)	0	7 (3.8)	0	10 (5.1)	0
Acute kidney injury	8 (5.4)	6 (4.0)	7 (4.6)	4 (2.6)	8 (4.4)	5 (2.7)	9 (4.6)	6 (3.0)
Syncope	3 (2.0)	3 (2.0)	6 (3.9)	5 (3.3)	8 (4.4)	7 (3.8)	9 (4.6)	8 (4.1)
Atrial fibrillation	3 (2.0)	1 (0.7)	7 (4.6)	3 (2.0)	7 (3.8)	3 (1.6)	8 (4.1)	4 (2.0)
Lower respiratory tract infection	8 (5.4)	4 (2.7)	8 (5.3)	5 (3.3)	8 (4.4)	5 (2.7)	8 (4.1)	5 (2.5)
Sepsis	2 (1.3)	2 (1.3)	4 (2.6)	4 (2.6)	5 (2.7)	5 (2.7)	5 (2.5)	5 (2.5)
Pulmonary embolism	3 (2.0)	3 (2.0)	3 (2.0)	3 (2.0)	3 (1.6)	3 (1.6)	4 (2.0)	4 (2.0)

Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone
Data Pool 1: EFC14335 and TCD14079 Part A
5, 10, and 20 mg/kg QW/Q2W isatuximab
Note: Percentages are calculated using the number of patients treated as denominator.
MedDRA 21.0
CTCAE 4.03

Among the most frequent TEAEs in the pivotal trial, resolution of most AEs was documented. The median duration to resolution was similar in both arms for upper respiratory tract infection (11 days and 13 days in the Pd and IPd arms, respectively); for dyspnoea and nausea, the median duration to resolve was higher in the Pd arm compared to the IPd arm (16 versus 10 days and 24 versus 8 days, respectively). The duration of the most frequent Grade ≥3 TEAEs was similar between the two arms. Among the most frequent SAEs, the main difference was seen in pathological fractures: the median duration to resolve was lower in the Pd arm compared to the IPd arm (28 versus 110 days), although there was a small number of episodes for most of the frequent SAEs.

AEs by organ system or syndrome

The TEAEs by primary SOC with the greatest difference in incidence (≥10%) between the IPd and Pd groups in study EFC14335 were 'Injury, poisoning and procedural complications (infusion reactions)', 'Infections and infestations', 'Blood and lymphatic system disorders' including thrombocytopenia and neutropenia, 'Cardiac disorders' and 'Nervous system disorders'.

Except for nervous system and cardiac disorders (discussed below), differences between treatment arms in these SOCs are discussed in the section *other significant adverse events*.

In the IPd and Pd groups in study EFC14335, the incidence of TEAEs (reported in ≥15% of patients) was ≥5% greater in group IPd for neutropenia, infusion related reaction, upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, and nausea. The only Grade ≥3 TEAEs with a reported incidence ≥5% greater in group IPd were neutropenia and febrile neutropenia. There were no TEAEs (any grade or Grade ≥3) for which the incidence was ≥5% greater in the Pd group compared to the IPd group.

The exposure-adjusted rates for TEAES reported at a ≥10% incidence in the IPd arm and ≥5% more frequently than in the Pd arm were: neutropenia (1.12 and 0.85 incidence rate per patient year in the IPd and Pd arms, respectively); upper respiratory tract infection (0.51 and 0.38); and diarrhoea (0.45 and 0.41); bronchitis (0.42 and 0.17); dyspnoea (0.24 and 0.19); nausea (0.25 and 0.18); febrile neutropenia (0.18 and 0.04); vomiting (0.18 and 0.06).

Nervous system disorders TEAEs

In study EFC14335, the overall incidence of nervous system disorders TEAEs was higher in the IPd arm than in the Pd arm (40.8% versus 28.9%). Comparing the IPd and Pd groups in study EFC14335, the following TEAEs in the Nervous system disorders SOC (incidence ≥5% for all grades, or ≥2% for Grades ≥3) were reported with an incidence ≥2% higher in the IPd group: headache (9.9 vs 5.4%), tremor (7.9 vs 4.0%), and dizziness (5.3% vs 2.7%). All the incidences of headache, tremor, and dizziness were reported as non-serious and as not treatment-related, all had their onset during the treatment period, and none led to definitive treatment discontinuation, across all the groups in Data Pool 1.

Cardiac disorders TEAEs

In study EFC14335, the overall incidence of TEAES in the Cardiac disorders SOC was higher in the IPd arm than in the Pd arm (14.5% versus 4.0%), and consisted most frequently of cardiac arrhythmias in the IPd arm (11.2% and 2.0%). The most frequent cardiac arrhythmia was atrial fibrillation, reported in 7 (4.6%) of the IPd patients, and in 3 (2.0%) of the Pd patients.

Adverse events of special interest

Infusion reactions (IRR)

In the IPd arm of EFC14335, IRRs occurred in 38.2%. Most IRRs were Grade 2 (31.6%). Grade 3 or 4 IRRs were both reported in 1.3%. IRRs led to isatuximab interruption in 28.9% of patients and to discontinuation of isatuximab in 2.6%. A single episode was reported in 89.7% of patients, the remaining patients had 2 episodes. The IRR occurred at the first infusion in all patients and had a duration of 1 day in 98.4%. The most frequent symptoms of IRs were dyspnoea, cough, chills, and nausea. Signs and symptoms of Grade 3 or higher infusion reactions included dyspnoea, hypertension and bronchospasm.

Fixed volume infusion

In study TCD14079 Part B in 47 patients enrolled from 11 study sites based in the US who received a fixed dilution volume of 250 mL and infusion rates in mL/hour, overall, IRs of any grade were reported in 19 patients (40.4%), and in 20 episodes in 871 infusions (2.3%). All the IRs were Grade 2 and no patient had IR of Grade ≥3. All but 1 of the patients who experienced IRs had only a single episode, and all only during their first infusion of isatuximab; one patient (2.1%) had 2 IR episodes during the first infusion. The onset of all the IRs occurred during the same day of the isatuximab infusion, and all the IRs recovered on the same day. No new safety signal noted with fixed volume administration.

The safety data were also compared with the pivotal EFC14335 study:

- Median number of cycles: 9, compared to 10 in EFC14335;
- TEAE Grade ≥3: 74.5%, compared to 86.8% in EFC14335;
- SAE: 57.4%, compared to 61.8% in EFC14335;
- TEAE leading to definitive treatment discontinuation: 10.6%, compared to 7.2% in EFC14335;
- TEAE leading to death: 12.8%, compared to 7.9% in EFC14335;
- Infusion reactions: 40.4%, compared to 38.2% in EFC14335.

Infections

In study EFC14335, there was a 16.5% and 12.6% difference between the IPd and Pd arms in the incidence of AEs of all grades and Grade ≥3, respectively, in the Infections and infestations disorders SOC. The AEs contributing the most to this imbalance were upper respiratory tract infection (28.3% versus 17.4%) and bronchitis (23.7% versus 8.7%). Except for Herpes virus infections (9.9% versus 2.7%), the incidence of opportunistic infections (Cytomegaloviral infections, Candida infections, Aspergillus infections, Pneumocystis infections, and Herpes viral infections) was similar in the IPd vs Pd arm.

The incidence of Grade 3 or higher infections was 42.8%. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 21.7% of patients in isatuximab regimen group compared to 16.1% in comparator regimen (pomalidomide and low-dose dexamethasone) group, and Grade 4 in 3.3% of patients in isatuximab regimen group compared to 2.7% in comparator regimen group. Discontinuations from treatment due to infection were reported in 2.6% of patients in isatuximab regimen group compared to 5.4% in comparator regimen group. Fatal infections were reported in 3.3% of patients in isatuximab regimen group and 4.0% in comparator regimen group.

Respiratory AEs (lower respiratory AEs and respiratory infections)

In study EFC14335, the incidence of lower respiratory AEs was 36.8 vs 25.5% in the IPd vs Pd arm (Grade ≥3 7.9 vs 3.4%). AEs contributing the most to this imbalance were dyspnoea and productive cough. The incidence of all grade and Grade ≥3 respiratory infections, respectively, was 74.3 vs 53.0% and 36.2 vs 24.2% in the IPd vs Pd arm. AEs contributing the most to this imbalance were upper respiratory tract infection, pneumonia, bronchitis, and nasopharyngitis.

Neutropenia and neutropenic complications

In study EFC14335, the incidence of Grade 3-4 laboratory neutropenia was 84.8 vs 70.1% in the experimental and control arm. Grade 4 neutropenia was twice as frequent in the IPd arm. Grade ≥3 febrile neutropenia occurred in 11.8 vs 2.0% in IPd vs Pd and the incidence of neutropenic infections was 25.0 vs 19.5% (Grade ≥3 13.2 vs 9.4%). In the IPd arm in 1 patient the neutropenic complication led to a fatal outcome (influenza pneumonia with concurrent Grade 4 neutropenia). In the Pd arm 3 patients had a neutropenic complication with fatal outcome. The incidence of Grade 3-4 neutropenia was higher in IPd compared with isatuximab single agent (84.3 versus 15.1%).

Thrombocytopenia and haemorrhages

In the pivotal trial, 30.9% patients in the IPd arm and 24.5% in the Pd arm had Grade 3-4 thrombocytopaenia. The incidence of haemorrhage was similar in the IPd arm (8.6%) compared to Pd arm (11.4%).

Tumour lysis syndrome (TLS)

Out of 576 patients treated with isatuximab, TLS was reported in 3 patients (0.5%), including 1 patient in the IPd arm of the pivotal study.

Second primary malignancies (SPMs)

In the pivotal study, SPMs were reported in 1 patient in the Pd arm (skin SCC) and in 6 patients in the IPd arm (4 skin SCCs, 1 breast post-radiation angiosarcoma, 1 MDS ultimately transforming to AML). One skin SCC case was considered related to IPd.

In all patients treated with isatuximab SPMs were diagnosed in 17 (3.0%) patients with a median interval of 7.16 months (range 0.5 to 26.5). In addition to the cases of the pivotal trial, in the Pooled IPd group (Pool 1), another 2 patients were diagnosed with SPMs (1 with BCC and malignant neoplasm conjunctiva; 1 SCC). Among patients treated with isatuximab single agent, 8 patients developed SPMs (1 MDS; 2 solid non-skin malignancies (1 prostate cancer, 1 SCC oral cavity); 5 skin cancers (1 BCC and SCC, 2 BCC, 1 SCC, 1 malignant melanoma)). In the ILd combination study 1 patient developed prostate cancer.

