CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761113Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original Biologics License Application
Application Number(s)	BLA 761113
Priority or Standard	Standard
Submit Date(s)	April 30, 2019
Received Date(s)	April 30, 2019
PDUFA Goal Date	April 30, 2020
Division/Office	Division of Hematologic Malignancies 2
Review Completion Date	February 28, 2020
Established Name	Isatuximab
(Proposed) Trade Name	SARCLISA
Pharmacologic Class	CD38 – directed cytolytic antibody
Code name	SAR650984
Applicant	Sanofi Aventis U.S. LLC
Formulation(s)	Concentrate for solution for infusion
Dosing Regimen	Isatuximab 10 mg/kg IV on Days 1, 8, 15, and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMPP= Division of Medical Policy Programs
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
ASCT	autologous stem cell transplantation
B-ALL	B-acute lymphocytic leukemia
B-CLL	B-chronic lymphocytic leukemia
BLA	biologics license application
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CA	chromosomal abnormalities
CBER	Center for Biologics Evaluation and Research
CD38	cluster of differentiation 38
CDC	complement dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT4W	C_{trough} at 4 weeks
DDI	drug-drug interaction
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DOR	duration of response
DP	drug product
ECG	electrocardiogram
eCTD	electronic common technical document

EC_{50}	half maximal effective concentration
ETASU	elements to assure safe use
EU	European Union
FDA	Food and Drug Administration
FDS	formulated drug substance
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FITC	fluorescein isothiocyanate
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IFN-γ	interferon gamma
IgG1	immunoglobulin G1
IMiD	immunomodulatory drug
IND	Investigational New Drug
IPd	isatuximab in combination with pomalidomide and dexamethasone
IR	infusion reaction
IRC	independent review committee
IRT	interactive response technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety, international staging system
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
Ld	lenalidomide in combination with low dose dexamethasone
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MM	multiple myeloma
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NDMM	newly diagnosed multiple myeloma
NHL	non-Hodgkin lymphoma
NOAEL	no-observed adverse effect level
NK	natural killer
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cell
PBRER	Periodic Benefit-Risk Evaluation Report
Pd	pomalidomide in combination with low dose dexamethasone
PD	pharmacodynamics, progressive disease
PFS	progression-free survival
PI	prescribing information, proteasome inhibitor
PK	pharmacokinetics
PBS	phosphate buffered saline
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QW	once weekly
Q2W	once every 2 weeks
REMS	risk evaluation and mitigation strategy
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SCID	severe combined immunodefient
sCR	stringent complete response
SGE	special government employee
SOC	standard of care
SPM	second primary malignancies
T-ALL	t-acute lymphoblastic leukemia
TLS	tumor lysis syndrome
TNF-α	tumor necrosis factor alpha
TEAE	treatment emergent adverse event
TT1R	time to first response
TTP	time to progression
WBC	white blood cell
US	United States
VGPR	very good partial response

1 Executive Summary

1.1. Product Introduction

Drug: Isatuximab (SARCLISA)

Pharmacological Class: Isatuximab-irfc is an IgG1-derived monoclonal antibody that binds to CD38 expressed on the surface of hematopoietic and tumor cells, including multiple myeloma cells.

Proposed Indication: SARCLISA is a CD38 directed cytolytic antibody indicated, in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and proteasome inhibitor.

Dosing Regimen: With pomalidomide and dexamethasone: 10 mg/kg administered intravenously every week for the first cycle and every 2 weeks thereafter until disease progression or unacceptable toxicity. Premedication is required prior to infusions

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of SARCLISA (Isatuximab), according to 21 Code of Federal Regulations (CFR) 314.126 (a) (b), for the indication proposed:

"SARCLISA is a CD38 directed cytolytic antibody indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and proteasome inhibitor."

The approval of isatuximab in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and proteasome inhibitor is based on favorable risk-benefit profile based on the results of the Study EFC14335 (ICARIA-MM), a phase III randomized controlled trial of Isatuximab, pomalidomide and dexamethasone (IPd) and pomalidomide and dexamethasone (Pd). Patients were randomized 1:1 to receive either isatuximab, plus pomalidomide and dexamethasone (n = 154) or pomalidomide and dexamethasone (n = 153) in 28-day cycles until disease progression or unacceptable toxicity. Patients in both the IPd arm and Pd arm received 4 mg of pomalidomide for days 1–21 of each cycle, and the weekly equivalent of 40 mg or 20 mg dexamethasone for patients ≤ 75 years or > 75 years, respectively. Isatuximab was administered at the dose of 10 mg/kg intravenously weekly for the first cycle and once every two weeks for the subsequent cycles.

Efficacy:

- The primary endpoint for Study EFC14335 was progression free survival (PFS) assessed by independent review committee (IRC).

The study met the primary endpoint of PFS for the intention-to-treat (ITT) population. Median PFS was significantly longer in the IPd arm (11.53 months, 95% CI: 8.936 to 13.897) than in the Pd arm (6.47 months, 95% CI: 4.468 to 8.279), respectively. The stratified HR was 0.596 (95% CI: 0.436 to 0.814) characterizing a reduction of 40.4% in risk for disease progression or death with IPd compared to Pd.

- In the analysis based on IRC assessment, the ORR (PR or better) was significantly higher in the IPd arm than in the Pd arm (60.4% versus 35.3%). The 1-sided stratified CMH p-value was <0.0001, demonstrating a significant difference in ORR between the two arms in favor of IPd at the 0.025 level.

Safety

The most common adverse reactions (≥20%) in the isatuximab, pomalidomide and dexamethasone arm was neutropenia, infusion related reactions, pneumonia, upper respiratory tract infections and diarrhea. Important safety risks with the IPd combination include neutropenia, infusion related reactions and second primary malignancies. Adverse reactions were managed with dose reductions, temporary treatment discontinuations, supportive therapies, and/or standard medical care. The rates of definitive treatment discontinuation due to adverse reactions and fatal AEs was less than 10%. The safety profile of this agent is acceptable for this patient population with a serious and life-threatening disease.

The efficacy and safety results of Study EFC14335 demonstrate an acceptable benefit risk profile in the proposed patient population.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Multiple myeloma (MM) is a plasma cell malignancy that accounts for approximately 1-2% of all cancers and approximately 17% of hematologic malignancies in the United States. In 2020, it is estimated that there will be 32,270 new cases of myeloma in the United States and 12,830 deaths from the disease. MM is diagnosed most frequently among people aged 65-74 with a median age at diagnosis of 69 years. Five year survival rates for patients with MM are 52.2% (SEER 18 2009-2015).

The clinical presentation of MM is often related to the infiltration of plasma cells into the bone or other organs, as well as kidney damage from excess light chains. The most common symptoms at the time of diagnosis include anemia, bone pain, fatigue, weakness and weight loss. Despite the availability of multiple treatments, myeloma is thought to be an incurable disease, with the majority of patients experiencing recurring remissions and relapses. The goal of treatment is often aimed at creating longer periods of time without disease progression. Improving outcomes in patients with relapsed/refractory disease is an unmet medical need.

There are multiple treatment regimens approved for use in MM including alkylating agents, corticosteroids, immunomodulatory drugs (IMiDs), proteasome inhibitors and monoclonal antibodies.

The Applicant submitted a biologic license application (BLA) for isatuximab (b) (4)

The proposed regimen for isatuximab in combination with pomalidomide and dexamethasone is 10 mg/kg administered intravenously every week for the first cycle and every 2 weeks thereafter until disease progression or unacceptable toxicity.

The benefit-risk assessment for this BLA is primarily based on Study EFC14335 . Study EFC14335 was an open label, phase III randomized controlled trial comparing isatuximab, pomalidomide, dexamethasone (IPd) to pomalidomide and dexamethasone (Pd) in subjects with multiple myeloma who have received ≥2 prior lines of therapy including lenalidomide and a proteasome inhibitor (PI). The primary endpoint

was progression free survival (PFS) determined by independent review committee (IRC). The estimated median PFS was 11.53 months in the IPd group compared to 6.47 months in the Pd group. There was a reduction of 40.4% in risk for disease progression or death with IPd compared to Pd; stratified HR 0.596 (95% CI: 0.436 to 0.814). Overall survival data are immature.

Overall, the safety profile of the IPd regimen was similar to those already known with other monoclonal antibodies in combination with immunomodulatory drugs (lenalidomide or pomalidomide) and dexamethasone. Grade 3-4 TEAEs were reported more frequently in the IPd arm compared to the Pd arm (84.9% versus 69.1%) and serious TEAEs were also reported more frequently in the IPd arm compared to the Pd arm (61.8% and 53.7%).

Infusion related reactions, neutropenia and second primary malignancies are important safety risks noted with the isatuximab, pomalidomide and dexamethasone combination on Study 14335. Infusion reactions occurred in 38.0% of patients in Study EFC14335 and were mostly Grade 1 or 2; only 4 patients experienced Grade 3 or 4 infusion related reactions. SPMs were reported at higher rates in the IPd arm(3.9%) compared to the Pd arm (0.7%). Neutropenia as a laboratory abnormality was reported in 96% of patient and Grade 3 or 4 neutropenia in 84.8% of patients in the IPd arm. Serious adverse reactions in >5% of patients who received IPd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Dose modifications and supportive care were effective in managing the adverse events and majority of these events resolved. The incidence of Grade 5 (fatal) TEAEs (7.9% and 9.4% in the IPd and Pd arms, respectively) and any TEAEs leading to definitive treatment discontinuation of all study treatments (7.2% and 12.8% in the IPd and Pd arms) in study 14335 were generally low.

Isatuximab when combined with pomalidomide and dexamethasone resulted in a statistically significant and clinically meaningful improvement in progression free survival and overall response rate. The safety profile of isatuximab in combination with pomalidomide and dexamethasone is acceptable in the indicated population, a heavily pre-treated population with a life-threatening illness.
As such, the risk-benefit assessment supports regular approval for the proposed indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Multiple myeloma (MM) is the second most common hematological malignancy • Therapy armamentarium for patients with relapsed or refractory myeloma has improved considerably over the past three years with	Relapsed or refractory multiple myeloma remains an incurable disease

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	approval of multiple new therapies with improvement in response rate and progression free survival • However, MM remains incurable with a 5-year survival rate of 52.2%	
Current Treatment Options	• Currently approved therapies for patients with relapsed or refractory MM include proteasome inhibitor-based therapies, histone deacetylase inhibitor, or monoclonal antibodies. • Despite advances in therapy, patients with MM often relapse or develop refractory disease.	There is still a significant unmet need for effective therapies for disease control in patients with relapsed or refractory MM.
Benefit	• The clinical benefit of isatuximab in combination withpomalidomide and dexamethasone (IPd) was determined by the efficacy results from the study EFC14335 (ICARIA-MM) that enrolled patients to two arm: 1. IPd and 2. pomalidomide and dexamethasone (Pd). The primary endpoint was progression free survival (PFS) assessed by independent review committee (IRC). • The median progression free survival (PFS) was 11.53 months in the IPd group compared to 6.47 months in the Pd group. The hazard ratio (HR, IPd/Pd) was 0.596 (95% CI: 0.436 to 0.814); stratified log-rank test p value = 0. 001). • Treatment with IPd also improved overall response rate (ORR) compared to Pd alone (60.4% versus 35.3%).	Evidence of effectiveness was supported by a statistically significant and clinically meaningful improvement in PFS and ORR with the addition of isatuximab to pomalidomide and dexamethasone in Study EFC14335.
Risk and Risk Management	• The safety profile of isatuximab in combination with pomalidomide and dexamethasone was evaluated in Study EFC14335. Safety of isatuximab in combination of pomalidomide and dexamethasone is consistent with other monoclonal antibodies approved in combination with pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma. • Potential risks associated with isatuximab include infusion reactions, infections, neutropenia and second primary malignancies.	The safety profile of isatuximab in combination with pomalidomide and dexamethasone is acceptable for the intended population. Toxicities were manageable with appropriate treatment interruption and/or dose modifications which are clearly delineated in labeling. Warnings and Precautions in labeling

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Infusion reactions were reported in 38.0% of patients in Study EFC14335; less than 5% were Grade 3 or 4. There were no Grade 5 infusion related reactions. • The most common adverse reactions (≥20%) were neutropenia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea. • There is no proposal or indication for a risk management plan.	detail the serious risks of the drug including the risk of second primary malignancies. The safe use of isatuximab with pomalidomide and dexamethasone can be managed through accurate labeling and routine oncology care. No REMS is indicated.

1.4. Patient Experience Data

[FDA will complete this section.]

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		x□	Patient reported outcome (PRO)	Section 6.1 Study Endpoints
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		

	□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

Section 1 is the FDA's Assessment.