Haemolytic disorders and blood cell (red blood cell and platelet) transfusion

It is known that anti-CD38 monoclonal antibodies can bind to CD38 on reagent RBCs, causing interference with blood bank serologic tests, which is also shown for isatuximab. In study EFC14335, the indirect antiglobulin test (IAT) was positive during IPd treatment in 67.7% of the 99 tested patients, 47 (47.5%) of which were negative at baseline and 20 (20.2%) of which were missing at baseline. Of patients with at least one positive post-baseline IAT test, 29.9% received a RBC transfusion. No complications of haemolysis were reported post-RBC transfusion in the IPd arm. No haemolytic disorders occurring <8 days after blood cell transfusions were reported in any patients.

Serious adverse event/deaths/other significant events

Serious TEAEs in Pool 1 are presented in the below table 38. The serious TEAEs reported in ≥3% of patients in group EFC14335 IPd 10 mg/kg were pneumonia, febrile neutropenia, disease progression, infusion related reaction, urinary tract infection, neutropenia, acute kidney injury, and pathological fracture (in 15.1% to 3.3% of patients, respectively). In group EFC14335 Pd, they were pneumonia, disease progression, and acute kidney injury (in 15.4% to 4.0% of patients).

The SOCs with serious TEAEs reported at a ≥5% higher incidence in the IPd arm than in the Pd arm were infections and infestations (39.5% vs 30.9%), blood and lymphatic system disorders (11.8% vs 6.7%), and injury, poisoning and procedural complications (7.2% vs 1.3%). The only serious TEAEs reported with >3% difference between treatment arms were febrile neutropenia (6.6% IPd vs. 2% Pd) and infusion related reaction (3.9% vs. 0.7%).

Table 34. Number (%) of patients with serious TEAEs with an incidence >= 2% (all grade) on all IPd by SOC and PT - Data Pool 1 - safety population.

	EFC14335				Pooled[a]			
	Pd (N=149)		IPd 10 mg/kg (N=152)		IPd(10 mg/kg) (N=183)		All IPd doses[b] (N=197)	
Primary System Organ Class Preferred Term [n(%)]	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any event	80 (53.7)	70 (47.0)	94 (61.8)	89 (58.6)	111 (60.7)	105 (57.4)	120 (60.9)	114 (57.9)
Infections and infestations	46 (30.9)	42 (28.2)	60 (39.5)	57 (37.5)	67 (36.6)	64 (35.0)	69 (35.0)	66 (33.5)
Pneumonia	23 (15.4)	22 (14.8)	23 (15.1)	22 (14.5)	30 (16.4)	29 (15.8)	31 (15.7)	30 (15.2)
Bronchitis	1 (0.7)	1 (0.7)	3 (2.0)	3 (2.0)	3 (1.6)	3 (1.6)	4 (2.0)	4 (2.0)
Urinary tract infection	2 (1.3)	2 (1.3)	6 (3.9)	6 (3.9)	7 (3.8)	7 (3.8)	7 (3.6)	7 (3.6)
Influenza	2 (1.3)	1 (0.7)	3 (2.0)	3 (2.0)	4 (2.2)	4 (2.2)	4 (2.0)	4 (2.0)
Lower respiratory tract infection	3 (2.0)	3 (2.0)	4 (2.6)	4 (2.6)	4 (2.2)	4 (2.2)	4 (2.0)	4 (2.0)

	EFC14335				Pooled[a]			
	Pd (N=149)		IPd 10 mg/kg (N=152)		IPd(10 mg/kg) (N=183)		All IPd doses[b] (N=197)	
Primary System Organ Class Preferred Term [n(%)]	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Diverticulitis	1 (0.7)	1 (0.7)	2 (1.3)	1 (0.7)	3 (1.6)	2 (1.1)	4 (2.0)	2 (1.0)
Sepsis	2 (1.3)	2 (1.3)	4 (2.6)	4 (2.6)	5 (2.7)	5 (2.7)	5 (2.5)	5 (2.5)
Blood and lymphatic system disorders	10 (6.7)	9 (6.0)	18 (11.8)	18 (11.8)	22 (12.0)	22 (12.0)	26 (13.2)	26 (13.2)
Neutropenia	2 (1.3)	2 (1.3)	5 (3.3)	5 (3.3)	8 (4.4)	8 (4.4)	11 (5.6)	11 (5.6)
Thrombocytopenia	1 (0.7)	1 (0.7)	3 (2.0)	3 (2.0)	4 (2.2)	4 (2.2)	4 (2.0)	4 (2.0)
Febrile neutropenia	3 (2.0)	3 (2.0)	10 (6.6)	10 (6.6)	10 (5.5)	10 (5.5)	10 (5.1)	10 (5.1)
Anaemia	1 (0.7)	0	3 (2.0)	2 (1.3)	3 (1.6)	2 (1.1)	4 (2.0)	3 (1.5)
Metabolism and nutrition disorders	6 (4.0)	5 (3.4)	8 (5.3)	7 (4.6)	10 (5.5)	9 (4.9)	11 (5.6)	10 (5.1)
Hyperglycaemia	0	0	3 (2.0)	3 (2.0)	4 (2.2)	4 (2.2)	4 (2.0)	4 (2.0)
Nervous system disorders	7 (4.7)	5 (3.4)	8 (5.3)	7 (4.6)	10 (5.5)	9 (4.9)	10 (5.1)	9 (4.6)
Syncope	1 (0.7)	1 (0.7)	4 (2.6)	4 (2.6)	5 (2.7)	5 (2.7)	5 (2.5)	5 (2.5)
Cardiac disorders	3 (2.0)	3 (2.0)	6 (3.9)	6 (3.9)	6 (3.3)	6 (3.3)	7 (3.6)	7 (3.6)
Atrial fibrillation	1 (0.7)	1 (0.7)	3 (2.0)	3 (2.0)	3 (1.6)	3 (1.6)	4 (2.0)	4 (2.0)
Respiratory, thoracic and mediastinal disorders	8 (5.4)	7 (4.7)	10 (6.6)	9 (5.9)	11 (6.0)	10 (5.5)	13 (6.6)	12 (6.1)
Dyspnoea	2 (1.3)	1 (0.7)	4 (2.6)	3 (2.0)	5 (2.7)	4 (2.2)	6 (3.0)	5 (2.5)
Pulmonary embolism	2 (1.3)	2 (1.3)	3 (2.0)	3 (2.0)	3 (1.6)	3 (1.6)	4 (2.0)	4 (2.0)
Musculoskeletal and connective tissue disorders	6 (4.0)	4 (2.7)	13 (8.6)	9 (5.9)	16 (8.7)	12 (6.6)	16 (8.1)	12 (6.1)
Arthralgia	2 (1.3)	1 (0.7)	4 (2.6)	4 (2.6)	4 (2.2)	4 (2.2)	4 (2.0)	4 (2.0)
Pathological fracture	3 (2.0)	2 (1.3)	5 (3.3)	2 (1.3)	6 (3.3)	3 (1.6)	6 (3.0)	3 (1.5)
Renal and urinary disorders	10 (6.7)	8 (5.4)	9 (5.9)	6 (3.9)	10 (5.5)	7 (3.8)	11 (5.6)	8 (4.1)
Acute kidney injury	6 (4.0)	4 (2.7)	5 (3.3)	3 (2.0)	6 (3.3)	4 (2.2)	7 (3.6)	5 (2.5)
General disorders and administration site conditions	13 (8.7)	12 (8.1)	16 (10.5)	14 (9.2)	20 (10.9)	18 (9.8)	21 (10.7)	19 (9.6)
Pyrexia	2 (1.3)	1 (0.7)	3 (2.0)	1 (0.7)	4 (2.2)	2 (1.1)	4 (2.0)	2 (1.0)
Disease progression	7 (4.7)	7 (4.7)	7 (4.6)	7 (4.6)	11 (6.0)	11 (6.0)	12 (6.1)	12 (6.1)
Injury, poisoning and procedural complications	2 (1.3)	0	11 (7.2)	8 (5.3)	14 (7.7)	11 (6.0)	16 (8.1)	13 (6.6)
Infusion related reaction	1 (0.7)	0	6 (3.9)	4 (2.6)	7 (3.8)	5 (2.7)	7 (3.6)	5 (2.5)
Traumatic fracture	0	0	3 (2.0)	2 (1.3)	4 (2.2)	3 (1.6)	6 (3.0)	5 (2.5)

Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone

Data Pool 1: EFC14335 and TCD14079 Part A

5, 10, and 20 mg/kg QW/Q2W isatuximab

MedDRA 21.0

Deaths

Comparing the IPd and Pd groups in study EFC14335, the incidence of death during the treatment period was similar between the two groups (11 [7.2%] and 13 [8.7%] patients, respectively). The causes of death consisted of disease progression in 6 (3.9%) and 5 (3.4%) of the patients, AEs in 3 (2.0%) and 6 (4.0%), and "Other" causes in 2 (1.3%) of the patients in both groups.

During the post-treatment period, the incidence of death was lower in the IPd arm (34 [22.4%]) compared to the Pd arm (44 [29.5%]), with the causes of death following the same pattern as during the treatment period, except that there were no AEs leading to death during the post treatment period in either group, and the incidence of disease progression was lower in the IPd group than the Pd group (24 [15.8%] versus 33 [22.1%]) patients.

Fatal TEAEs in the context of disease progression

The number of patients with fatal TEAEs by SOC and PT in the context of disease progression is presented in Table 39. Comparing the IPd and Pd groups in study EFC14335, the incidence of fatal TEAEs in the context of disease progression was similar (8 [5.3%] and 7 [4.7%] patients, respectively), and the incidence of each TEAE was also similar between the groups. Most TEAEs occurred in 1 patient, with the exception of disease progression, which occurred in 6 (3.9%) patients in the IPd group and 4 (2.7%) patients in the Pd group.

Table 35. Number (%) of patients with fatal TEAEs in the context of disease progression by SOC and PT - Data Pool 1 - safety population.