X _____

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Multiple myeloma (MM) is an incurable disease despite the availability of major new drug classes like immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies. With over 100 000 new cases per year, MM is the third most frequent hematological malignancy worldwide, after leukemia and non-Hodgkin lymphoma. Multiple myeloma treatment has improved remarkably over the last 2 decades with the introduction of autologous stem cell transplantation (ASCT) and the introduction of numerous novel agents, including 3 generations of immunomodulator agents (thalidomide, lenalidomide, and pomalidomide), 2 generations of proteasome inhibitors (bortezomib, then carfilzomib and ixazomib) and most recently, the first anti-CD38 antibody (daratumumab) and anti-SLAMF7 antibody (elotuzumab). These novel agents have improved the life expectancy of patients with MM; however multiple myeloma remains a fatal disease in the vast majority of cases (Kumar et al 2012, Kumar et al 2014).

The outcomes of patients with multiple myeloma are dependent on several prognostic factors, including patient age, performance status, stage of disease at diagnosis, organ function impairment and cytogenetic risk factors. Lower overall survival has been reported in patients with international staging system (ISS) Stage III disease or high-risk cytogenetic abnormalities, with renal (Dimopoulos et al 2010) and pulmonary dysfunction (Trakada et al 2019), and for patients aged >65 years who are ineligible for ASCT. Overall survival is particularly low among patients who have received three or more prior lines of therapy, or are refractory to a proteasome inhibitor and immunomodulatory drug, with a median overall survival (OS) of 7.9 months (Usmani et al 2016).

Multiple myeloma is associated with significant disease burden for patients. Quality of life for MM patients is influenced by the balance between disease-related symptoms, treatment-related toxicity, and treatment response (Maes et al 2018). Patients with MM experience a variety of disease-related events and symptoms, including renal failure, anemia, fatigue, exertional dyspnea, 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 (Zweegman et al 2017).

Novel agents and combinations are needed to improve disease control and delay progression, prevent myeloma-related complications and ultimately improve survival. Agents with alternative or improved target specificity, and new combination approaches triggering multiple cytotoxic mechanisms, are needed to overcome resistance to available therapies and further

improve patient outcomes (Sonneveld et al 2013). Genetic and molecular analyses have revealed the complexity and heterogeneity of MM, highlighting the need for therapeutic strategies that encompass multiple modes of action (Varga et al 2018).

The FDA's Assessment:
The reviewer agrees with the Applicant's analysis of condition. Despite availability of multiple approved treatment options including stem cell transplantation for patients diagnosed with multiple myeloma, the disease remains incurable.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

The isatuximab in combination with pomalidomide and dexamethasone (IPd) regimen was developed in order to address an unmet clinical need, providing a new and better option for patients who have received at least 2 prior lines of treatment, including both lenalidomide and a PI, and were refractory to last therapy.

The data in 6 Phase 3 or large Phase 2 trials with pomalidomide/dexamethasone show an objective response rate (ORR) of 26 to 40%, median progression-free survival (PFS) of 4 to 5 months (with the exception of 8.4 months in KEYNOTE-183 study) and median OS of 12 to 16 months (Dimopoulos et al 2016, Dimopoulos et al 2018, Jelinek et al 2018, Leleu et al 2013, Miguel et al 2013, Richardson et al 2014). These outcomes indicate the unmet need with current pomalidomide/dexamethasone treatment.

Other agents approved as single agent or in combination in a third-line or later setting of MM include daratumumab, which is another anti CD38 mAb, panobinostat, elotuzumab.

Daratumumab

Daratumumab, a humanized anti CD38 mAb in the same class as isatuximab, has been approved by FDA and EMA for relapsed refractory MM (RRMM) treatment, as well as newly diagnosed MM (NDMM).

It was approved as monotherapy in the United States (US; November 2015) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Daratumumab monotherapy was approved based on data from an uncontrolled Phase 2 study in 106 patients previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs). In this study, ORR was 29.2%, median PFS was

3.7 months (95% CI: 2.8-4.6) and median OS was 17.5 months (95% CI: 13.7-not estimable) (Lonial et al 2016).

Daratumumab was approved in the US (November 2016) and in the EU (April 2017) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. It was approved in the US (June 2017) in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Daratumumab was approved in combination with pomalidomide in the United States based on data from an uncontrolled Phase 2 study in 103 patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. In this study, ORR was 60% (42% VGPR or better), median PFS was 8.8 months (95% CI: 4.6-15.4) and median OS was 17.5 months (95% CI: 13.3-not estimable) (Chari et al 2017).

Daratumumab has also been approved in the US (May 2018) and in the EU (August 2018) in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Daratumumab is approved as a 16 mg/kg dosing with weekly IV administrations in combination with Pd for 8 weeks followed by every 2-week administrations for 16 weeks, followed by every 4-week administrations. The initial infusion can take over 7 hours, and thus may be split over 2 days (Arnall et al 2019). In the Phase 1 monotherapy study, the median durations of infusion for 16 mg/kg dosing were 7.7 and 6.7 hours for the first and second infusions, and 3.3 hours for subsequent infusions (Lokhorst et al 2015).

Patients with a history of chronic obstructive pulmonary disease or asthma (for whom access to daratumumab clinical trials was dependent on prior history and baseline pulmonary function) may require additional post-infusion prophylactic medications (short- and long-acting bronchodilators and inhaled corticosteroids) to manage respiratory complications. Following the first four infusions, if the patient experiences no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

To reduce the risk of delayed infusion reactions (IRs), administration of oral corticosteroids on each of the 2 days following all daratumumab infusions is recommended (beginning the day after the infusion) in monotherapy and the day after the daratumumab infusion in combination therapy (DARZALEX™ [daratumumab] prescribing information).

Panobinostat

Panobinostat is 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. The approval was based on a pre-specified subgroup analysis of the Phase 3 PANORAMA 1 study in patients with 1-3 prior treatments. Patients with creatinine clearance <60 ml/min were excluded from the study.

Panobinostat in combination with bortezomib and dexamethasone is associated with a significant toxicity in the absence of any overall survival benefit, and is not a recommended treatment option in the current clinical practice guidelines (San-Miguel et al 2016,Moreau et al 2017). The most common Grade 3/4 adverse events (AEs) and hematologic laboratory abnormalities among patients who received panobinostat were thrombocytopenia (67%), lymphopenia (53%), neutropenia (34%), diarrhea (25%), and fatigue/asthenia (25%); the percentage of on-treatment deaths was higher in the panobinostat-bortezomib-dexamethasone arm (n=30; 8%) than in the placebo-panobinostat-bortezomib-dexamethasone arm (n=18; 5%) (FARYDAK® [panobinostat] prescribing information). Although panobinostat has been approved, its role in the treatment paradigm of myeloma continues to be explored (Yee and Raje 2018).

Elotuzumab

Elotuzumab is currently approved in combination with lenalidomide and dexamethasone for the treatment of MM in patients who have received at least one prior therapy, and is approved in the United States in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor. With single agent elotuzumab therapy, no objective responses have been observed (Zonder et al 2012). The approval in combination with pomalidomide and dexamethasone was based on a randomized Phase 2 study, including 117 patients, with 60 patients treated with elotuzumab in addition to Pd (EPd) and 57 patients treated with Pd. Patients with creatinine clearance <45 ml/min were excluded from the study (Dimopoulos et al 2018). The median PFS was 10.3 months in the EPd arm compared to 4.7 months in the Pd arm (HR of 0.54 [95% CI: 0.34-0.86]; p=0.008). The ORR was 53% with EPd (20% VGPR or better) and 26% with Pd. Overall survival data were immature but a trend favoring EPd (HR 0.62) was noted.

Table 1: Summary of Treatment Options Relevant to Proposed Indication

Product Name	Relevant Indication	Year of FDA Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Pomalidomide	In combination with dex, for patients with MM who have received at least 2 prior therapies including len and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.	2013	4 mg per day taken orally on Days 1-21 of repeated 28-day cycles until disease progression.	ORR: 26 to 40% Median PFS: 4 to 5 months (with the exception of 8.4 months in one study) Median OS: 12 to 16 months	Venous and arterial thromboembolism; hematologic toxicity; hepatotoxicity (including fatal); severe cutaneous reactions Including hypersensitivity reactions; Tumor Lysis Syndrome (TLS).

					Most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upperrespiratory tract infections, back pain, and pyrexia (6.1).
Daratumumab	In combination with pom and dex for the treatment of patients with MM who have received at least 2 prior therapies including len and a PI.	2017	16 mg/kg actual body weight administered as an IV infusion weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks until disease progression.	ORR: 60% Median PFS: 8.8 months Median OS: 17.5 months	Infusion reactions; interference with cross-matching and red blood cell antibody screening; neutropenia; thrombocytopenia. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, constipation, nausea, vomiting, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, back pain, arthralgia, dizziness, insomnia, cough and dyspnea.
Panobinostat	In combination with bortezomib and dex, is indicated for the treatment of patients with MM who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.	2015	20 mg orally once every other day 3x doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles.	ORR: 59% Median PFS: 10.6 months OS: Not statistically difference with bortezomib and dex arm	Severe diarrhea; severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes; hemorrhage (including fatal), hepatotoxicity. The most common adverse reactions (incidence of at least 20%) in clinical studies are diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting. Grade 3/4 AEs and hematologic laboratory abnormalities include thrombocytopenia (67%), lymphopenia (53%), neutropenia (34%), diarrhea (25%), and fatigue/asthenia (25%).

Elotuzumab	In combination with pom and dex for the treatment of adult patients with MM who have received at least two prior therapies including len and a PI.	2018	10 mg/kg administered IV every week for the first two cycles and 20 mg/kg every 4 weeks thereafter until disease progression or unacceptable toxicity.	ORR: 52% Median PFS: 10.3 months	Infusion reactions, infections, second primary malignancies, hepatotoxicity, interference with assays used to monitor M-protein. Most common adverse reactions (20% or higher) were constipation and hyperglycemia.

The FDA's Assessment:

The reviewer agrees with the Applicant's analysis of current treatment options for the proposed multiple myeloma population.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
BLA 761113 is the first BLA for isatuximab. Isatuximab is not available commercially in any market.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

provide a concise summary of the regulatory history of the drug development for this particular application under review.

The Applicant's Position:

October 1, 2008: A Pre-IND meeting was held with Sanofi and FDA to discuss adequacy of the planned nonclinical studies and subsequent use of SAR650984 in the first-in-human studies. Feedback received during this meeting and through subsequent communication, addressed questions concerning the nonclinical approach, determination of the proposed starting dose and other discussion points regarding the first-in-human study. The IND was prepared based on these interactions with the FDA.

December 7, 2009: IND 103217 for SAR650984 was submitted to FDA for the treatment of hematological malignancies expressing the CD38 antigen. FDA issued a Safe to Proceed letter on December 29, 2009 for study TED10893, titled "A Phase I dose escalation safety and pharmacokinetic study of multiple intravenous administrations of a humanized monoclonal antibody (SAR650984) against CD38 in patients with selected CD38+ hematological malignancies."

September 4, 2012: The protocol for study TCD11863 titled "A Phase 1b study of SAR650984 (anti-CD38 mAb) in combination with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma,"was submitted to IND 103217 (Seq No. 0023).

(b) (4)

November 22, 2013: Sanofi submitted a meeting request to discuss an accelerated development plan. This request was denied on December 20, 2013.

March 6, 2014: Sanofi submitted a meeting request to obtain agreement on proposed patient reported outcomes (PRO) in planned Phase 3 privotal studies. A Type C meeting was granted and FDA provided a written response to the April 16, 2014 briefing package on May 20, 2014.

May 22, 2014: Sanofi received notice that FDA granted orphan drug designation for SAR650984 for treatment of multiple myeloma.

September 5, 2014: The protocol for study TCD14079, titled, "A Phase 1b study of SAR650984 (aAnti-CD38 mAb) in combination with pomalidomide and dexamethasone for the treatment of relapsed/refractory multiple myeloma," was submitted to IND 103217 (Seq No. 0102).

October 16, 2014: Sanofi submitted a meeting request to gain the Agency's agreement on the proposed comparability plan to change from SAR650984 (b) (4) clinical drug product to SAR650984 (b) (4) A Type C meeting was granted and held on February 10, 2015.

October 29, 2014: Sanofi submitted a meeting request to gain the Agency's agreement on the nonclinical safety plan through Phase 3 and registration and conversion to a new bioanalytical assay to measure anti-drug antibodies in patients enrolled in SAR650984 clinical studies. A Type C meeting was granted and FDA provided a written response to questions submitted with the December 15, 2014 briefing package on March 13, 2015.

July 14, 2016: The protocol for study ACT14596, titled "Phase 2, safety and efficacy study of isatuximab, an anti-CD38 monoclonal antibody, administered by intravenous infusion in patients with relapsed or refractory T-acute lymphoblastic leukemia or T-lymphoblastic lymphoma" was submitted to IND 103217 (Seq No. 0178).

July 14, 2016: Sanofi submitted a meeting request to discuss pivotal study EFC14335 and the rationale for the selected isatuximab dose and regimen. A Type B meeting was granted and held on October 4, 2016.

July 25, 2016: Sanofi submitted a meeting request to discuss the CMC development program proposed to support the registration of isatuximab (SAR650984). A Type B meeting was granted and FDA provided a written response to questions submitted with the August 25, 2016 briefing package on September 30, 2016.

November 3, 2016: The protocol for study EFC14335, titled "A Phase 3 randomized, open-label, multicenter 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" was submitted to IND 103217 (Seq No. 0200).

January 4, 2017: The protocol for study TCD13983, titled "A dose escalation, safety, pharmacokinetic and pharmacodynamic study, of SAR650984 administered intravenously in combination with bortezomib, cyclophosphamide and dexamethasone in adult patients with newly diagnosed multiple myeloma non eligible for transplantation" was submitted to IND 103217 (Seq No. 0205).

April 17 and April 25, 2017: June 20, 2017: Sanofi submitted a meeting request to discuss the design of pivotal studies EFC15246 and EFC12522. A Type B meeting was granted and held on June 20, 2017.

July 10, 2017: The protocol EFC15246, titled "Randomized, open label, multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib (Kyprolis®) and dexamethasone versus carfilzomib with dexamethasone in patients with relapsed and/or refractory multiple myeloma previously treated with 1 to 3 prior lines" was submitted to IND 103217 (Seq No. 0235).

July 24, 2017: The protocol EFC12522, titled "A Phase 3 randomized, open-label, multicenter study assessing the clinical benefit of isatuximab (SAR650984) in combination with bortezomib (Velcade®), lenalidomide (Revlimid®) and dexamethasone versus bortezomib, lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma not eligible for transplant" was submitted to IND 103217 (Seq No. 0237).

October 16, 2017: Sanofi submitted a meeting request to discuss the proposed study design, study endpoints, and registration strategy for patients with newly diagnosed multiple myeloma who are eligible for stem cell transplantation. A Type B meeting was granted and was held on January 11, 2018.

October 19, 2017: Sanofi submitted a meeting request to obtain feedback on the proposed list of studies, the pooling strategies, and planned content for the summary of efficacy, integrated summary of effacicay, summary of safety, and integrated summary of safety for the isatuximab Biologic License Application (BLA). A Type C meeting was granted and FDA provided a written response to questions in the December 7, 2017 briefing package on January 21, 2018.

May 17, 2018: Sanofi submitted a proposed pediatric study design (PPSR) to elicit a Written Request for a pediatric study. The request was denied on August 14, 2018.

May 18, 2018: Sanofi submitted a request for the proprietary name "SARCLISA". FDA issued a conditional approval on November 14, 2018.

September 7, 2018: Sanofi submitted a meeting request to discuss the proposed study design, study endpoints, and registration strategy for patients with smoldering multiple myeloma. A Type B meeting was granted and was held on November 14, 2018.

January 17, 2019: Sanofi submitted a meeting request to discuss the key study results for protocol EFC14335, titled, "A Phase 3 randomized, open-label, multicenter 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," in support of a BLA submission at the end of April 2019. A Type B meeting was granted and held on March 20, 2019.

The FDA's Assessment:

The Applicant has included a comprehensive review of the regulatory activities related to the development of SAR650984. The FDA has not independently confirmed the interactions that are not pertinent to this submission. The relevant regulatory activities are noted below.

May 20, 2014	Orphan designation granted for treatment of patients with MM
February 10, 2015	Type C meeting, Comparability plan for change in process and formulation
March 13, 2015	Type C meeting –Non clinical safety development plan and use of P and A to measure anti-drug antibodies.
October 4, 2016	Type B meeting- End of Phase 2/Pre-Phase 3 to discuss pivotal study EFC14335.
September 30, 2016	Type B meeting-CMC development plan
January 21, 2018	Type C meeting (WRO) –review of planned analysis and content for BLA
March 29, 2018	Request for comments and advice –SAP for ISS and ISE
May 18, 2018	Request for proprietary name review
February 13, 2019	Submission of key results of EFC14335
March 20, 2019	Type B meeting-Review of phase 3 data and confirm BLA content

Source: FDA Analysis

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDAs Assessment:
Two clinical investigator sites were selected for inspection for Study EFC14335 in BLA 761113.

Ivan Spicka, M.D., Ph.D., Site #2030003
I. interni klinika - klinika hematologie
U Nemocnice 499/2
Prague 28, 128 00
Czech Republic
Inspection dates: September 24 to 27, 2019

Xavier Leleu, M.D., Ph.D., Site #2500007
Oncologie hématologique
2 rue de la Milétrie
Poitiers, 86000
France
Inspection dates: September 18 to 20, 2019
The FDA Office of Scientific Investigations (OSI) concluded based on the results of the inspections, "the study data derived from these clinical investigator sites are considered reliable, and the study in support of this application appears to have been conducted adequately. " See OSI review in DAARTS finalized on 11/05/2019

Product Quality

4.1.1. Product Overview

Isatuximab (SARCLISA) is an immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to a specific extracellular epitope of cluster of differentiation 38 (CD38) and triggers several mechanisms leading to the death of CD38 expressing tumor cells. It is produced from a mammalian cell line (Chinese Hamster Ovary, CHO) using a fed-batch production process.

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 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 vitro enhances cell lysis of CD38 expressing multiple myeloma cells by effector cells (ADCC), and by direct tumor 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 or pomalidomide alone.

Nomenclature

Proprietary name	Sarclisa
International Non-proprietary Name (INN)	isatuximab
Laboratory and Development Code(s)	SAR650984
Synonymous name	hu38SB19
Chemical Abstracts Index Name(s)	Immunoglobulin G1, anti – (human CD38 antigen) (human-Mus musculus monoclonal hu38SB19 heavy chain), disulfide with human-Mus musculus monoclonal hu38SB19 light chain, dimer
Chemical Abstracts Registry Number	1461640-62-9

4.1.2. Drug substance

Isatuximab formulated drug substance (FDS) is manufactured at Sanofi Chimie in Vitry-sur-Seine cedex, France. Isatuximab is an aqueous (b) (4) solution, pH 6.0, containing 20 mg/mL (b) (4) isatuximab protein, (b) (4) mM histidine, (b) (4)% (w/v) sucrose, and (b) (4)% (w/v) polysorbate 80.

Long-term and accelerated supportive stability studies support the proposed shelf life of (b) (4) months at (b) (4)°C.

4.1.3. Drug product

Isatuximab drug product (DP) is manufactured at Sanofi-Aventis Deutschland GmbH in Frankfurt am Main, Germany.

Isatuximab drug product is available as a sterile 20 mg/mL concentrate for solution for infusion in two single-use vial presentations: 500 mg/25 mL and 100 mg/5 mL. The concentrate solution components are isatuximab, sucrose, histidine hydrochloride monohydrate, histidine, polysorbate 80 and water for injection.

The drug products are packaged:

- For the 500 mg/ 25 mL presentation:
  in a 30 mL (b) (4) colorless clear glass vial closed with (b) (4) (b) (4) stoppers. The stoppered vials are crimped with an aluminium seal with a blue flip-off cover.

- For the 100 mg/ 5 mL presentation:
  in a 6 mL (b) (4) colorless clear glass vial closed with (b) (4) (b) (4) stoppers. The stoppered vials are crimped with an aluminium seal with a gray flip-off cover.

Isatuximab (b) (4) product was used to conduct the phase 2 and 3 clinical studies and is intended for the commercial product. Stability testing supports support the proposed shelf life of 36 months when isatuximab is stored between 2°C and 8°C, protected from light.

The FDA's Assessment: See Office of Product Quality review for issues regarding the drug substance manufacturing processes and drug product and the immunogenicity assays used in the clinical studies that support this submission. Product Quality issues and recommendations including any PMR/PMC's will be reviewed by the FDA product Quality team. The FDA product quality team recommended approval of isatuximab.

4.2. Clinical Microbiology

The FDA's Assessment:
See Office of Microbiology review for specific recommendations regarding the drug product microbiology and PMR/PMCs. The FDA microbiology review team recommended approval.

4.3. Devices and Companion Diagnostic Issues

A companion device or diagnostic was not included with this submission.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

CD38 is a transmembrane glycoprotein. CD38 is mostly expressed in human hematopoietic cells/tissues, and in the pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells and bone at lower levels. High CD38 levels are expressed in human peripheral blood mononuclear cells (PBMC), natural killer (NK) cells and monocytes. The highest levels of CD38 expression have been reported on differentiated plasma cells. CD38 is upregulated in many hematopoietic malignancies, including multiple myeloma (MM). CD38 is not only a receptor mediating cell adhesion and signal transduction, but also a multifunctional enzyme involved in the production of nucleotide metabolites. Noticeably, this enzymatic activity mediates the conversion of NAD+ into cyclic adenosine diphosphate-ribose (cADPR) and further hydrolyzes cADPR to ADP-ribose (ADPR; Martin et al., Cells, 8: 1522-1547, 2019). These nucleotide ribose products play important physiological roles such as calcium mobilization and regulation of humoral immune responses (Ernst et al., Frontier in Immunology, 4: 1-7, 2013).

Isatuximab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeted against the CD38 antigen that bound to purified human CD38 with a K_D value of 0.12 nM. The antibody bound to human and chimpanzee CD38, but did not bind to CD38 from the mouse, rat, rabbit, pig, or cynomolgus and rhesus monkey. The in vitro activity of isatuximab was assessed in MM cell lines (LP-1, MOLP-8, or NCI-H929). Isatuximab induced Fc-dependent as well as Fc-independent MM cytotoxicity, alone or in combination with pomalidomide. Upon binding to CD38, the cell killing effects (in the presence of effector cells such as PMBCs or stromal cells, or in the absence of effector cells) were through Fc mediated mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), cytokine release (e.g., IFN-γ and TNF-α from NK cells), and cross-linking mediated apoptosis and phagocytosis (ADCP). In MM cells, the ADCC activity with isatuximab was demonstrated by NK-mediated lysis of 27-37% (EC_{50} values of 1.1 to 50.8 pM). Isatuximab induced CDC activity in LP-1 and MOLP-8 MM cells with 82 and 62% cell lysis (EC_{50} values of 0.18 and 1.53 nM), respectively. At a concentration of 1 µg/mL, isatuximab induced ADCP in LP-1 (~34%) and MOLP-8 (~54-59%) cells. Isatuximab-induced apoptosis was observed in only one of the MM cell lines tested (MOLP-8) with a maximum percentage of Annexin-V-positive cells of 29% (pro-apoptotic activity was defined as >10%). In the absence of autologous plasma or macrophages, isatuximab demonstrated apoptotic activity in primary cells from patients with MM (Annexin-V-positive cells: 14-16% in 3 samples and 28-40% in 4 samples).

Isatuximab triggered an immunomodulatory mechanism by manipulating NK cells and monocytes, both expressing high CD38 levels. Isatuximab exerted direct cell lysis of CD38 negative tumor cells. The direct killing effect of isatuximab may be via the activation of NK cells and an increase in their lytic activity. Isatuximab can also induce cytokine release (e.g., IFN-γ and TNF-α) from NK cells. Treatment of co-cultured primary monocytes and autologous NK

cells (in a human buffy coat sample) with isatuximab resulted in an increased percentage of CD80+ monocytes (i.e., the M1 population of monocytes). Thus, isatuximab promoted M1 polarization, without the induction of the M2 polarization marker CD206 on monocytes. The Applicant examined the expression levels of CD38 in PBMCs of healthy donors and patients with MM. In PBMCs from healthy donors, the percentage of $CD38^{high}$ subsets was higher among regulatory T cells (Treg, $CD4+CD25^{high}Foxp3+$) compared to conventional T cells (Tcon, CD4+CD25-). In PBMCs from MM patients, $CD38^{high}$ Tregs were more abundant than in normal donors; this may be potentially due to the inhibition of conventional T cells by regulatory T cells. Isatuximab treatment restored the proliferation of conventional T cells by suppressing regulatory T cells.

In addition to the aforementioned Fc-dependent effects, isatuximab was shown to induce caspase (caspase 3/7)-dependent apoptosis in MM cells which is a CD38-specific but Fc-independent mechanism. Furthermore, research also indicated that isatuximab can trigger a lysosomal cell death pathway (i.e., lysosome-mediated non-apoptotic cell killing pathway; Jiang et al., Leukemia 30: 399-408, 2016).