	EFC14335		Pooled[a]	
Primary System Organ Class Preferred Term [n(%)]	**Pd (N=149)**	**IPd 10 mg/kg (N=152)**	**IPd(10 mg/kg) (N=183)**	**All IPd doses[b](N=197)**
Any event	7 (4.7)	8 (5.3)	11 (6.0)	12 (6.1)
Infections and infestations	0	1 (0.7)	1 (0.5)	1 (0.5)
Lymphangitis	0	1 (0.7)	1 (0.5)	1 (0.5)
Pneumonia bacterial	0	1 (0.7)	1 (0.5)	1 (0.5)
Urinary tract infection	0	1 (0.7)	1 (0.5)	1 (0.5)
Blood and lymphatic system disorders	0	1 (0.7)	1 (0.5)	1 (0.5)
Neutropenia	0	1 (0.7)	1 (0.5)	1 (0.5)
Nervous system disorders	1 (0.7)	0	0	0
Cauda equina syndrome	1 (0.7)	0	0	0
Renal and urinary disorders	2 (1.3)	1 (0.7)	1 (0.5)	1 (0.5)
Acute kidney injury	1 (0.7)	0	0	0
Renal failure	1 (0.7)	1 (0.7)	1 (0.5)	1 (0.5)
General disorders and administration site conditions	4 (2.7)	6 (3.9)	9 (4.9)	10 (5.1)
Disease progression	4 (2.7)	6 (3.9)	9 (4.9)	10 (5.1)
Investigations	0	1 (0.7)	1 (0.5)	1 (0.5)
Hepatic enzyme increased	0	1 (0.7)	1 (0.5)	1 (0.5)

Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone

Data Pool 1: EFC14335 and TCD14079 Part A

5, 10, and 20 mg/kg QW/Q2W isatuximab

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

MedDRA 21.0

Note: fatal TEAEs are defined as TEAEs with grade 5 during treatment period or as any grade TEAEs with fatal outcome during post-treatment period.

Primary System Organ Class Preferred Term [n(%)]	EFC14335		Pooled[a]	
	Pd (N=149)	IPd 10 mg/kg (N=152)	IPd(10 mg/kg) (N=183)	All IPd doses[b](N=197)

Fatal TEAEs or Grade 5 post-treatment AEs not in the context of disease progression

The number of patients with fatal TEAEs or Grade 5 post treatment AEs not in the context of disease progression is presented in Table 40. Comparing the IPd and Pd groups in study EFC14335, the incidence of fatal TEAEs or Grade 5 post treatment AEs not in the context of disease progression was similar (8 [5.3%] and 10 [6.7%] patients, respectively). Across all TEAEs, the incidence of each was similar for both groups, with most TEAEs occurring in only 1 patient, with the exception of septic shock, which occurred in 2 (1.3%) patients in the Pd group and no patients in the IPd group. Overall the incidence of deaths due to infections in both arms (4 [2.6%] patients in IPd arm and 6 [4%] in Pd arm) was higher compared to other SOCs.

In study EFC14335, fatal TEAEs were considered treatment-related in 2 (1.3%) patients in the Pd group (pneumonia and urinary tract infection), and in 1 (0.7%) patient in the IPd group (sepsis).

Table 36. Number (%) of patients with fatal TEAEs or Grade 5 post-treatment AEs not in the context of disease progression by SOC and PT - Data Pool 1 - safety population.

Primary System Organ Class Preferred Term [n(%)]	EFC14335		Pooled[a]	
	Pd (N=149)	IPd 10 mg/kg (N=152)	IPd(10 mg/kg) (N=183)	All IPd doses[b] (N=197)
Any event	10 (6.7)	8 (5.3)	9 (4.9)	9 (4.6)
Infections and infestations	6 (4.0)	4 (2.6)	4 (2.2)	4 (2.0)
Lung infection	0	1 (0.7)	1 (0.5)	1 (0.5)
Pneumonia	1 (0.7)	1 (0.7)	1 (0.5)	1 (0.5)
Pneumonia influenzal	0	1 (0.7)	1 (0.5)	1 (0.5)
Sepsis	1 (0.7)	1 (0.7)	1 (0.5)	1 (0.5)
Septic shock	2 (1.3)	0	0	0
Upper respiratory tract infection	1 (0.7)	0	0	0
Urinary tract infection	1 (0.7)	0	0	0
Nervous system disorders	2 (1.3)	0	0	0
Cerebral haemorrhage	1 (0.7)	0	0	0
Haemorrhage intracranial	1 (0.7)	0	0	0
Cardiac disorders	0	1 (0.7)	1 (0.5)	1 (0.5)
Atrial fibrillation	0	1 (0.7)	1 (0.5)	1 (0.5)
Gastrointestinal disorders	0	0	1 (0.5)	1 (0.5)
Intestinal perforation	0	0	1 (0.5)	1 (0.5)
Hepatobiliary disorders	0	1 (0.7)	1 (0.5)	1 (0.5)
Hepatic failure	0	1 (0.7)	1 (0.5)	1 (0.5)
General disorders and administration site conditions	2 (1.3)	3 (2.0)	3 (1.6)	3 (1.5)
Death	1 (0.7)	2 (1.3)	2 (1.1)	2 (1.0)
Multiple organ dysfunction syndrome	0	1 (0.7)	1 (0.5)	1 (0.5)
Sudden death	1 (0.7)	0	0	0

Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone

Primary System Organ Class Preferred Term [n(%)]	EFC14335 Pd (N=149)	EFC14335 IPd 10 mg/kg (N=152)	Pooled[a] IPd(10 mg/kg) (N=183)	Pooled[a] All IPd doses[b] (N=197)

Data Pool 1: EFC14335 and TCD14079 Part A
5, 10, and 20 mg/kg QW/Q2W isatuximab

Of note, there was 1 patient with any grade 5 AE (TEAE and post-treatment period) and 1 patient with any fatal AE (grade 5 TEAE with fatal outcome during treatment period). One patient died due to transformation to AML in the post-treatment period. The AE started before the data cut-off, but the patient died after cut-off. The patient with treatment-related sepsis died within the treatment period (<30 days after last dose of study treatments) and is therefore not calculated as post-treatment fatal AE.

Laboratory findings

Haematology and chemistry

Comparing groups IPd and Pd in study EFC14335, Grade 3-4 neutropenia, lymphopenia, and WBC count decreased were reported more frequently in the IPd group (and the difference was ≥5%), except for Grade 4 lymphopenia (8.2% versus 12.5%, for Pd vs IPd respectively) and Grade 3 neutropenia (38.8% versus 24.3% Pd vs IPd). The incidence of Grade 3-4 anaemia and platelet count decreased was similar in the 2 groups, and the difference was <5%, except for Grade 3 platelet count decreased (14.5% versus 9.5% IPd vs Pd). Clinical chemistry parameters were similar for the IPd vs Pd group.

Liver and renal function

No substantial differences in hepatic parameters were observed between both treatment arms of the pivotal study, except for a higher incidence of Grade 1 alkaline phosphatase in group IPd vs group Pd (34.9% vs 16.3%). Among all patients treated with isatuximab (Pool 4), 6 reports were observed with values within the Hy's law range; however, among these patients none of the 6 reports met the definition of Hy's Law cases, because of alternative aetiologies i.e. progressive disease, cardiac failure, subcutaneous infection, cholecystitis, and lenalidomide use. Regarding "Grade 3 creatinine increased", the incidence in Pd group was 8.8% vs ≤3.6% in the 3 IPd groups. No Grade 4 creatinine increased was observed in the 4 groups. The incidence of patients worsening to end stage renal function impairment during treatment in the IPd group was 2.6% (4 patients) versus 7.4% (11 patients) in the Pd group in study EFC14335. This difference was mostly seen in patients with mild renal function impairment at baseline (1.7% vs 7.5%) and in patients with moderate impairment at baseline (3.8% vs 13.0%).

Vital signs

In study EFC14335, potentially clinically significant abnormalities (pre-defined threshold and changes from baseline) were more common in IPd for heart rate decrease (6.6% IPd vs 1.4% Pd) and increase (6.6 vs 1.4%), systolic blood pressure decrease (22.4% vs 6.1%) and increase (18.4% vs 14.3%), diastolic blood pressure decrease (10.5% vs 2.7%), and body weight decrease (35.8% vs 19.4%).

Electrocardiogram

Comparing groups IPd and Pd in study EFC14335, an ECG that was normal at baseline and abnormal during treatment was reported in 22.0% (20 of 91 patients) and 25.5% (26 of 102) of patients, respectively. A total of 48 patients from the IPd group had at least 1 abnormal ECG (regardless of

baseline status). In 21 of the 48 EFC14335 IPd patients, ECG abnormalities were deemed possibly clinically significant and were also associated with AEs that might be related to ECG abnormalities. None of the cases with ECG abnormalities possibly related to AEs were assessed as having a direct causal relationship, as all were attributable to pre-existing and/or concomitant conditions. One case (acute myocardial ischaemia) was assessed as likely indirectly related. This patient, with comorbidity of metabolic syndrome and ischaemic heart disease, experienced an infusion reaction during the first infusion and the ECG showed evidence of acute myocardial ischaemia, consistent with an acute coronary event.

An analysis of ECG monitoring data collected in the monotherapy study TED10893 Phase 1 does not suggest any clinically meaningful QTcF prolongation induced by isatuximab at any dose level. No reports of electrocardiogram QT prolongation reported interval abnormal, electrocardiogram QT prolonged, long QT syndrome, torsade de pointes, or ventricular tachycardia occurred as AEs in Data Pool 4.

Safety in special populations

Table 37. Treatment-emergent adverse event by age group (Pool 4 - Safety population).