The combination of isatuximab and pomalidomide resulted in enhanced anti-MM activity compared to isatuximab or pomalidomide alone, as demonstrated both in primary MM cells and in an animal model of MM. In vitro experiments demonstrated that the combination of isatuximab and pomalidomide resulted in enhanced direct cytotoxicity and lysis of CD38+ MM cells by effector cells (e.g., via ADCC) compared to that of isatuximab alone. This may be attributed to pomalidomide potentially enhancing the effector functions or upregulating CD38 in MM cells (Feng et al., Clinical Cancer Research 23: 4290-4300, 2017). In NOD SCID mice bearing human MM MOLP-8 tumor cells, the combination of isatuximab and pomalidomide enhanced the anti-tumor activity of isatuximab compared to the single-agent isatuximab or pomalidomide treatment.

In an in vitro experiment assessing the secondary pharmacology, isatuximab did not induce significant depletions of any subpopulations of PBMCs. As CD38 expression is higher in NK cells and monocytes than in PBMCs, isatuximab induced increases in the apoptotic percentage in NK cells, not in other subpopulations of PBMCs.

No specific absorption, distribution, metabolism, or elimination studies were conducted in animals with isatuximab. The tissue distribution of isatuximab was assessed in a tissue cross reactivity (TCR) test by immunohistochemistry (IHC) staining. The TCR test indicated that isatuximab-specific binding was mainly in the lymphoid tissues (spleen, thymus, lymph node and tonsil) and in the bone marrow; binding was also detected in the pituitary gland (endothelial cells) and prostate gland (glandular epithelial cells). In addition, specific isatuximab binding was detected in infiltrating or resident round cells (including Kupffer's cells in the liver) in most tissues. Staining of non-lymphoid tissue elements (prostate, pituitary gland, lung, brain) was interpreted as evidence of cross-reactivity that may possibly indicate potential unintended target sites.

The safety assessment of isatuximab for general toxicity is mainly based on the mechanism of action (MOA) and findings in patients. The antibody does not bind to its target in animal species typically used in toxicology studies; however, a repeat-dose toxicology study in monkeys was conducted to investigate the potential off-target effects of isatuximab. There were no significant findings of non-targeted or non-specific toxicities of isatuximab. Isatuximab did not induce hemolysis of human whole blood and it was compatible with human plasma. Isatuximab was also well tolerated via various administration routes in a local tolerance evaluation test in rabbits.

Due to the lack of an appropriate pharmacologically relevant animal species for a study assessing the effects of isatuximab on embryo-fetal development, the evaluation of the reproductive and developmental toxicity of isatuximab is based on a weight of evidence (WOE) approach using literature on the involvement of CD38 in reproduction and development. Effects observed in target antigen CD38 knockout animal models include the depletion of fetal CD38 positive immune cells and a decrease in bone density. Additional data also suggest the involvement of CD38 in regulating humoral immune response, feto-maternal immune tolerance and early embryonic development. Based on the mechanism of action and these data, the determination has been made that isatuximab can cause fetal harm when administered to a pregnant woman, and this risk has been communicated in the isatuximab label. The contraception duration listed in the label is until at least 5 months after the last dose and covers a period of at least 5 half-lives for isatuximab ($T_{1/2}$= 28 days). Due to the potential depletion of fetal immune cells, a clinical consideration has been added to include the recommendation to defer administration of live vaccines to neonates and infants exposed to isatuximab *in utero* until a hematology evaluation is completed. Additionally, lactating women are advised not to breastfeed.

Isatuximab (Sarclisa) is indicated in combination with pomalidomide. Therefore, the isatuximab prescribing information includes a reference to the pomalidomide prescription information for pregnancy, contraception (including pregnancy testing) and lactation information.

No genotoxicity study was conducted or is warranted for an antibody. No fertility and early embryonic development, or carcinogenicity studies have been conducted or are warranted based on the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Not applicable.

The FDA's Assessment

There are no referenced NDAs, BLAs, or DMFs related to the nonclinical pharmacology or toxicology of isatuximab.

5.3. Pharmacology

Primary pharmacology

The Applicant's Position:

Isatuximab (isa), also named SAR650984, is derived from the murine anti-CD38 antibody, mu38SB19, that binds specifically to human CD38 with an apparent dissociation constant (K_D) of 0.12 nM. The antibody mu38SB19 demonstrated superior direct pro-apoptotic activity against CD38 expressing tumor cell lines compared to previously identified anti-CD38 antibodies. Isatuximab, (hu38SB19 v1.00), which bears the constant regions of human IgG1 and binds human CD38 with equal affinity (K_D) as the murine version, retained the pro-apoptotic activity and demonstrated CDC and ADCC activity.

5.3.1. Isatuximab in vitro activity against tumor cell lines

The applicant evaluated the ability of isatuximab to kill tumor cells by ADCP, ADCC, CDC or apoptosis induction in vitro against a panel of cell lines including the MM cell lines LP-1, MOLP-8 or NCI-H929 with surface CD38 levels varying from 233 000 to 790 000 antigens per cell (Table 2), and other cell lines derived from various hematologic malignancies including Non-Hodgkin's lymphoma (NHL; Ramos, Daudi, Raji, SU-DHL-8, Mamalwa, WSU-DLCL2), B-chronic lymphocytic leukemia (B-CLL; JVM-13), B-acute lymphocytic leukemia (B-ALL; NALM-6) and T-acute lymphoblastic leukemia (T-ALL; DND-41, TALL-1, MOLT-4, CCRF-CEM).

Phagocytosis

Phagocytosis was evaluated by the monocytic cell line THP-1 (effector) of the (target) MM cell lines LP-1, MOLP-8 and NHL cell line SU-DHL-8 labelled with the green fluorochrome PKH67 by measuring the percent of double positive labelled cells for PKH67 and CD14 following 1-2 hours incubation with isatuximab at an effector (E) to target (T) cell ratio (E:T) of 3:1 with 5 $x10^4$ target cells/well via flow cytometry.

Isatuximab at 1 µg/mL induced ADCP by THP-1 cells with a percentage range of cell killing of 33.9 to 34.9% in LP-1, 54.1 to 58.6% in MOLP-8 and 55.1 to 56.2% in SU-DHL-8 versus 9.5, 10.9 and 6.3% for controls, respectively.

Antibody-dependent cell-mediated cytotoxicity

The applicant evaluated the induction of ADCC by freshly purified human natural killer (NK) cells by measuring lactate dehydrogenase release. The effector NK cells (E) were incubated for 4 hours with tumor target cells (T) at an E:T ratio of 3:1 or 4:1 together with isatuximab.

The maximum percentage of NK-mediated lysis by isatuximab ranged from 27 to 100% depending on the cell line and the half maximal effective concentration (EC_{50}) values were between 0.7 and 50.8 pM (0.10 and 7.61 ng/mL).

For the MM cell lines LP-1, MOLP-8 and NCI-H929, the maximum percentage of NK-mediated lysis by isatuximab was 37, 28 and 27% with corresponding EC_{50} values of 13.5, 1.1 and 50.8 pM (or 2.02, 0.16 and 7.61 ng/mL), respectively.

The NHL cell line Ramos was one of the more sensitive cell lines to ADCC activity mediated by isatuximab with a maximum percentage of NK-mediated lysis of 97% and a corresponding EC_{50} value of 3.2 pM (or 0.48 ng/mL) (Table 2).

Complement-dependent cytotoxicity

The applicant evaluated the CDC activity of isatuximab by measuring the percentage of cells that remained viable following 2-hour incubation with isatuximab in the presence of human complement. The viable cells were detected with the Alamar blue reagent. The percentage of lysis was determined by subtracting percent viability from 100.

Isatuximab-induced cell lysis by the human complement was observed in 2 of the 3 tested cell lines, LP-1 and MOLP-8, with percentages of cell lysis of 82 and 62% and corresponding EC_{50} values of 0.18 and 1.53 nM (or 27.3 and 228.2 ng/mL), respectively (Table 2).

The T-ALL DND-41 cell line was one of the most sensitive cell lines to CDC activity mediated by isatuximab with a maximum percentage of cell lysis by the human complement of 93% and a corresponding EC_{50} value of 0.11 nM (or 16 ng/mL) (Table 3).

Apoptosis

The applicant measured the induction of apoptosis (pro-apoptotic activity) of tumor cell lines with flow cytometry using fluorescein isothiocyanate (FITC) conjugated Annexin-V (a marker of early apoptosis) after ≥20 hours of incubation with isatuximab at 10^{-8} M. This concentration corresponded to saturation conditions in terms of antigen.

Isatuximab showed pro-apoptotic activity against 7 out of 15 tested cell lines. The activity was considered positive above 10% of Annexin-V-positive cells. It was active against 5 of the 6 NHL cell lines tested: Daudi, Ramos, SU-DHL-8, Raji, and Namalwa and against the T-ALL cell line DND-41. Isatuximab showed minor activity against the B-CLL cell line JVM-13. In order to determine the EC_{50} values for the pro-apoptotic activity in these cell lines, isatuximab was assayed at concentrations from 10^{-7} to 10^{-13} M.

Amongst the MM cell lines LP-1, MOLP-8 and NCI-H929, isatuximab-mediated apoptosis was observed in only 1 of the 3 tested cell lines, MOLP-8, with a percentage of Annexin-V-positive cells of 29% (Table 2).

The NHL SU-DHL-8 and T-ALL DND-41 cell lines were among the most sensitive cell lines to pro-apoptotic activity mediated by isatuximab with a percentage of Annexin-V-positive cells of 88 and 56% and corresponding EC_{50} values of 0.03 and 0.10 nM (Table 3), respectively.

Table 2 - Isatuximab in vitro activity against MM cell lines

	CD38 expression[1]	ADCP[2]	ADCC[1]		CDC[1]		Pro-apoptotic activity[1]	
Cell line	ABC in 1,000	Max % phagocytosis	EC_{50} in pM	Max % lysis	EC_{50} in nM	Max % lysis	EC_{50} in nM	Max %Ann. V+[3,4]
LP-1	487	33.9	13.5	37	0.18	82	-	-
MOLP-8	790	58.2	1.1	28	1.53	62	ND	29
NCI-H929	233	ND	50.8	27	-	-	-	-

Abbreviations: ABC: antibodies bound per cell, ADCP: antibody-dependent cellular phagocytosis, ADCC: antibody-dependent cellular cytotoxicity; CDC: complement-dependent cytotoxicity, MM: multiple myeloma, ND: not determined
-: denotes absence of activity, maximal effective concentration (EC_{50}) could not be calculated
Pro-apoptotic activity is considered positive above 10% of Annexin-V-positive cells.

1. IMV23-012 study
2. ONVT0117 study ((b) (4) formulation stored at +5°C)
3. Maximum percentage of Annexin-V-positive cells
4. Pro-apoptotic activity is considered positive above 10% of Annexin-V-positive cells

Table 3 - Isatuximab in vitro activity against cell lines used for in vitro MABEL determination

	CD38 expression[1]	ADCC		CDC		Pro-apoptotic activity	
Cell line	ABC in 1,000	EC_{50} in pM	Max % lysis	EC_{50} in nM	Max % lysis	EC_{50} in nM	Max %Ann. V+ [2,3]
Ramos	255	**3.2**[4]	97	0.17	23	0.01	30
SU-DHL-8	220	2.1	82	1.61	27	0.03	88
DND-41	612	1.5	58	0.11	93	0.1	56

Abbreviations: ABC: antibodies bound per cell, ADCP: antibody-dependent cellular phagocytosis, ADCC: antibody-dependent cellular cytotoxicity; CDC: complement-dependent cytotoxicity

1. IMV23-012 study
2. Maximum percentage of Annexin-V positive cells
3. Pro-apoptotic activity is considered positive above 10% of Annexin-V-positive cells
4. In bold, data used for in vitro MABEL determination

5.3.2. Isatuximab ex vivo activity against primary MM patient cells

The applicant evaluated the pro-apoptotic effect of isatuximab using bone marrow aspirates from relapsed and newly diagnosed MM patients in the presence or absence of autologous plasma and/or macrophages.

In the absence of autologous plasma and/or macrophages isatuximab demonstrated an anti-MM effect in 4/7 samples tested (28 to 40% increase of Annexin-V+ cells) and a moderate response in the 3 other samples (14 to 16% increase of Annexin-V+ cells).