	Isatuximab[a] All (N=576)			
n(%)	**<65 (N=270)**	**65-74 (N=224)**	**75-84 (N=80)**	**>=85 (N=2)**
Patients with any TEAE	261 (96.7)	214 (95.5)	76 (95.0)	2 (100)
Patients with any serious TEAE	124 (45.9)	102 (45.5)	38 (47.5)	0
Patients with any serious TEAE with fatal outcome	22 (8.1)	13 (5.8)	10 (12.5)	0
Patients with any serious TEAE with hospitalization/prolong existing hospitalization outcome	113 (41.9)	96 (42.9)	34 (42.5)	0
Patients with any serious TEAE with life-threatening outcome	23 (8.5)	17 (7.6)	13 (16.3)	0
Patients with any serious TEAE with disability/incapacity outcome	1 (0.4)	0	0	0
Patients with any serious TEAE with other medically important outcome	15 (5.6)	13 (5.8)	6 (7.5)	0
Patients with any TEAE leading to treatment discontinuation	16 (5.9)	13 (5.8)	12 (15.0)	0
Patients with any psychiatric disorders	62 (23.0)	58 (25.9)	15 (18.8)	1 (50.0)
Patients with any nervous system disorders	110 (40.7)	99 (44.2)	28 (35.0)	1 (50.0)
Patients with any accidents and injuries	34 (12.6)	29 (12.9)	14 (17.5)	0
Patients with any cardiac disorders	20 (7.4)	29 (12.9)	10 (12.5)	0
Patients with any vascular disorders	39 (14.4)	32 (14.3)	12 (15.0)	0
Patients with any cerebrovascular disorders	2 (0.7)	4 (1.8)	1 (1.3)	0
Patients with any infections and infestations	155 (57.4)	145 (64.7)	49 (61.3)	1 (50.0)
Patients with any anticholinergic syndrome	0	0	0	0
Patients with any quality of life decreased	0	0	0	0
Patients with any sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	56 (20.7)	51 (22.8)	18 (22.5)	1 (50.0)

Data Pool 4: EFC14335 (IPd arm only), TCD14079 Part A, TED10893, TED14154 Part A, TCD11863, and TCD13983 ICBd

IPd: isatuximab in combination with pomalidomide and dexamethasone

[a]: Isatuximab has been pooled within each data pool according to combination therapy and regardless the dose level/schedule of isatuximab. "Other combo" includes ICBd and ILd.

Intrinsic factors

Age groups <65, 65 to 74, and ≥75 years

In study EFC14335, the number of elderly patients was greater in the IPd arm compared the Pd arm, respectively, with 43.4% versus 35.6% of the patients aged 65 to 74 years, and 21.1% versus 16.8% aged 75-84 years. In study EFC14335, only 3 patients ≥85 years of age were enrolled in group Pd versus 0 in group IPd.

Table 38. The overall incidence of TEAEs in the study EFC14335 by age group.

	IPd			**Pd**	
Incidence	<65 years	65 to 74 years	≥75 years	<65 years	≥75 years
All grade TEAEs	98.1%	100%	100%	x	x
Grade ≥3 TEAEs	85.2%	x	93.8%	64.7%	75.0%
TEAEs with fatal outcome	11.1%	x	6.3%	5.9%	14.3%

Furthermore, a trend towards more definitive treatment discontinuations, and serious TEAEs was observed in the older age group in the IPd arm, with again a similar trend in the Pd arm.

Gender

In the IPd arm of study EFC14335, the incidence of Grade ≥3 TEAEs was similar among males and females, 85.2% and 89.1%, respectively. The incidence of grade 5 TEAEs with fatal outcome during the treatment period (including deaths in the context of progressive disease), serious TEAEs, and TEAEs leading treatment discontinuation was higher in males than in females, 9.1% versus 4.7%, 67.0% versus 54.7%, and 9.1% versus 4.7%. In the Pd arm, similar trends toward higher incidence in male versus female was observed for serious TEAEs (55.9% versus 51.9%) and fatal TEAES (10.3% versus 7.4%), but not for TEAEs leading to treatment discontinuation (11.8% versus 13.6%).

When TEAEs reported at a ≥10% incidence overall were assessed based on sex (≥10% difference within a treatment arm), in both treatment arms, neutropenia and thrombocytopenia were more common in females than males and constipation was more common in males. In the IPd arm, females had a higher rate of infusion reactions than males and males had higher rates of diarrhea and back pain. In the Pd arm, females had higher rates of arthralgia than males.

Neutropenia (40.9% versus 53.1%) was the only Grade ≥3 TEAE with a ≥10% difference of incidence between males versus females, with a similar trend of 26.5% and 37.0% in the Pd arm.

Race

In the IPd arm, non-white and white patients were similar in the incidence of Grade ≥3 TEAEs (91.7% versus 87.1%), fatal TEAEs (4.2% versus 6.0%), and TEAEs leading to treatment discontinuation (8.3% versus 7.8%). In groups IPd and Pd, the incidence of serious TEAEs was lower in non-white patients compared to white patients (45.8% versus 64.7% in IPd and 36.8% versus 56.6% in Pd).

ECOG performance score

In study EFC14335, the incidence of serious TEAEs in patients who had ECOG scores of 2 (10.5% of patients) or 3 (0%) at baseline was 100% in the IPd arm vs 57.4% in ECOG 0 or 1. In the Pd group incidences were similar for ECOG 2/3 vs 0/1. For Grade ≥3 TEAEs in both IPd and Pd groups incidences were higher in ECOG 2/3 vs 0/1. ECOG scores of 2 or 3 at baseline were associated with a numerically

lower incidence of TEAEs leading to definitive treatment discontinuation (0 of 16 patients in IPd versus 4 of 14 [28.6%] in Pd) and numerically higher incidence of fatal outcomes during the treatment period (2 of 16 patients [12.5%] in IPd versus 1 of 14 patients [7.1%] in Pd) vs ECOG 0 or 1.

Renal status (≥60, <60 mL/min/1.73m2)

In the IPd arm of study EFC14335, the incidence of Grade ≥3 TEAEs was similar across renal status: 86% of patients with ≥60 mL/min/1.73 m^2 and 90.7% with <60 mL/min/1.73 m^2. The incidence of Grade 5 TEAEs, serious TEAEs, and TEAEs leading to definitive treatment discontinuation in patients with <60 mL/min/1.73 m2 was higher than in patients with >60 mL/min/1.73 m2, 9.3% versus 3.5%, 77.8% versus 51.2%, and 11.1% versus 5.8%. In group Pd, similar trends in renal status (≥60 [94 patients], <60 [47 patients]) were observed for Grade 5 TEAEs, serious TEAEs, TEAEs leading to definitive treatment discontinuations.

When TEAEs reported at a ≥10% incidence overall were assessed among patients with decreased renal function at baseline, there was a ≥10% difference in the incidence of pneumonia and pyrexia in both treatment arms compared to patients in the respective treatment arms with normal renal function. In the IPd arm, back pain was reported at a ≥10% higher incidence in patients with decreased renal function at baseline when compared with patients in the IPd arm with normal renal function at baseline. The only Grade ≥3 TEAE with an incidence ≥10% difference in IPd patients with <60 mL/min/1.73 m^2 versus ≥60 mL/min/1.73 m^2 was pneumonia (25.9% versus 12.8%), with a similar trend in the Pd arm.

Hepatic status

In the IPd arm of study EFC14335, the incidence of Grade ≥3 TEAEs was greater in patients with mild hepatic impairment (95.5%) versus normal hepatic status (85.4%). In comparison to patients with normal hepatic status, IPd patients in study EFC14335 with mild hepatic impairment had a greater incidence of Grade 5 TEAEs (13.6% versus 6.2%) but the incidence of TEAEs leading treatment discontinuation and of serious TEAEs was similar (9.1% versus 6.9%, and 63.6% versus 61.5%, respectively. In the Pd arm, the incidence of the TEAEs leading to treatment discontinuation was greater in patients with mild hepatic impairment (7 [31.8%]) compared to normal status (12 [9.5%]). There was only 1 patient with moderate hepatic impairment.

In study EFC14335, no SOCs with an incidence of Grade ≥3 TEAEs ≥10% greater in IPd patients with mild hepatic impairment versus patients with normal status was observed. Grade ≥3 TEAEs with a ≥10% difference in incidence in patients with mild impairment versus normal status consisted of thrombocytopenia (27.3% versus 9.2%), with a similar trend for Pd (18.2% and 11.1%).

ISS stage

Among the 197 patients treated in the IPd group, 85, 70, and 37 were Stage I, II, and III at study entry, respectively. The median number of cycles started by patient for Stages I, II, and III in the IPd group were 11, 9, and 8, respectively; and the median duration of exposure for each Stage group was 45.14, 37.00, and 36.14 weeks, respectively. In the IPd group, any Grade ≥3 TEAEs were reported in 81.2%, 90.0%, and 91.9% of patients with Stage I, II, and III, respectively; any serious TEAEs were reported in 47.1%, 64.3%, and 86.5% of patients, respectively; any TEAEs leading to definitive treatment discontinuation were reported in 5.9%, 4.3%, and 10.8% of patients, respectively; any Grade ≥3 treatment-related TEAEs were reported in 68.2%, 77.1% and 75.7% of patients, respectively; and any serious treatment-related TEAEs were reported in 25.9%, 40.0%, and 43.2% of patients, respectively.

Extrinsic factors

Isatuximab formulation: P1F1 and P2F2

Among all 576 isatuximab-treated patients in Data Pool 4, patients treated with P1F1 (283) and P2F2 (293), respectively, were similar in terms of the incidence of TEAEs leading the treatment discontinuation (7.4% versus 6.8%), serious TEAEs (45.6% versus 46.1%), fatal TEAEs (6.4% versus 6.5%) and laboratory thrombocytopenia Grade 3-4 (21.2% versus 23.9%). The incidence of IRs was 50.5% in P1F1 and 42.0% in P2F2. The incidence of Grade 3-4 laboratory neutropenia was 30.4% versus 55.3%.

Table 39. Overview treatment-emergent adverse events by isatuximab formulation - Safety population.

	Isatuximab[a]			
AE groups **Isatuximab formulation, n(%)**	**IPd** **(N=197)**	**Isa(+/-Dex)** **(N=305)**	**Other combo** **(N=74)**	**All** **(N=576)**
Patients with any TEAE				
P1F1	23/23 (100)	184/186 (98.9)	74/74 (100)	281/283 (99.3)
P2F2	173/174 (99.4)	99/119 (83.2)	0/0	272/293 (92.8)
Patients with any treatment-related TEAE				
P1F1	23/23 (100)	132/186 (71.0)	73/74 (98.6)	228/283 (80.6)
P2F2	160/174 (92.0)	73/119 (61.3)	0/0	233/293 (79.5)
Patients with any grade ≥3 TEAE				
P1F1	19/23 (82.6)	113/186 (60.8)	63/74 (85.1)	195/283 (68.9)
P2F2	152/174 (87.4)	38/119 (31.9)	0/0	190/293 (64.8)
Patients with any treatment-related grade ≥3 TEAE				
P1F1	16/23 (69.6)	27/186 (14.5)	47/74 (63.5)	90/283 (31.8)
P2F2	127/174 (73.0)	13/119 (10.9)	0/0	140/293 (47.8)
Patients with any grade 5 TEAE with a fatal outcome during treatment period				
P1F1	3/23 (13.0)	9/186 (4.8)	6/74 (8.1)	18/283 (6.4)
P2F2	13/174 (7.5)	6/119 (5.0)	0/0	19/293 (6.5)
Patients with any treatment-related grade 5 TEAE with a fatal outcome during treatment period				
P1F1	0/23	0/186	0/74	0/283
P2F2	1/174 (0.6)	0/119	0/0	1/293 (0.3)
Patients with any serious TEAE				
P1F1	14/23 (60.9)	79/186 (42.5)	36/74 (48.6)	129/283 (45.6)
P2F2	106/174 (60.9)	29/119 (24.4)	0/0	135/293 (46.1)
Patients with any treatment-related serious TEAE				
P1F1	7/23 (30.4)	11/186 (5.9)	16/74 (21.6)	34/283 (12.0)
P2F2	60/174 (34.5)	8/119 (6.7)	0/0	68/293 (23.2)
Patients with any TEAE leading to definitive treatment discontinuation				
P1F1	1/23 (4.3)	9/186 (4.8)	11/74 (14.9)	21/283 (7.4)
P2F2	12/174 (6.9)	8/119 (6.7)	0/0	20/293 (6.8)

Table 40. Overview of other significant adverse events by isatuximab formulation - Safety population.

AE groups Isatuximab formulation, n(%)	Isatuximab[a] IPd (N=197)	 Isa(+/-Dex) (N=305)	 Other combo (N=74)	 All (N=576)
Patients with IRs during treatment period				
P1F1	11/23 (47.8)	92/186 (49.5)	40/74 (54.1)	143/283 (50.5)
P2F2	66/174 (37.9)	57/119 (47.9)	0/0	123/293 (42.0)
Patients with any IR of grade ≥3 (excluding symptoms) during treatment period				
P1F1	0/23	4/186 (2.2)	6/74 (8.1)	10/283 (3.5)
P2F2	5/174 (2.9)	5/119 (4.2)	0/0	10/293 (3.4)
Patients with lower respiratory AEs during treatment and post treatment period				
P1F1	14/23 (60.9)	72/186 (38.7)	35/74 (47.3)	121/283 (42.8)
P2F2	69/174 (39.7)	17/119 (14.3)	0/0	86/293 (29.4)
Patients with respiratory infections during treatment and post treatment period				
P1F1	15/23 (65.2)	83/186 (44.6)	44/74 (59.5)	142/283 (50.2)
P2F2	127/174 (73.0)	33/119 (27.7)	0/0	160/293 (54.6)
Patients with laboratory neutropenia of grade 3 or 4 during treatment period				
P1F1	21/23 (91.3)	29/186 (15.6)	36/74 (48.6)	86/283 (30.4)
P2F2	145/174 (83.3)	17/119 (14.3)	0/0	162/293 (55.3)
Patients with laboratory thrombocytopenia of grade 3 or 4 during treatment period				
P1F1	9/23 (39.1)	29/186 (15.6)	22/74 (29.7)	60/283 (21.2)
P2F2	53/174 (30.5)	17/119 (14.3)	0/0	70/293 (23.9)

Other subgroups

Current or former smokers had more infectious AEs than Never smokers. In addition, the Applicant provided data per geographic region, but due to limited number of patients in some of the regions, it is difficult to draw conclusions. When looking at number of prior lines of therapy (1-3 vs >3) no concerning differences were observed.

Immunological events

Among 564 patients treated with isatuximab evaluable for ADA (Data Pool 4), 1 patient was ADA positive at baseline and 13 (2.3%) developed ADAs during treatment with isatuximab. Among these 13 patients, the median time to onset was 1 month and the ADA response was transient in 10 patients, persistent in 2, and remained indeterminate in 1.

There was no confirmed positive ADA response in study EFC14335 (IPd arm), and hence, no neutralizing ADA assessment was done.

Although the number of patients with ADA positive status is small, the analysis of IRs, TEAEs, SAEs, TEAEs leading to definitive discontinuation of study treatment, neutropenia, neutropenic complications, thrombocytopenia, and haemorrhagic complications revealed no evidence of an impact of ADA to isatuximab on clinical safety.

Safety related to drug-drug interactions and other interactions

No safety data related to drug-drug interactions were performed. Please refer to the Pharmacokinetics section for a more detailed assessment.

Discontinuation due to adverse events

In study EFC14335, the incidence of TEAEs leading to definitive treatment discontinuation in groups IPd and Pd was 7.2% and 12.8%, respectively. Of these TEAEs, those reported in ≥2 patients, included death (2 patients) in group IPd, and thrombocytopenia (7), pneumonia (3), neutropenia (2), and septic shock (2) in group Pd.

In study EFC14335, the all grade TEAEs leading to any dose modification (dose delay, dose interruption, or dose omission) of isatuximab and reported in ≥10% of patients were neutropenia (33.6%), infusion related reaction (28.3%), pneumonia (13.2%), and upper respiratory tract infection (10.5%). The only TEAE leading to a dose interruption of isatuximab reported in >2 patients was infusion related reaction in 28.3% of patients.

Post marketing experience

There is no post-marketing experience with isatuximab.

2.6.1. Discussion on clinical safety

In total 576 patients were treated with isatuximab. The main safety data for this Application are provided by the pivotal Phase 3 EFC14335 study and the Phase 1b TCD14079 Part A study in RRMM patients who have received at least two lines of therapy. In the experimental arm of EFC14335, isatuximab (P2F2) was administered to 152 patients at the dose of 10 mg/kg QW/Q2W combined with Pd. In the control arm 149 patients were administered Pd.

Isatuximab exposure of at least 12 months occurred in 99 patients and 23 had at least 18 months of exposure. For the requested indication, treatment duration is until progression or unacceptable toxicity and therefore long-term exposure might occur, but the safety data for long-term exposure, especially >12 months, are limited. Long-term studies are therefore not very extensive and do not represent the intended long-term use of the product. Since the median number of cycles was 10 (~9.1 months), this is acceptable for approval. In order to gain more information about long-term exposure post-marketing, the Applicant will evaluate the safety data at time of final OS analysis for study ECF14335 and provide an addendum to the CSR (see clinical safety recommendation).

Of all patients treated with isatuximab, 293 patients (50.9%) were treated with the P2F2 commercial formulation (174 in the IPd group).

The incidence of AEs was higher in the IPd vs Pd group for treatment-related AEs (90.8% vs 79.9%), Grade ≥3 AEs (86.8% vs 70.5%; treatment-related Grade ≥3 AEs 71.7% vs 47.7%), and serious AEs (61.8% vs 53.7%) including treatment-related serious AEs (35.5% vs 16.1%). The incidence of AEs with a fatal outcome during the treatment period was 7.2% vs 8.7%, respectively, and AEs leading to definitive treatment discontinuation was 7.2% vs 12.8%. As would be expected, the addition of isatuximab to Pd is in general more toxic than the doublet Pd combination.

Of the most frequently reported AEs, neutropenia, febrile neutropenia, infusion related reaction (IRR), upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, nausea, and vomiting were observed more frequently in the IPd vs Pd arm. For the most common Grade ≥3 AEs, neutropenia and febrile neutropenia occurred more often in the experimental arm.

For treatment-related AEs a similar pattern was observed. The most common SAEs in group IPd included pneumonia, febrile neutropenia; furthermore disease progression, IRR, urinary tract infection, neutropenia, acute kidney injury, and pathological fracture were also observed. Less frequently reported AEs that occurred more often in the IPd group were nervous system disorders and cardiac

disorders. Because the AEs were reported as non-serious, not treatment-related, and none led to permanent treatment discontinuation, no serious safety concerns about nervous system disorders arise. Concerning cardiac disorders, AEs more frequently reported in the IPd group were cardiac arrhythmias (11.2 vs 2.0%), mostly due to atrial fibrillation (4.6 vs 2.0%). Renal and urinary disorders (including acute kidney injury), skeletal-related AEs and thromboembolic AEs were reported at a similar incidence in the 2 treatment arms. Based on the provided data regarding the duration of the most prevalent AEs, Grade 3-4 AEs, and SAEs and their resolution, the toxicity profile of isatuximab is manageable and reversible.

Isatuximab monotherapy seems to be better tolerated than the combination with Pd. The comparison with other combination schedules is difficult, because of in-between study comparison and the limited sample size in especially the ICBd group, but the results do not raise concerns. It was noted that in combination of all pools (Pool 4), cardiac arrhythmias were reported in 7.8% (1.7% Grade ≥3). Atrial fibrillation was reported in 2.6% (1.2% Grade ≥3). In 2 patients atrial fibrillation had a fatal outcome. There is no conclusive evidence that there is a potential mechanism causing arrhythmias during treatment with isatuximab. No isatuximab specific binding was detected in the heart tissue in a cross reactivity study. In ECG monitoring studies, isatuximab did not lead to clinically meaningful QTc prolongation and there was no apparent exposure-response relationship between PK exposure parameters and the incidence of cardiac disorders and cardiac arrhythmias. Atrial fibrillation is included as ADR in section 4.8 of the SmPC.

In the pivotal study, the incidence of death was similar between the two treatment arms (7.2% IPd vs. 8.7% Pd). There were no AEs leading to death in the post-treatment period. One case of sepsis was considered as treatment-related in the IPd arm. For this case no further information was available on the location of the infection nor the results from the microbiology tests. In 8 patients of the IPd arm the fatal AE was categorised in the context of disease progression. In 8 patients the fatal AEs were not in the context of disease progression in the IPd arm and the most common causes were infections, mainly of the respiratory tract. A role for pneumonia could not be demonstrated in these fatal infections. Other causes of fatal AEs not in the context of disease progression, were "Death" in 2 patients, atrial fibrillation, and hepatic failure.

In the pivotal study in 12.8% vs 7.2% of patients an AE led to treatment discontinuation in Pd vs IPd group. Premature discontinuation of the isatuximab component of IPd combination was caused by grade ≥3 IRRs. AEs that most frequently led to a dose modification of isatuximab were neutropenia, pneumonia, upper respiratory tract infection, and IRR. The main reason for definitive treatment discontinuation was progressive disease (PD), occurring in a higher proportion of patients in the Pd arm (43.4% IPd vs 59.1% Pd). Discontinuation due to AEs was also reported more frequently in the Pd arm (7.2% IPd vs 12.8% Pd). It is reassuring that among all 576 patients treated with isatuximab, the only AE leading to discontinuation of study treatment reported in >2 patients was IRR (2.6%).