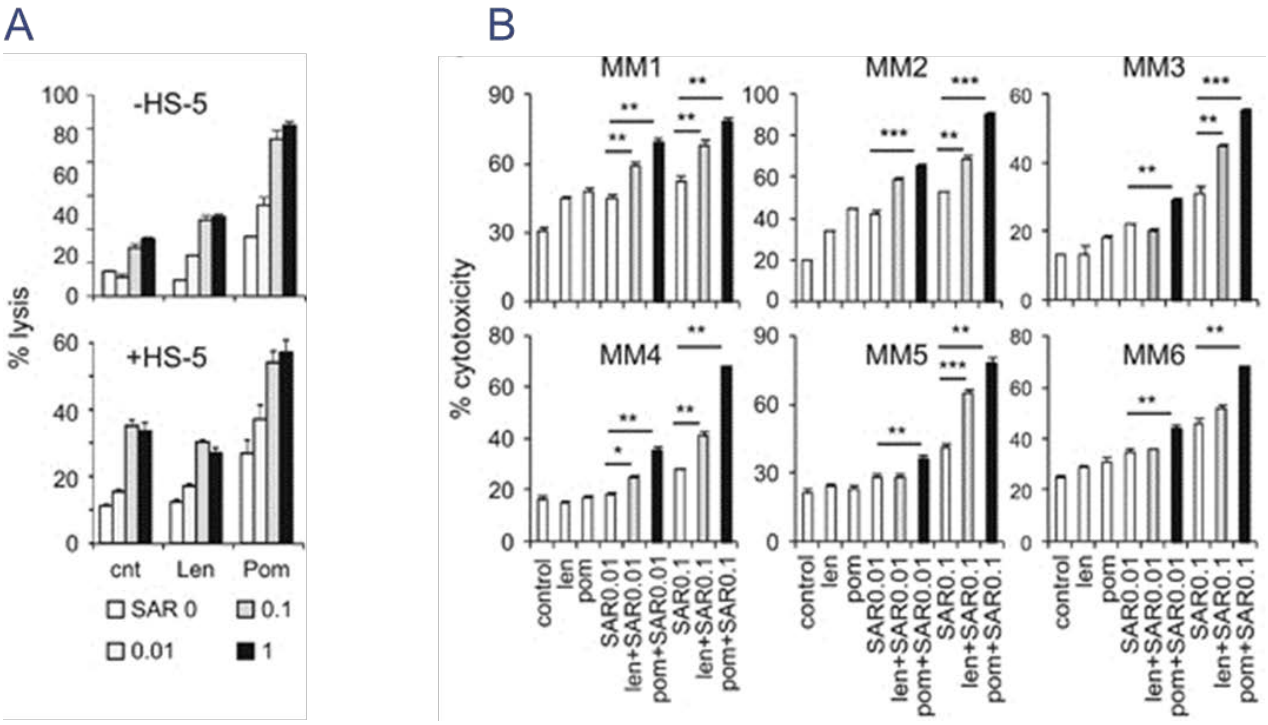
In the presence of autologous plasma and/or macrophages isatuximab and autologous plasma showed increased cell killing in 1 of 2 MM samples.

5.3.3. Isatuximab/pomalidomide combination anti-MM activity

In vitro

The applicant performed in vitro experiments that demonstrate that the combination of isatuximab and pomalidomide result in enhanced direct cytotoxicity and lysis of CD38+ MM cells by effector cells (ADCC) compared to that of isatuximab alone. Pretreatment of peripheral blood mononuclear cells (PBMCs) with 2 µM pomalidomide increased isatuximab-induced lysis of MM1S MM cells from below 40% to above 50% or 80% in the presence or absence of HS-5 stromal cells, respectively (Figure 1A). In patient-derived MM cells, both sensitive and resistant to pomalidomide or lenalidomide, isatuximab-induced cytotoxicity was significantly increased in the presence of pomalidomide (Figure 1B).

Figure 1 – Anti-MM activity of isatuximab in combination with IMiDs



A) Lysis of MM1S cells by PBMCs pretreated with lenalidomide or pomalidomide in the presence (+) or absence (−) of HS-5 stromal cells and isatuximab (0.01, 0.1 and 1 µg/mL)
B) Lysis of CD138+ cells in bone marrow aspirates from MM patients sensitive (n = 2, MM1,2) or resistant (n = 4, MM3-6) to lenalidomide/pomalidomide with isatuximab (SAR; 0.01, 0.1 µg/mL) and 2 µM lenalidomide or pomalidomide
From Jiang et al.
Abbreviations: cnt=control, len=lenalidomide, MM=multiple myeloma, PBMC=peripheral blood mononuclear cells, pom=pomalidomide, SAR=isatuximab, SEM=standard error of mean
*P<0.05, **P<0.01, ***P<0.001

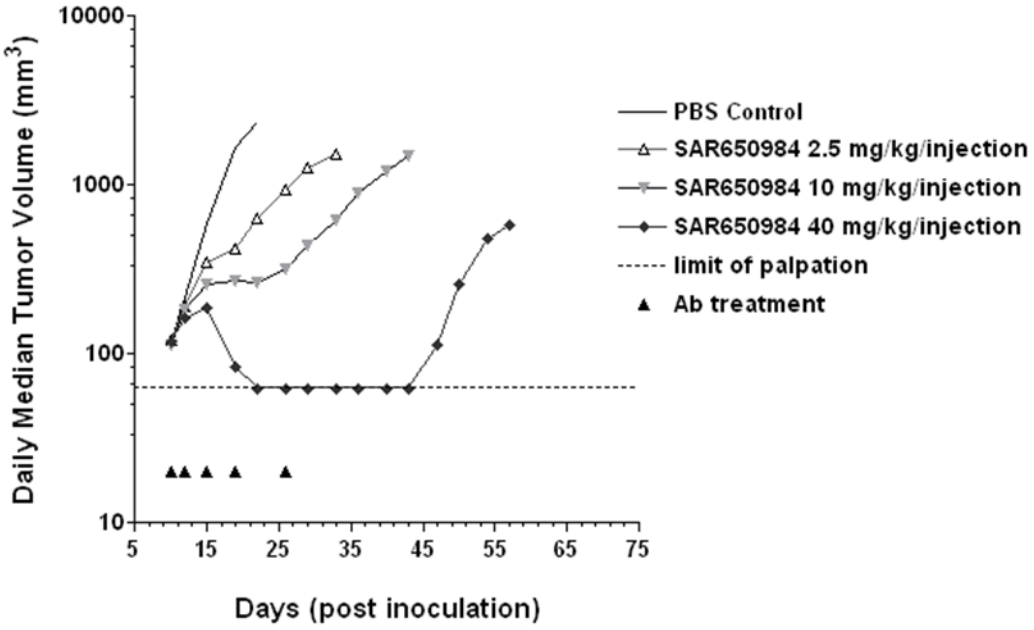
In vivo

Pharmacological activity of isatuximab as single agent

Reference ID: 4568595

The applicant evaluated the pharmacological anti-tumor activity of isatuximab in SCID mice bearing SU-DHL-8 tumors. Mice were divided into four treatment groups that received vehicle (phosphate buffered saline (PBS) for control, and 5 IV doses of isatuximab at 2.5, 10 or 40 mg/kg on Days 11, 14, 18, 21 and 26 following tumor cell inoculations. The lowest dose of 2.5 mg/kg was chosen in order to obtain an inactive or minimally active dose. When the median tumor volume was calculated for each treatment group and the results plotted against days post-inoculation on a semi-log plot, a clear dose response was observed as depicted in Figure 2. Isatuximab was active at all doses tested with a log cell kill total of 4.9, 2.6, and 1.2 with tumor growth inhibition (T/C; corresponding to the daily median tumor volume of the treated/daily median tumor volume of the control) x 100) of 5.0, 14.6 and 25.1% at Day 19 at 40, 10, and 2.5 mg/kg, respectively.

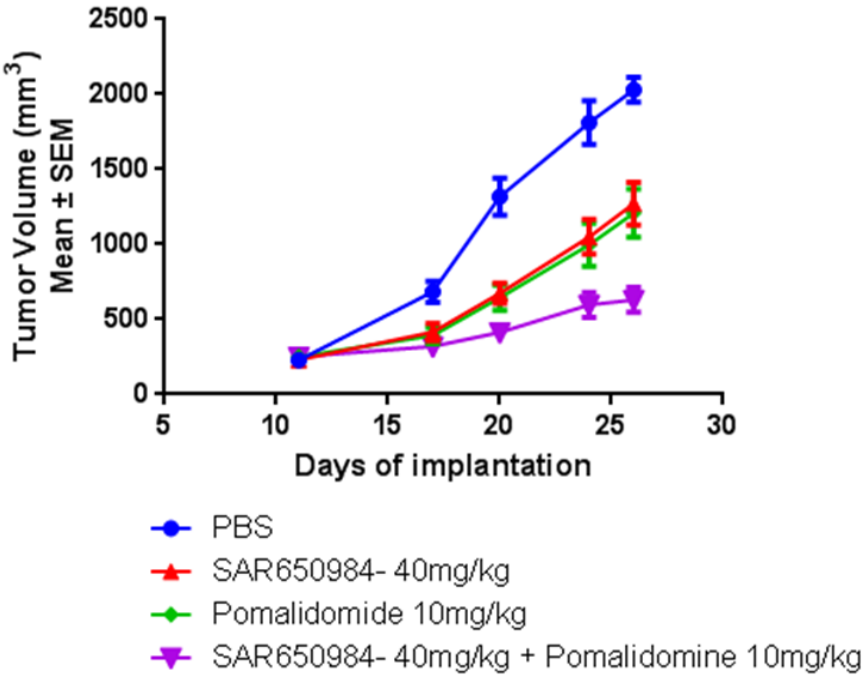
Figure 2 - Median Tumor Volume for PK study



Pharmacology activity of isatuximab in combination with lenalidomide and pomalidomide

The applicant also performed in vivo experiments using a MOLP-8 multiple myeloma mouse xenograft model to evaluate the antitumor activity of isatuximab in combination with pomalidomide (T/C=22%) compared to the activity of isatuximab (T/C=56%) and pomalidomide alone (T/C=46%) without affecting body weight (Figure 3).

Figure 3 - Efficacy of isatuximab (40 mg/kg twice a week) alone and in combination with pomalidomide (10 mg/kg daily for 14 days) in female NSG mice bearing subcutaneously implanted MOLP-8 tumors



Abbreviations: PBS=phosphate buffered saline, SAR650984=isatuximab, NSG= NOD SCID gamma, SEM=standard error of mean

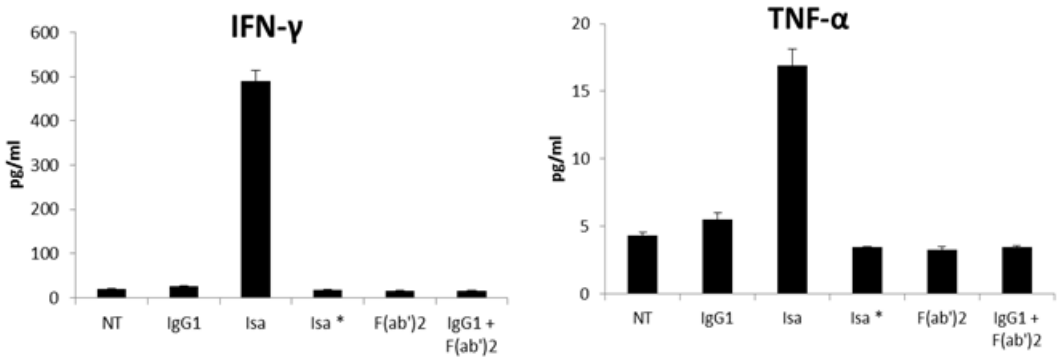
5.3.4. Isatuximab immunomodulatory activity

NK cells and monocytes

The applicant evaluated the effect of isatuximab treatment in human PBMCs, NK cells and monocytes, which express high CD38 levels, using the NK-92 human cell line as well as primary cells freshly isolated from the peripheral blood of healthy donors.

Isatuximab's effect on NK cells was analyzed by quantifying the release of interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) following a 24-h treatment of human NK cells freshly isolated from the peripheral blood of healthy donors. Isa * (Isatuximab variant with 101K and Y102E amino acid substitutions in the VH1 region unable to bind C38), F(ab')2 (Isatuximab variant unable to bind CD16) and IgG1 were used as controls. The release of IFN-γ and TNF-α induced by isatuximab was higher than that of non-treated or IgG treated NK cells. F(ab')2 alone did not trigger cytokine release. These data indicate that isatuximab can activate NK cells in the absence of CD38+ target tumor cells and that the Fc portion of isatuximab might be required for activation.