In the IPd arm of EFC14335, IRRs occurred in 38.2%. It is reassuring that grade 3 or 4 IRRs were both reported in only 1.3% of patients, 89.7% had one single episode and discontinuation was reported in 2.6% (SmPC section 4.4 and 4.8). There was no evidence of dose-dependency or a correlation between IRRs and cytokine release. The Applicant also performed secondary analyses to identify potential IRRs that were not reported as IRRs by the investigators. These additional analyses showed similar numbers compared to the investigator reporting. To decrease the risk and severity of infusion reactions, patients should be pre-medicated prior to Sarclisa infusion with acetaminophen, H2 antagonists or proton pump inhibitors, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment. Vital signs should be frequently monitored during the entire Sarclisa infusion. When required, interrupt Sarclisa infusion and provide appropriate medical and supportive measures. In case symptoms do not improve after interruption of Sarclisa infusion, recur after initial improvement with appropriate medicinal products, require hospitalization or are life-

threatening, permanently discontinue Sarclisa and institute appropriate management (SmPC section 4.4).

The incidence of Grade 3-4 laboratory neutropenia was 84.8% vs 70.1% in the experimental and control arm. Grade 4 neutropenia was twice as frequent in the IPd arm. Grade ≥3 febrile neutropenia occurred in 11.8% vs 2.0% in IPd vs Pd and the incidence of neutropenic infections was 25.0% vs 19.5% (Grade ≥3 13.2 vs 9.4%). In the IPd arm in 1 patient the neutropenic complication led to a fatal outcome (influenza pneumonia with concurrent Grade 4 neutropaenia). In the Pd arm 3 patients had a neutropenic complication with fatal outcome. The incidence of Grade 3-4 neutropenia was higher in IPd compared with isatuximab single agent (84.3% versus 15.1%). In the protocol of the pivotal study 14335 (as well as in the SmPC section 4.4), there were no specific recommendations for the administration of G-CSF which could have been administered at the investigator's discretion. Although comparison of patients who received and those who did not receive concomitant G-CSF is difficult to assess, as the EFC14335 study was not designed for such a comparison, G-CSF concomitant to IPd decreases the number of neutropenic episodes and the severity of episodes. This is reflected in the SmPC section 4.4.

In the pivotal trial, 30.9% patients in the IPd arm and 24.5% in the Pd arm had Grade 3-4 thrombocytopaenia. The incidence of haemorrhage was similar in the IPd arm (8.6%) compared to Pd arm (11.4%). In Combination of all pools, 23% had Grade 3-4 thrombocytopaenia. The incidence of Grade 3-4 thrombocytopaenia was higher in IPd compared with isatuximab single agent (31.6% versus 15.4%). Overall, haemorrhage occurred in 12.7% all grades and 1.5% of Grade ≥3, including 2 Grade 5 events (intestinal perforation and procedural haemorrhage).

In the study EFC14335, the incidence of lower respiratory AEs was 36.8% vs 25.5% in the IPd vs Pd arm (Grade ≥3, 7.9% vs 3.4%). AEs contributing the most to this imbalance were dyspnoea and productive cough. The incidence of all grade and Grade ≥3 respiratory infections, respectively, was 74.3% vs 53.0% and 36.2% vs 24.2% in the IPd vs Pd arm. AEs contributing the most to this imbalance were upper respiratory tract infection, pneumonia, bronchitis, and nasopharyngitis. When comparing to isatuximab monotherapy, incidences were higher with the combination treatments. Pneumonia was reported in one patient treated with IPd in the pivotal trial (Grade 3 pneumonia during Cycle 1).

In study EFC14335, there was a 16.5% and 12.6% difference between the IPd and Pd arms in the incidence of AEs of all grades and Grade ≥3, respectively, in the Infections and infestations disorders SOC. The AEs contributing the most to this imbalance were upper respiratory tract infection and bronchitis. The incidence was higher in IPd compared with isatuximab single agent for all grades and Grade ≥3. Overall, herpes zoster was reported in 1.4%, and herpes zoster disseminated in 0.2%. As can be concluded from the numbers above, infections are a risk with IPd treatment. Except for Herpes virus infections (9.9% versus 2.7%), the incidence of opportunistic infections (Cytomegaloviral infections, Candida infections, Aspergillus infections, Pneumocystis infections, and Herpes virus infections) was similar in the IPd vs Pd arm. The higher incidence of infections and the information concerning the possible use of antibiotic, antifungal, and antiviral prophylaxis is described in the section 4.4 of the SmPC. No AEs of reactivated HBV or HCV were reported in the pivotal study, but data remain limited and there is no evidence that viral reactivation is not a risk with isatuximab treatment. Viral reactivation is included as important potential risk in the RMP. In addition, pomalidomide and daratumumab have a known risk of hepatitis B reactivation. There have been no cases of hepatitis B reactivation, whether treatment emergent or post-treatment, reported throughout the entire Data Pool 4 for isatuximab, however the potential risk of viral reactivation remains. Taking into account the seriousness of the risk in the class, with some fatal cases, a follow-up questionnaire will be used in order to obtain all the relevant information and, if needed, take measures without delay.

In the pivotal study SPMs were reported in 6 patients in the IPd arm (4 skin SCCs, 1 breast post-radiation angiosarcoma, 1 MDS ultimately transforming to AML) and 1 patient in the Pd arm (skin SCC). One skin SCC case developing during the 3rd cycle of treatment was considered related to IPd. In all patients treated with isatuximab SPMs were diagnosed in 17 (3.0%) patients. According to the Applicant the overall incidence of SPMs observed in patients treated with isatuximab is within the background incidence of SPMs in patients treated for MM. Although the occurrence of SPM is expected in elderly patients that had multiple lines of prior therapy, it is noted that the incidence of SPMs was higher in the IPd vs Pd arm. The occurrence of SPMs is adequately described as a warning in the SmPC section 4.4 and will be monitored via routine pharmacovigilance activities.

Out of 576 patients treated with isatuximab, TLS was reported in 3 patients (0.5%).

The interference with IAT (indirect antiglobulin test [indirect Coombs test]) was classified as an important identified risk. Information regarding this risk is sufficiently described in the SmPC and educational material will be provided to healthcare professionals and blood banks, as is also used for daratumumab. The anticipated duration of interference based on isatuximab half-life is reflected in the SmPC section 4.5. Additional data on the interference with the indirect Coombs test will be collected in the planned PASS (See RMP).

Regarding liver function, 6 reports were observed with values within the Hy's law range among all patients treated with isatuximab (Pool 4) however, none of the 6 reports met the definition of Hy's Law cases. Alternative aetiologies are likely to have caused the abnormal liver test results in these 6 patients (i.e. progressive disease, cardiac failure, subcutaneous infection, cholecystitis, and lenalidomide use).

Chemistry tests for renal function showed that for Grade 3 creatinine increased, the incidence in group Pd was 8.8% vs 2.6% in the IPd arm. The incidence of patients worsening to end stage renal function impairment was also lower in the IPd group vs Pd (2.6% vs 7.4%). The median calculated creatinine clearance was similar in the IPd and Pd arm, as was the incidence of severe impairment based on the calculated creatinine clearance. End stage occurred less often in the IPd group (2.9% vs 7.9%). These results are considered important for the target population with renal impairment as this is a common clinical feature of end organ damage in MM (SmPC section 5.1).

In study EFC14335, potentially clinically significant abnormalities were more common in IPd for heart rate decrease (6.6% IPd vs 1.4% Pd) and increase (6.6% vs 1.4%), systolic blood pressure decrease (22.4% vs 6.1%) and increase (18.4% vs 14.3%), diastolic blood pressure decrease (10.5% vs 2.7%), and body weight decrease (35.8% vs 19.4%). These trends should be interpreted within the context of the longer duration of treatment exposure in IPd versus Pd (median 41.0 weeks vs 24.0 weeks, respectively), and more frequent monitoring during isatuximab infusion in IPd arm. In addition, the excess of potentially clinically significant abnormalities for some tests did not translate into an increase in the incidence of TEAEs in the vascular disorders and investigation SOCs.

An abnormal ECG during was described in 22.0% in the IPd group and 25.5% of the Pd group of the pivotal trial. A total of 48 patients from the IPd group had at least 1 abnormal ECG (regardless of baseline status). In 21 of the 48 EFC14335 IPd patients, ECG abnormalities were deemed possibly clinically significant and were also associated with AEs that might be related to those ECG abnormalities. None of the cases with ECG abnormalities possibly related to AEs were assessed as having a direct causal relationship, as all were attributable to pre-existing and/or concomitant conditions. The Applicant performed thorough ECG monitoring in a monotherapy study (TED10893). The analysis of the thorough ECG monitoring data collected in this study does not suggest any clinically meaningful QTcF prolongation induced by isatuximab at any dose level. However, the effect of the combination with Pd was not investigated. Cardiac failure, atrial fibrillation, and myocardial infarction are known adverse events of pomalidomide and in the isatuximab safety database atrial fibrillation, including fatal cases, is described (SmPC section 4.8).

There are no available data on isatuximab use in pregnant women. Women of childbearing potential treated with isatuximab should use effective contraception during treatment and for 5 months after cessation of treatment. Animal reproduction toxicity studies have not been conducted with isatuximab. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of isatuximab in pregnant women is not recommended. It is unknown whether isatuximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; however, a risk to the breast-fed child cannot be excluded during this short period just after birth. For this specific period, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isatuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Afterwards, isatuximab could be used during breast-feeding if clinically needed. No human and animal data are available to determine potential effects of isatuximab on fertility in males and females (SmPC sections 4.6 and 5.3).

The safety profile showed some differences in subgroups. For the general safety profile, the safety profile seemed to be worse in patients older than 75 years (none of the patients in the pivotal trial was >85 years), males, patients with impaired renal function, and mild hepatic impairment. A similar pattern was seen in the Pd arm and therefore it does not raise concerns.

In the IPd Pool, 23 patients received P1F1 and 172 patients P2F2. The small number of patients receiving P1F1 hampers the comparison, but no alarming differences were observed. Among all 576 isatuximab-treated patients, patients treated with P1F1 (n=283) and P2F2 (n=293), were similar in terms of the incidence of AEs leading to treatment discontinuation, serious AEs, fatal AEs, and laboratory thrombocytopaenia Grade 3-4. The incidence of IRRs was 50.5% in P1F1 and 42.0% in P2F2. The incidence of Grade 3-4 laboratory neutropenia was 30.4% versus 55.3%, but incidences were similar when looking at the pivotal study specifically. There is no concern that there are major safety differences in the two formulations.

564 patients were evaluable for ADA. One patient had positive findings at baseline, 13 (2.3%) developed ADA during treatment with isatuximab with median onset of 1 month and transient response in 10, persistent in 2 and indeterminate in 1 case. It is reassuring that there was no confirmed positive response in the IPd arm of the pivotal study. Consequently, no neutralising ADA assessment was performed.

The posology regimen is based on a fixed volume infusion (see SmPC section 4.2). The safety findings in study TCD14079 Part B are consistent with those reported in the primary safety analysis CSR.

Based on data from 576 patients treated with isatuximab and 197 with the IPd combination, toxicity increases when combining isatuximab with Pd therapy compared to isatuximab monotherapy or Pd with an increase in Grade $\geqslant$3 AEs and serious AEs. This did not result in an increase in discontinuation of study treatments or deaths and the toxicity seems manageable and reversible. The type of AEs are in general as expected based on the working mechanisms of the IPd components with infusion related reactions, cytopaenias, and (respiratory) infections.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the type of AEs are in line with the known toxicity of Pd backbone therapy and anti-CD38 therapy and the added toxicity of combining isatuximab with Pd is considered acceptable for use in the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 2 prior anti-myeloma therapies that included at least 2 consecutives cycles of lenalidomide and a PI

given alone or in combination given that efficacy results are clinically relevant and robust.

The CHMP considers the following measures necessary to address issues related to efficacy (recommendation; see also clinical efficacy):

Submission of final safety and OS analysis, including subgroup analyses by best response to previous therapy and by refractoriness to lenalidomide, PI inhibitors or both, from study EFC14335.

2.7. Risk Management Plan

Safety concerns

Important identified risk	Interference with indirect antiglobulin test (indirect Coombs test) and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay, transfusion haemolysis)
Important potential risks	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 authorization				
Not Applicable				
Category 2 -Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not Applicable				
Category 3-Required additional pharmacovigilance activities				
Non-interventional PASS survey to measure the effectiveness of the isatuximab educational materials, to minimize the risk of interference with indirect antiglobulin test and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay,	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 with indirect antiglobulin test (indirect Coombs test) and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay, transfusion haemolysis)	Protocol submitted to PRAC Protocol approval by PRAC Start of data collection (the EU PAS register: before data collection starts) End of data collection	Q4 2020 (based on EC decision in Jun-2020) Estimated Q2 2021 Estimated Q3-Q4 2021 (within 6 months after PRAC approval or protocol) Estimated Q4 2022-Q1 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
transfusion haemolysis). Planned			Final report of study results	Estimated Q2-Q3 2023 (within 6 months after end of data collection)
A Phase 1b/2 study to evaluate the safety, pharmacokinetics, and preliminary 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)	**Primary objectives:** • Phase 1: to characterize the safety and tolerability of isatuximab in kidney transplant candidates. • Phase 2: to evaluate the efficacy of isatuximab in desensitization of patients awaiting kidney transplantation. **Secondary objectives:** • Phase 2: to characterize the safety profile of isatuximab in kidney transplant candidates. • To characterize the PK profile of isatuximab in kidney transplant candidates. • To evaluate the immunogenicity of isatuximab. • To assess the overall efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	Interference with indirect antiglobulin test (indirect Coombs test) and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay, transfusion haemolysis)	Final report of study results	2025

Risk minimisation measures

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Important identified risk		
Interference with indirect antiglobulin test (indirect Coombs test) and possible resulting adverse clinical consequences for the patient (bleeding due to transfusion delay, transfusion haemolysis	**Routine risk communication**: SmPC section 4.5. PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4. **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2).	**HCPs and Blood Banks brochure** **Patient Alert Card**
Important potential risks		
Viral reactivation	**Routine risk communication**: SmPC and PL: not labeled **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None	
Missing information	Not Applicable	

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 02 March 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that isatuximab has not been previously authorised in a medicinal product in the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Sarclisa (isatuximab) is included in the additional monitoring list as It is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application, is for a marketing authorisation for isatuximab, 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.

3.1.2. Available therapies and unmet medical need

The proposed target population of isatuximab is in very advanced stage of disease (third line setting and beyond). In this setting, pomalidomide, daratumumab and panobinostat have been approved, although the latter is not recommended in the ESMO clinical practice guideline as it is associated with significant toxicity. The choice of therapy in the relapsed 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 the case of biochemical relapse, treatment can be delayed).

Multiple Myeloma is typically more aggressive after each relapse, leading to decreased duration of response and culminates in treatment-refractory disease with short survival times. Additional treatment options are needed.

3.1.3. Main clinical studies

The main evidence for efficacy is based on the single phase III multicentre, randomised, open-label study EFC14335/ICARIA comparing isatuximab + pomalidomide and dexamethasone (IPd, n=154) with pomalidomide and dexamethasone alone (Pd, n=153). Included relapsed/refractory (R/R) MM patients had received at least two prior treatment regimens, including both lenalidomide and bortezomib, and had demonstrated disease progression on the last therapy.

3.2. Favourable effects

The primary endpoint PFS per IRC based on the ITT population, as reported after 162 events at the data cut-off (11 Oct 2018), showed a statistically significant improvement for IPd compared with Pd, with a HR of 0.596 (95% CI 0.436, 0.814; p=0.001). Median PFS improved from 6.47 (4.47 to 8.28) months in the Pd arm to 11.53 (8.94 to 13.90) months in the IPd arm.

PFS subgroup (including the high risk cytogenetic population) and sensitivity analyses generally supported the primary analysis, with HRs around 0.5-0.7 (range 0.414 to 0.827).

The following secondary endpoints of clinical relevance supported the primary endpoint:

The overall response rate (ORR) based on IRC assessment significantly improved from 35.3% with Pd to 60.4% in IPd (p<0.0001). Moreover, the depth of response (VGPR or better) was significantly increased from 8.5% in Pd to 31.8% in IPd (one-sided p<0.0001).

The median time to progression (TTP) based on IRC assessment was almost 5 months longer in the IPd arm (12.71 months; 95% CI 11.20, 15.211) than in the Pd arm (7.75 months; 95% CI 5.027, 9.758).

The median time to next treatment was not reached in the IPd arm (range 12.123, NR) and was 9.10 months (range 6.374, 12.255; with HR 0.538, 95% CI: 0.382, 0.758, p =0.0003) in the Pd arm, indicating that the addition of isatuximab to Pd treatment resulted in a delay of the next myeloma therapy.

Although no significant difference in overall survival (OS) was observed at the planned interim analysis, results showed a trend in favour of the IPd arm with a HR of 0.687 (95% CI 0.461, 1.023, p=0.0631). The probability of surviving 12 months in IPd was 72% compared to 63% in Pd.

Although the secondary endpoints DOR (13.27 vs. 11.07 months), median time to first IRC determined response (TT1R; 1.94 vs. 3.02 months), and time to best response (TTBR; 4.30 vs. 5.06 months) were not statistically significant different between the two treatment arms, a trend in favour of isatuximab was observed for all three endpoints.

3.3. Uncertainties and limitations about favourable effects

Overall survival data are not (yet) mature. Even though a trend in favour of the IPd arm was observed at the interim analysis, the trend towards longer OS should be interpreted in the context of the subsequent therapy. Final OS analysis, including subgroup analyses by best response to previous therapy and by refractoriness to lenalidomide, PI inhibitors or both, from study EFC14335 will be submitted in line with the CHMP recommendation.

The results of the PRO measures appear to indicate no significant improvement of QoL by addition of isatuximab to Pd, but also no deterioration of QoL/cancer related symptoms. However, results should be interpreted with caution due to the open-label design of the study and the missing data due to non-response.

Efficacy of isatuximab after daratumumab treatment is unknown, since only 1 patient was included in the pivotal trial who had previously received daratumumab treatment. Results of the currently ongoing Study TCD14079 part B and TED14154 Part B that allowed enrolment of patients previously exposed to daratumumab, suggest that isatuximab has some activity in that population. Interpretation of the data is difficult due to the limited number of subjects, variations in inclusion/exclusion of the study population between both studies, and the single arm design, therefore there is insufficient data available to conclude on the efficacy of isatuximab in patients previously treated with daratumumab.

3.4. Unfavourable effects

In total 576 patients were treated with isatuximab. Of all patients treated with isatuximab, exposure of at least 12 months occurred in 99 patients and 23 had at least 18 months of exposure. In total 293 patients were treated with the P2F2 commercial formulation (174 in the IPd combination). Exposure of the IPd combination was longer than of Pd, but during treatment relative dose intensity (RDI) for the separate drugs in the combination was lower for the experimental arm and more dose adjustments were needed in the triplet arm.

The incidence of AEs was higher in the IPd group vs Pd for treatment-related AEs, treatment-related Grade ≥3 AEs, and treatment-related serious AEs. Of the most frequently reported AEs, neutropaenia, febrile neutropaenia, infusion related reaction (IRR), upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, nausea, and vomiting were observed more frequently in the IPd vs Pd arm, also when adjusted for exposure. For Grade ≥3 AEs, neutropaenia and febrile neutropaenia occurred more often in the experimental arm. Less frequently reported AEs that occurred more often in the IPd group were nervous system disorders and cardiac disorders (mainly atrial fibrillation). Renal and urinary disorders (including acute kidney injury), skeletal-related AEs and thromboembolic AEs were reported at a similar incidence in the 2 treatment arms. Based on the provided data regarding the duration of the most prevalent AEs, Grade 3-4 AEs, and SAEs and their resolution, it seems that the toxicity profile of isatuximab is manageable and reversible. The type of AEs was similar across all patients treated with isatuximab. Isatuximab monotherapy seems to be better tolerated than the combination with Pd.

In the pivotal study, the incidence of AEs with a fatal outcome during the treatment period was 7.2% vs 8.7% in the IPd vs Pd group. In 8 patients of the IPd arm the fatal AE was categorised in the context of disease progression and in 8 not in the context of disease progression. In the last group deaths were mainly caused by infections. One case of sepsis was scored as treatment-related in the IPd arm.

In the pivotal study in 12.8 vs 7.2% of patients an AE led to treatment discontinuation. AEs that most frequently led to a dose modification of isatuximab were neutropaenia, pneumonia, upper respiratory tract infection, and IRR.