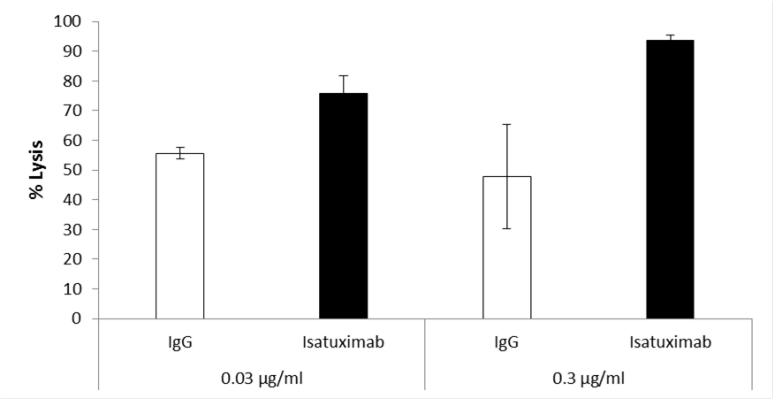
Figure 4 - Isatuximab-induced release of IFN-γ and TNF-α from primary NK cells

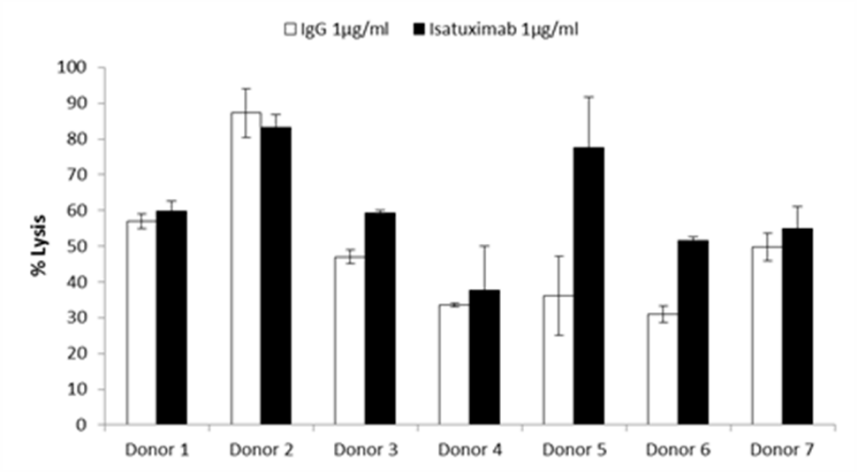


Abbreviations: NK: Natural killer; IFN-γ: Interferon-γ; Isa: Isatuximab; TNF-α: Tumor necrosis factor-α
Isa *: Isatuximab variant unable to bind CD38

Isatuximab's impact on the cytolytic activity of NK cells on K562 tumor cells was quantified using the calcein release method. Over 90% of K562 (CD38 negative) cells were lysed 30 minutes after adding NK-92 cells pre-incubated for 3h with isatuximab at 0.3 µg/mL. In contrast, a lysis below 50% was reached by IgG pretreated NK-92 cells (Figure 5, top panel). 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 of K562 in donor 3 by 12.12%, in donor 5 by 41.44% and in donor 6 by 20.50% (Figure 5, bottom panel).

Figure 5 - Isatuximab effect on the lysis of K562 cells by NK-92 cells (top) and primary NK cells isolated from the blood of healthy donors (bottom)

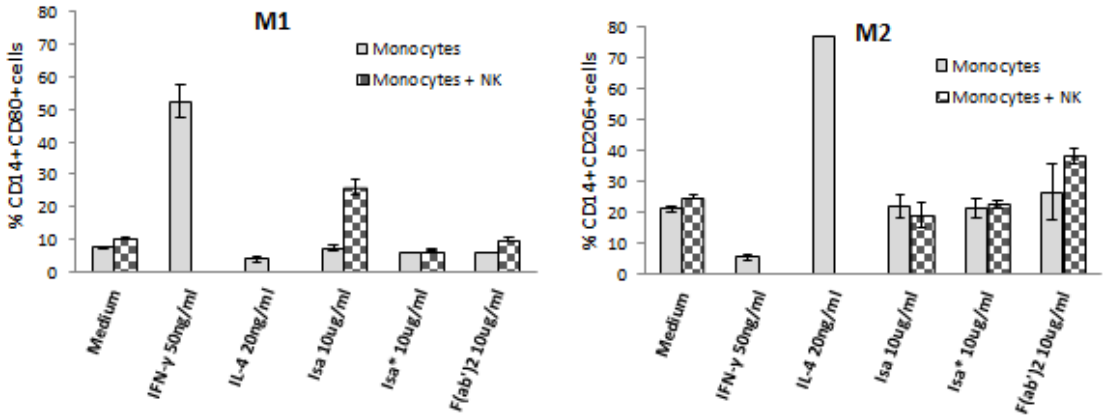




Abbreviation: NK: Natural killer

Isatuximab treatment of monocytes alone does not increase M1 polarization marker CD80 in human primary monocytes. However, treatment of co-cultured primary monocytes and autologous NK cells with 10 µg/mL isatuximab results in increased percentage of CD80+ monocytes, likely due to the IFN-γ released by NK cells (Figure 6, left panel). Isatuximab does not induce M2 polarization marker CD206 on monocytes cultured alone or in the presence of NK cells (Figure 6, right panel).

Figure 6 - Isatuximab effect on M1/M2 polarization of human monocytes

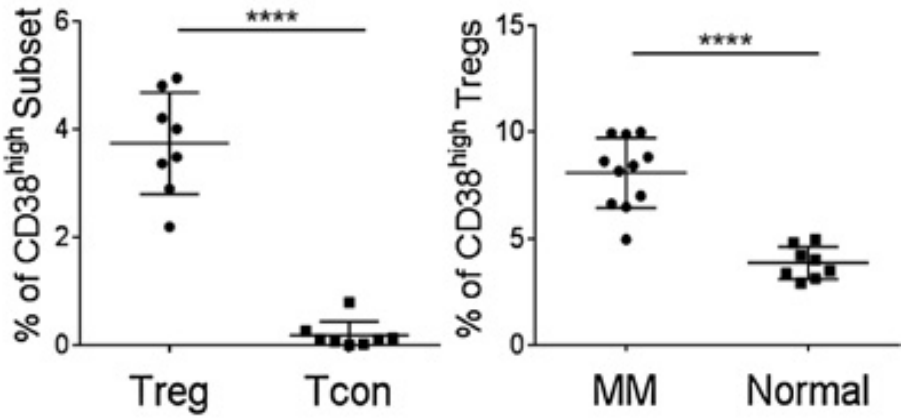


Abbreviations: IFN-γ = interferon-γ; IL-4 = interleukin-4; Isa *: Isatuximab variant unable to bind CD38

Regulatory T cells

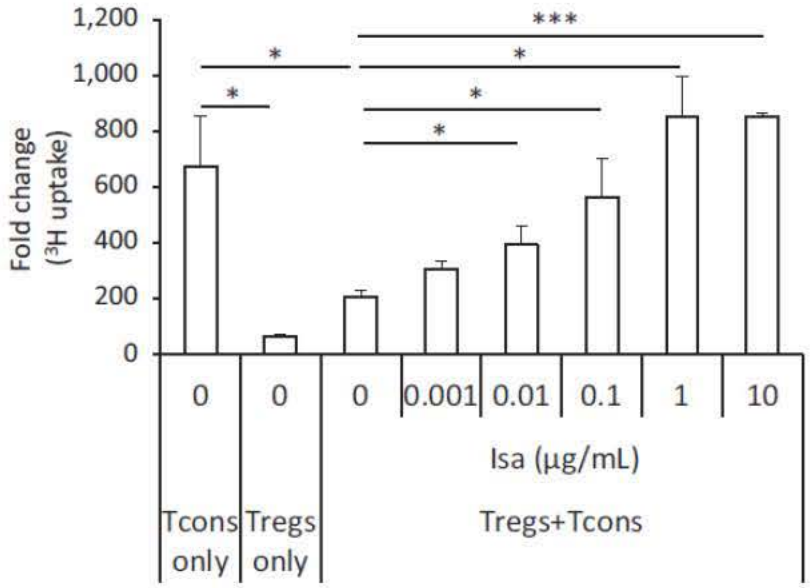
Both regulatory (Treg, CD4+CD25^{high}Foxp3+) and conventional T (Tcon, CD4+CD25-) cells express CD38. In PBMCs from healthy donors (n = 8), the percentage of CD38^{high} subsets is higher among Tregs compared to Tcons (Figure 7, left panel). In PBMCs from MM patients (n = 11), CD38^{high} Tregs are more abundant than in normal donors (n = 8) (Figure 7, right panel). Tregs from MM patients inhibit proliferation of autologous Tcons. Isatuximab restores the proliferation of Tcons in a dose dependent manner (Figure 8).

Figure 7 - CD38 expression on regulatory (Treg) vs conventional (Tcon) T cells from healthy donors (left panel) and frequency of CD38^{high} Tregs in MM patients vs healthy donors (right panel)



Abbreviations: MM = multiple myeloma
Treg : regulatory T-cell; Tcon: conventional T-cell
**** p<0.0001

Figure 8 - Isatuximab effect on the proliferation of conventional T cells inhibited by Tregs



Abbreviations: Tregs: regulatory T-cells; Tcons: conventional T-cells
* p<0.05; *** p<0.001

The FDA's Assessment:

The FDA agrees with the primary pharmacology data presented that describes isatuximab's pharmacological effects including ADCC, ADCP, and CDC activities and the apoptosis of tumor cells and the enhanced anti-tumor activities in combination with pomalidomide. Additionally, the FDA agrees that isatuximab has immunomodulatory effects including the activation of NK cells and the suppression of T-regulatory cells summarized by the Applicant.

The study report for Study IMV23-011 was reviewed. The FDA found the data in the report supportive of the Applicant's introductory remarks regarding the binding specificity of isatuximab (Mu38SB19) to human CD38. The FDA notes that the data in Table 3 titled (b) (4), contains data (b) (4) and is not relevant to the current BLA marketing application.

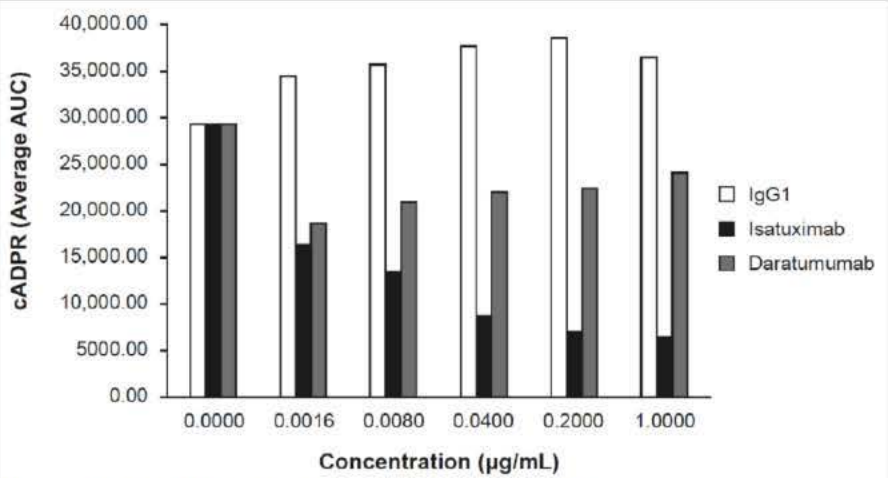
The following study reports and literature references that are included in the BLA submission were reviewed to support the mechanism of action of isatuximab.

Isatuximab inhibits the enzymatic activity of CD38

Study title: Comparative CD38 enzyme inhibition by isatuximab batches (b) (4)
Study #ONVT0119, Module 4 of the BLA.

Isatuximab induced concentration-dependent inhibition of cyclic adenine diphosphate ribose (cADPR) synthesis from NAD and the hydration of cADPR to ADPR. These products were suggested to play a role in calcium mobilization and regulation of humoral immune responses.

Article: "Therapeutic opportunities with pharmacological inhibition of CD38 with isatuximab" (Martin et al., Cells, 8: 1522-1547, 2019)
CD38 has both ADP ribosyl-cyclase activity and hydrolase enzymatic activity, namely, conversion of nicotinamide adenine dinucleotide [NAD] to cADPR and ADPR in CD38-expressing cell lines. Isatuximab was identified as an allosteric antagonist capable of inhibiting the CD38 ADP-ribosyl cyclase enzymatic activity. Such antagonist activity was attributed to specific amino acid residues on the heavy chain of isatuximab allowing isatuximab to access the catalytic site of CD38. Treatment of MM cells with isatuximab resulted in suppression of cADPR (see figure below) and ADPR formation in the CD38-positive LP-1 MM cell line.



(Figure from Martin's reference cited above)

Isatuximab induced non-Fc -related cytotoxicity of MM cells
Article: "SAR650984 directly induces multiple myeloma cell death via lysosomal-associated and apoptotic pathways, which is further enhanced by pomalidomide" (Jiang et al., Leukemia 30: 399-408, 2016)
Isatuximab was shown to induce caspase (caspase 3/7)-dependent apoptosis in MM cells which is a CD38-specific but Fc-independent mechanism, or to trigger a lysosomal cell death pathway (i.e., lysosome-mediated non-apoptotic cell killing pathway). In the absence of Fc-cross-linking or effector cells, isatuximab-induced anti-tumor activities (mainly via an apoptotic mechanism) were enhanced in the presence of pomalidomide.