In the IPd arm of EFC14335, IRR occurred in 38.2%, mostly Grade 2. IRRs led to isatuximab interruption in 28.9% of patients and to discontinuation of isatuximab in 2.6%. In the vast majority, the IRR occurred once and at the first infusion with a duration of 1 day. Incidence of IRR was 48.9% with isatuximab monotherapy and 47-56% with other isatuximab combinations.

In the pivotal study second primary malignancies (SPMs) were reported in 1 patient in the Pd arm and in 6 patients in the IPd arm. One skin SCC case was considered related to IPd. In all patients treated

with isatuximab SPMs were diagnosed in 3.0% with a median interval of 7.16 months (range 0.5 to 26.5).

In study EFC14335, the incidence of lower respiratory AEs was 36.8% vs 25.5% in the IPd vs Pd arm (Grade ≥3 7.9% vs 3.4%). AEs contributing the most to this imbalance were dyspnoea and productive cough. The incidence of all grade and Grade ≥3 respiratory infections, respectively, was 74.3% vs 53.0% and 36.2% vs 24.2% in the IPd vs Pd arm. Upper respiratory tract infection, pneumonia, bronchitis, and nasopharyngitis contributed the most to this imbalance. When comparing to isatuximab monotherapy, incidences were higher with the combination treatments.

In study EFC14335, there was a 16.5% and 12.6% difference between the IPd and Pd arms in the incidence of AEs of all grades and Grade ≥3 infections, respectively, which was mainly caused by upper respiratory tract infection and bronchitis. The incidence was higher in IPd compared with isatuximab single agent.

Grade 4 neutropaenia was twice as frequent in the IPd arm and also neutropaenic complications (febrile neutropenia, neutropaenic infections) were more prevalent in the IPd arm. Grade 3-4 thrombocytopaenia occurred more often in the IPd arm as well, but the incidence of haemorrhage was similar in the IPd arm compared to Pd arm.

Out of 576 patients treated with isatuximab, tumour lysis syndrome (TLS) was reported in 3 patients (0.5%). In addition, there is a risk of interference with indirect antiglobulin test and possible resulting adverse clinical consequences for the patient, but no haemolytic disorders occurring <8 days after blood cell transfusions were reported in any patient treated with isatuximab.

One patient was ADA positive at baseline, 13 (2.3%) developed ADA during treatment with isatuximab with median onset of 1 month and transient response in 10, persistent in 2 and indeterminate in 1 in all patients treated with isatuximab. There was no confirmed positive response in the IPd arm of the pivotal study and therefore no neutralising ADA assessment was performed.

3.5. Uncertainties and limitations about unfavourable effects

For the requested indication, treatment duration is until progression or unacceptable toxicity and therefore long-term exposure might occur, but the safety data for long-term exposure (>12 months, bearing in mind the CI95% upper bound for median PFS of 13.9 months) are limited. Due to the limited number of patients who have been treated with isatuximab in clinical studies, rare side effects may not yet have been identified. To date, limited long term safety data is available. To gain more information about long-term exposure, the Applicant will evaluate the safety data at time of final OS analysis of study ECG14335 and provide an addendum to the CSR.

There have been no reported cases of hepatitis B reactivation with isatuximab treatment, but a potential risk of viral reactivation remains. Taking into account the seriousness of the risk in daratumumab, with some fatal cases, this will be monitored post-marketing.

In addition, the incidence of SPMs seems to be higher when isatuximab is added to Pd treatment.

3.6. Effects Table

Table 41. Effects Table for Sarclisa (isatuximab) in combination with Pd for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a PI (22 Nov 2018).

Effect	Short Description	Unit	Treatment N=153	Control N=154	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS by IRC	Time from the date of randomization to the first documented date of PD or death due to any cause	Months	11.53 HR 0.596 (95% CI 0.436, 0.814; p=0.001)	6.47	Supported by sensitivity and subgroup analyses. Not yet supported by mature OS data, although a trend was observed in favour of IPd. Efficacy in primary refractory patients unknown. No support PRO data, but no detrimental effect either. However, open-label design of the study and missing data due to non-response.	CSR
ORR by IRC	sCR, CR, VGPR, and PR, as best overall response	%	60.4%	35.3%	CR rate (4.5% IPd) likely underestimated due to M-protein interference. VGPR better in IPd arm (27.3% vs. 6.5% Pd).	CSR
OS	Time from the date of randomization to date of death from any cause	Months	NC (13.90 to NC) HR 0.687 (95% CI 0.461-1.023; p= 0.0631)	NC (NC to NC)	Interim analysis	CSR
Unfavourable Effects						
AEs	Overall (treatment-related)	%	99.3 (90.8)	98.0 (79.9)	All isatuximab treated patients (n=576): 96.0 (80.0)	CSR
Grade ⩾3 AEs	Overall (treatment-related)	%	86.8 (71.7)	70.5 (47.7)	All isatuximab treated patients: 66.8 (39.9)	CSR
SAEs	Overall (treatment-related)	%	61.8 (35.5)	53.7 (16.1)	All isatuximab treated patients: 45.8 (17.7)	CSR

Effect	Short Description	Unit	Treatment N=153	Control N=154	Uncertainties/ Strength of evidence	References
AESI-IRR	Overall (Grade ⩾3)	%	38.2 (2.6)	0 (0)	All isatuximab treated patients: 46.2 (3.5)	CSR
AESI-Infections	Overall (Grade ⩾3)	%	80.9 (42.8)	64.4 (30.2)	All isatuximab treated patients: 60.8 (24.7)	CSR
	Lower respiratory (Grade ⩾3)	%	74.3 (36.2)	53.0 (24.2)	All isatuximab treated patients: 52.1 (18.6)	CSR
AESI-SPM	Overall	%	3.9	0.7	All isatuximab treated patients: 3.0	CSR
AESI-Neutropenia	Grade ⩾3 (neutropenic complications)	%	84.8 (30.3)	70.1 (20.1)	All isatuximab treated patients: 43.1 (9.4)	CSR
AESI-Thrombocytopaenia	Grade ⩾3 (haemorrhage)	%	30.9 (8.6)	24.5 (11.4)	All isatuximab treated patients: 23.0 (12.7)	CSR

Abbreviations: AE = adverse event, AESI = AE of special interest, CSR = clinical study report, HR = hazard ratio, IRC = independent response committee, IRR = infusion related reaction, ORR = overall response rate, PFS = progression-free survival, SAE = serious adverse event, SPM = second primary malignancy, TTNT = time to next treatment, TTP = time to progression

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Relapsed and refractory multiple myeloma (R/R MM) with disease progression after at least 2 lines of treatment including lenalidomide and a PI represents an invalidating and life-threatening condition with an overall bad prognosis. Currently there are several treatment options registered in Europe for this population, that might offer timely remission of disease and related symptoms, delay of disease progression and improvement in survival, at the expense of substantial drug-induced toxicity. Definitive cure is not available at present. In this scenario, a further significant delay in disease progression with at least no detriment in survival associated with acceptable toxicity would represent a benefit for patients.

The most important benefit of isatuximab in combination with pomalidomide and dexamethasone in R/R MM is a statistically significant and clinically relevant improvement in PFS supported by a consistent improvement in ORR. PFS and ORR results are mature, IRC based, and supported by sensitivity and subgroup analyses showing consistent results. In view of the poor prognosis of the proposed R/R MM population, the magnitude of the improvement in median PFS (~5.1 months), is clinically relevant and supported by a trend in OS in favour of the IPd arm at the interim analysis.

Treatment with IPd leads to higher incidences of treatment-related AEs, Grade ≥3 AEs, SAEs compared to Pd treatment. Most frequently observed AEs that occurred more often in the IPd arm were infusion related reactions, infections, respiratory AEs, neutropaenia (including neutropaenic complications), and thrombocytopaenia. The type of AEs is not unexpected with a Pd backbone combined with anti-CD38 antibody. The toxicity profile of isatuximab is manageable and reversible. As is also known for daratumumab, isatuximab interfered with blood testing, which is described in the SmPC and educational material. In addition, the incidence of SPMs seems to be higher when isatuximab is added to Pd treatment. This will be monitored by routine PhV activities.

3.7.2. Balance of benefits and risks

The B/R balance is positive. The clinical benefit of adding isatuximab to pomalidomide and dexamethasone is considered demonstrated in relapsed and refractory multiple myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

When combining isatuximab with Pd therapy, toxicity increases compared to isatuximab monotherapy or Pd, but this did not result in an increase in discontinuation of study treatments or deaths. The type of AEs are in general as expected based on the working mechanisms of the IPd components. The added toxicity of combining isatuximab with Pd is acceptable considering the demonstrated clinical benefit.

3.8. Conclusions

The overall B/R of Sarclisa 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 is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sarclisa is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

Additional risk minimisation measures

The Healthcare professionals (HCPs) and blood bank educational material includes the following elements:

- The Summary of Product Characteristics
- The HCPs and Blood Banks brochure
- Patient Alert Card

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

Relevant information of the safety concern "Interference with indirect antiglobulin test (indirect Coombs test)":

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

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

- All patients should be blood typed and screened prior to start treatment with isatuximab. Phenotyping may be considered prior to starting isatuximab treatment as per local practice.
- There is currently no available information with regards to how long the interference with the indirect Coombs test may persist after the last infusion of isatuximab. Based on the half-life of isatuximab, isatuximab mediated positive indirect Coombs test may persist for approximately 6 months after the last isatuximab infusion therefore the HCP should advise the patient to carry the Patient Alert Card until 6 months after the treatment has ended.
- The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt isatuximab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

- In case of urgent need for transfusion, non-cross matched ABO/Rh compatible RBC units can be administered as per local bank practices.
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the risk of interference with indirect antiglobulin tests.
- Emphasize the need to consult the Summary of Product Characteristics (SmPC).
- Instruct the HCP regarding the need to give the Patient Alert Card to the patients and to advise them to consult the Package Leaflet (PL).

Patient Alert Card

The Patient Alert Card will contain the following brief and concise information regarding the risk of "Interference with indirect antiglobulin test (indirect Coombs test)" both for patients and HCPs consulted by the patient:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Sarclisa (isatuximab), and that this treatment is associated with the Important Identified Risk of Interference with indirect antiglobulin test (Indirect Coombs test), which may persist for approximately 6 months after the last isatuximab infusion
- A clear reference that the patient should continue to carry this card until 6 months after the treatment has ended.
- Contact details of the prescriber and the patient.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that isatuximab is a new active substance.