Secondary Pharmacology

The Applicant's Position:

The applicant conducted a GLP tissue cross-reactivity study that 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).

The applicant conducted in vitro studies to characterize the presence of CD38 on human blood cells and ealuate the in vitro biological effects of isatuximab on the different types of human blood cells. CD38 expression was shown to be expressed at low levels in normal human PBMCs. The highest levels were found in CD56-positive NK cells at 14 336 antibodies bound per cell (ABC) and in CD14-positive monocytes at 9116 ABC. In CD3-positive T-lymphocytes, CD38 expression was low at 3712 ABC and in CD19-positive B-lymphocytes it was even lower at 2874 ABC. In accordance with published findings, CD20 expression was found to be restricted to CD19-positive B-lymphocytes and much higher in these cells than CD38 at 85 919.

The applicant investigated the effect of isatuximab on cytokine release by normal PBMCs in vitro. Cytokine release by normal PBMCs or white blood cells (WBCs) preparations was assessed from 14 independent donors after isatuximab treatment. In all assays, the positive control antibody OKT3 induced a strong release of all the cytokines tested for each donor (except IL-12p70). For some donors, soluble alemtuzumab and TGN1412 mAb also stimulated cytokine release (IFN-γ, TNF-α and IL-6). In addition, the air-dried presentation of TGN1412 released high levels of IL-2 (2 donors tested). In contrast, 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. Even using the air-dried format, isatuximab treatment did not cause significant cytokine release for the 2 donors tested.

The applicant investigated whether or not isatuximab induced proliferation of normal blood cells in vitro. Addition of soluble isatuximab alone 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.

The applicant investigated isatuximab-related apoptosis or cell depletion of normal PBMCs in vitro. Isatuximab did not have an effect on the percentage of apoptotic cells of T-cells, B-cells or monocytes subpopulations isolated from PBMC. In 2 of 3 donors SAR650984 resulted in an increase in the percentage of apoptotic cells of isolated NK cells. Isatuximab had a very minor effect on PBMC depletion in vitro. When PBMCs were examined as isolated subpopulation, SAR650984 caused an increase in the number of apoptotic NK cells, while B-cells, T-cell and monocytes are unaffected. Under the same conditions, isatuximab increased the percentage of apoptotic Ramos tumor cells by 50%, while the other antibodies had no effect.

The applicant performed several studies in an attempt to identify a relevant species for the nonclinical safety evaluation of isatuximab. Despite the high percentage of identity (92 to 99%) of chimpanzee, rhesus monkey and cynomolgus monkey with the human CD38 sequence,

studies including target binding (flow cytometry) and tissue cross-reactivity (immunohistochemistry) to determine a preclinical species for testing of isatuximab only identified the chimpanzee as a potential relevant animal species. Since the chimpanzee is not an appropriate species for toxicity studies in general, other alternatives for preclinical safety assessment of isatuximab were explored. At the time of the preclinical development of isatuximab, no adequate transgenic mouse model was available. Consequently, no nonclinical safety studies have been conducted in such model.

The FDA's Assessment:

The FDA agrees with the off-target activity results of isatuximab based on the evaluation of tissue-cross reactivity, binding affinity, induction of cytokine release, proliferation, apoptosis and depletion of human normal blood cells and/or PMBCs. The FDA concurs with the conclusion that no pharmacologically relevant animal species is available for the safety assessment (e.g., in vivo safety pharmacology or toxicology studies) of isatuximab.

Safety Pharmacology

The Applicant's Position:

No specific in vitro or in vivo safety pharmacology studies were conducted with isatuximab. However, the applicant evaluated safety pharmacology endpoints in a weekly repeat-dose GLP intravenous toxicity study conducted with isatuximab in the cynomolgus monkey. No isatuximab-related effects were noted in this study on ECG parameters, blood pressure, gross behavior profile (including body temperature), and respiratory function up to the highest dose tested of 100 mg/kg/week.

In study TSK0154 , Cynomolgus monkeys (26-29 months of age) received NaCl 0.9% (vehicle control group) or aqueous solution of SAR650984 (batch C1053598) at 20, 50 or 100 mg/kg/week by a 0.5-hour intravenous infusion once a week for 3 weeks. Benefit of this study was also taken for introducing an additional group of monkeys (group 5) which received SAR650984 at 100 mg/kg/week under the same conditions using a batch beyond current shelf-life (batch VAB-LCX1-000004 approximately 28-month old) in order to demonstrate that the toxicity profile of an aged batch was not different from the one of a more recently manufactured batch. There were 3 animals/sex/group. After the last administration, the 3 animals/sex/group were euthanized following a 2-day (control group) or 3-day (treated group) observation period.

The parameters evaluated included mortality, clinical signs including examination at injection sites, body weight, ophthalmology, electrocardiography, blood pressure monitoring, neurobehavioral (including neurobehavioral evaluation and body temperature) and respiratory assessments, cytokines analysis, hematology, coagulation, clinical chemistry, and urinalysis. Plasma samples for toxicokinetic and anti-drug antibodies (ADA) determinations were obtained on Days 1 and 15 at several timepoints. The animals were euthanized and necropsied at the end

of the treatment. The absolute and relative weights of the selected organs were recorded, and representative tissue samples were examined microscopically in all the animals.

The weekly repeated intravenous administration of SAR650984 for 3 weeks to Cynomolgus monkeys at doses of 20, 50 or 100 mg/kg/week resulted in no SAR650984-related findings in any parameters and in any groups. There were also no SAR650984-related changes of toxicological significance in any parameters using a batch beyond current shelf-life (batch VAB-LCX1-000004 approximately 28-month old).

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 C_{max} and AUC 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.

The FDA's Assessment:

The FDA agrees that no specific in vitro or in vivo safety pharmacology studies are warranted.

5.4. ADME/PK

The Applicant's Position:

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 tumor xenografts). Animal studies to characterize the pharmacokinetic (PK) properties of isatuximab were conducted by the intravenous (IV) route, as this is the intended route of administration in humans. Doses and infusion times for these studies were selected from within the range used in the toxicology and pharmacology programs. No specific absorption, distribution, metabolism, elimination studies were conducted in animal models with isatuximab as it is a mAb, and is only recognized by the human.

Absorption

In the repeat-dose toxicology study in cynomolgus monkeys, 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). 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.

Distribution *No specific tissue distribution study with a radiolabelled compound was conducted. The distribution of isatuximab in tissue sections was evaluated by immunohistochemistry. In mice, isatuximab is characterized by a low volume of distribution (2.39 to 3.27 mL) which corresponds to blood volume in mice.*
Metabolism *No formal metabolism studies have been conducted with isatuximab. As a large protein, isatuximab, is expected to be metabolized by non-saturable proteolytic catabolism processes.*
Excretion *No specific elimination and excretion studies were conducted. As a large protein, isatuximab, is expected to be eliminated by non-saturable proteolytic catabolism processes. In the absence of the human CD38 target receptor in SCID mice, the PK parameters of isatuximab in SCID mice after a single IV dose were typical of an IgG1 Ab, with a low clearance (0.0662-0.161 mL/day) and a long terminal half-life of 14-26 days.* *In SCID tumor-bearing mice, where the tumor xenografts express human CD38 antigen receptors that can bind isatuximab, clearance decreased with increasing dose, ranging 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).*

TK data from general toxicology studies

SAR650984 - Repeat-dose (once weekly for 3 weeks) intravenous (0.5-hour infusion) toxicity study in cynomolgus monkeys; Study TSK0154

Mean (n=3 per sex/dose, CV %) plasma toxicokinetic parameters of SAR650984 on Week 1 and Week 3

			Week 1				Week 3		
Sex	Group	Dose (mg/kg/week)	C_{max} (µg/mL)	t_{max} [a] (h)	AUC_{0-3d} (µg*day/mL)	AUC_{0-7d} (µg*day/mL)	C_{max} (µg/mL)	t_{max} [a] (h)	AUC_{0-3d} (µg*day/mL)
M	2	20	634 (12)	0.58 [0.58-8]	1040 (14)	1930 (19)	1020 (27)	0.58 [0.58-8]	1920 (20)
	3	50	1300 (17)	0.58	2160 (16)	4060 (13)	2040 (8)	0.58[0.58-2]	4140 (12)
	4	100	2390 (8)	0.58	4430 (8)	8540 (8)	4360 (3)	0.58 [0.58-8]	9670 (5)
	5	100 [b]	2610 (3)	0.58	4530 (3)	8470 (4)	4060 (1)	0.58	8640 (8)
F	2	20	519 (4)	0.58	959 (3)	1870 (5)	994 (7)	0.58	2040 (2)
	3	50	1450 (20)	0.58	2350 (15)	4490 (15)	2800 (35)	0.58[0.58-2]	5540 (36)
	4	100	2840 (1)	0.58	4560 (1)	8600 (1)	4250 (5)	0.58[0.58-2]	9290 (4)
	5	100 [b]	2720 (6)	0.58	4120 (4)	7860 (2)	4090 (2)	0.58	7760 (12)

a: medial [min-max] for t_{max}; b: batch beyond current shelf-life (VAB-LCX1-000004)

TK data from reproductive toxicology studies

No study performed

TK data from Carcinogenicity studies

No study performed

The FDA's Assessment:

The FDA agrees with the results of the ADME studies and the PK parameters summarized by the Applicant.

In the repeat-dose toxicity study in monkeys (Study #TSK0154), there was no detection of anti-drug antibodies (ADAs) in any of the monkeys treated with isatuximab batch C1053598 at any of the dose levels tested (20, 50 and 100 mg/kg/week) or with the vehicle. However, 4 out of 6 animals in Group 5 dosed with 100 mg/kg/week of isatuximab batch VAB-LCX1-000004 (batch beyond current shelf-life) were found positive for ADA development (6 samples). The lower AUC values in these animals may be attributable to the presence of ADAs .

5.5. Toxicology

1.1.1. General Toxicology

The Applicant's Position:

Because an appropriate species for preclinical safety testing could not be identified, toxicology studies with isatuximab were limited to a repeat-dose (once weekly for 3 weeks) toxicity study in cynomolgus monkeys (preceded by a small exploratory study) in order to evaluate potential non-targeted and non-specific general toxicity, a local tolerance study in rabbits and an in vitro compatibility study with human whole blood and plasma.

Study title/ Study number: SAR650984 - Repeat-dose (once weekly for 3 weeks) intravenous (0.5-hour infusion) toxicity study in cynomolgus monkeys / TSK0154

Key Study Findings:

- The weekly repeated intravenous administration of isatuximab for 3 weeks to cynomolgus monkeys at doses of 20, 50 or 100 mg/kg/week resulted in no isatuximab-related findings in any parameters and in any groups.
- There were also no isatuximab-related changes of toxicological significance in any parameters using a batch beyond current shelf-life (batch VAB-LCX1-000004 approximately 28-month old).

Conducting laboratory and location: Sanofi-aventis recherché & developpement, Montpellier, France
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 20, 50, 100, 100* mg/kg/week
Route of administration:	IV
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	3 M, 3F per group, 5 groups
Age:	26-29 months
Satellite groups/ unique design:	*group received drug approximately 28 months old (current shelf-life of 18 months at the time of study) to demonstrate that the toxicity profile of an aged batch was not different from the one of a more recently manufactured batch
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No unscheduled deaths
Clinical Signs	No SAR650984-related clinical signs were observed in any groups. The animal 5F (Group 1- control) presented a rapid and transient convulsion/tremor episode during the ECG recording (animal restrained). Additionally, liquid feces were observed during the pretest and the dosing phases in treated animal groups as well as in control animal group and were thus considered as not SAR650984 related (data kept in the study records).
Body Weights	No SAR650984-related body weight changes were observed in females in any groups. Over the treatment duration, a slight trend for a decreased body weight was observed in all males from Group 5 (100 mg/kg/week, batch VAB-LCX1-000004) from Day 8 upwards. This loss was slight and was considered of no toxicological relevant.
Ophthalmoscopy	There were no SAR650984-related changes in any groups. The following observations recorded in two monkeys at each examination day, including pretest, were unrelated to treatment with the test article: • tigroid aspect of the non-tapetal fundus, bilateral, in animal 27M from Group 5; • optic disc excavation in the left eye from animal 29F from Group 5. These observations belong to the spontaneous abnormalities and to the physiological variations sometimes observed in this species.
ECG	There were no SAR650984-related changes in any groups The animals 8M (20 mg/kg/week), 15M (50 mg/kg/week) and 22F (100 mg/kg/week) showed on Day 1 (2 and 24 hours after dosing) a slight increase in heart rate (up to +16% when compared to pretest values). These variations remained in the range of control animals (up to +14% when compared to pretest values) and were not considered treatment-related. The animal 14M (50 mg/kg/week) showed on Day 1 (2 and 24 hours after dosing) an increase in heart rate (up to +35% at 24 hours after dosing when compared to pretest value). This isolated increase is probably due to a stressed behavior and was not considered as linked to treatment. No abnormal waveforms or arrhythmia were observed in any groups.
Hematology **Clinical Chemistry** **Urinalysis** **Gross Pathology** **Organ Weights** **Histopathology**	*No SAR650984-related changes in hematology, coagulation, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic examinations were observed in any groups.*
Anti-drug antibodies	All samples collected from animals treated with batch C1053598 (at 20, 50 and 100 mg/kg/week) were found negative as well as samples from control group (except one sample found not reportable for animal 1M on Week 1 at 168h).

	Post drug administration, 4 out of 6 animals dosed with 100 mg/kg/week of test article of batch VAB-LCX1-000004 (batch beyond current shelf-life) had a positive status (6 samples). The ADA titration of these samples ranged from 160 to 320, to be compared to the minimum required dilution (MRD) of the assay. The presence of ADA (positive status) on week 3 in samples from animals treated with SAR650984 Batch VAB-LCX1-000004 (group 5), may have a slight impact on SAR650984 exposure with concentrations slightly lower than in animals dosed using batch C1053598.
Other evaluations	No effects were observed on gross behavior profile, body temperature and on respiratory rate (evaluating the central and autonomic nervous systems) on Day 9, after repeated intravenous (0.5 hour infusion) administration of SAR650984 (batch C1053598) at 20, 50 and 100 mg/kg/week in Cynomolgus monkeys. There were also no SAR650984 -related changes on gross behavior profile, body temperature and respiratory rate using a batch beyond current shelf-life (batch VAB-LCX1-000004, 100 mg/kg/week).

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

Study title/ Study number: SAR650984: Single-dose local intravenous, paravenous, intra-arterial, intramuscular and subcutaneous tolerance study in female rabbits / TOL1117

Key Study Findings:

- A single intravenous, paravenous, intra-arterial, intramuscular or subcutaneous administration of isatuximab at concentrations of 1 or 5 mg/mL to female New-Zealand White rabbits produced no compound-related clinical signs or body weight changes.
- There were no compound-related macroscopic or microscopic findings at the injection sites for any route of administration.
- Isatuximab administration was considered to be well tolerated locally.

Conducting laboratory and location: Sanofi-aventis recherché & developpement, Montpellier, France
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 1, 5 mg/mL; single administation
Route of administration:	IV
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	2 or 3 F
Age:	20 weeks
Satellite groups/ unique design:	n/a
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No deaths occurred throughout the study
Clinical Signs	With the exception of a single occasion of reduced feces in one female (No. 20) on Day 2, considered to be incidental, there were no clinical signs noted throughout the study.
Body Weights	Body weight gain was overall similar among animals throughout the study.

Local tolerance	*Intravenous route* Minimal to moderate erythema was noted in all groups from 4 hours after injection mainly up to Day 4. Since the incidence and severity of the erythema were comparable between 0.9% NaCl, vehicle control and SAR650984-treated groups, erythema was not considered related to compound administration but attributed to trauma from the injection procedure. *Paravenous route* Minimal to slight erythema was the main local sign noted in most groups throughout the observation period with a comparable incidence and severity between 0.9% NaCl, vehicle controls and SAR650984-treated groups. This sign was not considered to be related to compound administration but incidental and/or attributed to trauma from the injection procedure. Edema was also noted locally in most animals at the end of injection and was considered related to the administration procedure. Scab/wound was noted on Day 8 in 2 ears treated with the vehicle and 2 ears treated with the 1 mg/mL solution. However, this was not observed in the ears treated with the 5 mg/mL solution (same vehicle composition); therefore this was considered to be incidental. *Intra-arterial route* Slight to moderate hematoma and/or erythema were noted mainly from the time of injection up to Day 4 with a comparable incidence and severity between 0.9% NaCl, vehicle controls and SAR650984-treated groups; this was therefore not considered related to compound administration but attributed to trauma from the injection procedure. Scab/wound was noted on Day 8 in 2 ears treated with the vehicle and 1 ear treated with the 1 mg/mL solution. However, this was not observed in the ears treated with 5 mg/mL solution (same vehicle composition); therefore this was considered to be incidental. *Intramuscular route* There were no local reactions observed in the thighs of rabbits treated with SAR650984 at 1 or 5 mg/mL. *Subcutaneous route* Overall local reactions in flanks treated with SAR650984 at 1 or 5 mg/mL, vehicle control or 0.9% NaCl consisted of edema on Day 1 (mainly at the end of injection) and were considered related to the administration procedure.
Other evaluations	There were no macroscopic observations that were attributable to either SAR650984 or the vehicle. Occasional red focus/area or scab/crust formation, were noted macroscopically at the saline, vehicle or SAR650984 injection sites for all routes of administration except the subcutaneous and intramuscular routes. These findings were attributed to trauma from the injection procedure and not to the test article or vehicle. There were no compound-related or placebo-related microscopic changes at the injection sites for any route of administration.

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

The FDA's Assessment:
There are errors in the "Methods" section of Study #TOL1117. The species/strain used should be rabbits/Lago; INR (NZW), and the route of administration should be intravenous, paravenous, intra-arterial, intramuscular or subcutaneous (IV, PV, IA, IM or SC). Otherwise, the FDA agrees with the Applicant's summary for the general toxicology study in monkeys and the local irritation/tolerance study in rabbits.

General toxicology; additional studies

The Applicant's Position:
No additional GLP studies were performed with isatuximab.

The FDA's Assessment:
The FDA concurs with the Applicant.

1.1.2. Genetic Toxicology

No genotoxicity studies were performed with isatuximab.

The FDA's Assessment:
The FDA concurs with the Applicant that genotoxicity studies are not warranted per ICH guidance S6.

1.1.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies were performed with isatuximab.

The FDA's Assessment:
The FDA concurs with the Applicant.

1.1.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The Applicant's Position:

No study or assessment conducted.

The FDA's Assessment:
FDA concurs.

Embryo-Fetal Development
The Applicant's Position:

No study or assessment conducted.

The FDA's Assessment:
Due to the lack of an appropriate pharmacologically relevant animal species, the evaluation of embryofetal development of isatuximab is based on a weight of evidence (WOE) assessment in lieu of conducting studies in animals. The WOE below contains some references included in this BLA submission.

Weight of Evidence (WOE) based embryofetal developmental toxicity assessment

Exposures to IgG antibodies during pregnancy
Article: "An interspecies comparison of placental antibody transfer: New insights into developmental toxicity testing of monoclonal antibodies (Pentsuk and van der Laan, Birth Defects Research (part B): 86: 328-344, 2009)

Transfer of IgG and large biologics with the Fc portion crossing the placenta is mainly mediated through Fc receptors (FcR). In humans and non-human primates (NHPs), IgG antibodies are known to be transported across the placenta during pregnancy. This transfer begins after the end of the embryonic period, increases during the fetal period, and at the time of term delivery, the neonate has a serum concentration of IgG antibodies that are equal to or exceed that of the pregnant female.

Article: "The placenta, transfer of immunoglobulins, and safety assessment of biopharmaceuticals in pregnancy" (DeSesso et al., Critical Reviews in Toxicology, 42(3): 185-210, 2012)

The authors concluded that there is likely a low risk of direct teratogenicity by maternal exposure to human or humanized Fc-containing biologics during pregnancy. However, fetal

growth and development taking place later in pregnancy can potentially be adversely affected by exposure to Fc-containing drugs.

CD38 expression during pregnancy and postpartum

Article: "Progesterone Modulation of Pregnancy-Related Immune Responses" (Shan et al., Frontiers in Immunology, 9: 1- 19, 2018)

CD38 expression on CD4 and CD8 T cells was reduced at recruitment, minimally before gestation Week 20, and then increased with advancing gestation. During pregnancy there is a significant increase in the percentage of $CD38^{+}CD8^{+}$HLA class II^{+} lymphocytes. This population peaks during the third trimester (Weeks 28-34) and decreases to normal levels 1 month after delivery.

Learning from CD38 genetically deficient animal models

In CD38 knockout animals, CD38 function is completely eliminated as opposed to the partial CD38 inhibition caused by isatuximab. While the information obtained from genetically deficient animals cannot predict the actual effects of the inhibition of CD38 in humans, it can provide insights into the potential role of CD38 in physiological functions in humans, such as the reproductive and developmental effects.

CD38 knockout mice:

- Bone resorption

Article: "Disordered osteoclast formation and function in a CD38 (ADP-ribosyl cyclase)-deficient mouse establishes an essential role for CD38 in bone resorption" (Sun et al., FASEB J 17: 369-375, 2003)

Key finding:

$CD38^{-/-}$ mice displayed a markedly reduced bone mineral density which recovered in 5 months.

Sun et al. investigated the role of CD38, as an ADP-ribosyl cyclase, in bone remodeling. The authors had shown previously that CD38 is expressed both in osteoblasts and osteoclasts. The bone remodeling may be attributable to the function of CD38 to mobilize internal Ca^{2+},stimulation of IL-6, and inhibition of bone resorption. The article reported that $CD38^{-/-}$ mice displayed a markedly reduced bone mineral density (BMD) at the femur, tibia, and lumbar spine at 3 months, with full normalization of the BMD at all sites at 5 months. Hematopoietic stem cells isolated ex vivo from $CD38^{-/-}$ mice showed an increase in osteoclast formation. These findings indicate the involvement of CD38 in osteoclast formation and bone resorption.

- Immune system

Maternal exposure to isatuximab may result in changes in immune function that could affect the maintenance of pregnancy, including effects on fetomaternal immune tolerance. In utero exposure to isatuximab may result in a deficient immune system in a fetus or in a new-born.

Article: "Mice deficient for the ecto-nicotinamide adenine dinucleotide glycohydrolase CD38 exhibit altered humoral immune responses" (Cockayne et al., Blood 92: 1324-1333, 1998)
Key finding:
CD38 may play an important role in regulating humoral immune responses.

CD38-/- mice exhibited marked deficiencies in antibody responses to T-cell–dependent protein antigens (i.e., IgM, IgG1 and IgE, but no changes in response to IgG2, IgG3 and IgA) and augmented antibody responses to at least one T-cell–independent type 2 polysaccharide antigen. Based on these data, CD38 may play an important role in vivo in regulating humoral immune responses.

Article: "Seminal CD38 is a pivotal regulator for fetomaternal tolerance" (Kim et al., PNAS 112 (5): 1559-1564, 2015)
Key finding:
Seminal CD38 is involved in fetomaternal immune tolerance. The deficiency of CD38 in the seminal fluid from CD38 knockout mice resulted in reduced pregnancy rates.

In this study, the authors demonstrated that a soluble form of CD38 (sCD38) released from seminal vesicles to the seminal plasma has an important role in facilitating maternal immune tolerance against the fetus and protecting the semiallogeneic fetus from resorption by inducing the development of uterine tolerogenic dendritic cells and $CD4^+$ forkhead box $P3^+$ ($Foxp3^+$) regulatory T cells. The abortion rate in BALB/c female mice mated with $CD38^{-/-}$ males was high compared with the rate in females mated with $CD38^{+/+}$ males, and this finding was associated with a reduction in the proportion of Tregs within the $CD4^+$ T-cell pool. These data indicate that the seminal CD38 may act as an immune suppressor to establish maternal immune tolerance against the fetus.

Article: "CD38 expression in early B-cell precursors contributes to extracellular signal-regulated kinase-mediated apoptosis" (Romero-Ramirez et al., Immunology 144: 271-281, 2014)
Key findings:
CD38 may be associated with the B-lineage differentiation pathway via ERK-related regulation. $CD38^{-/-}$ mice showed a significant increase in both the frequency of B-lineage cells and the absolute numbers of pre-pro-B cells in the bone marrow. B-cell precursors in mouse bone marrow express functional CD38 and implicate the early ligation of CD38 in the ERK-associated regulation of the B-lineage differentiation pathway.

CD38 knockout frogs:
Article: "The signaling protein CD38 is essential for early embryonic development" (Churamani et al., J Biol Chem 287(10): 6974-6978, 2012)
Key finding:
CD38 is required for vertebrate embryonic development, specifically skeletal muscle differentiation in frogs (xenopus laevis).

The role of CD38 in embryonic vertebrate development was assessed in a model in Xenopus laevis (aka, the clawed frog). Chemical or molecular inhibition of CD38 abolished ADP-ribosyl cyclase activity and disrupted elongation of the anterior-posterior axis and differentiation of the skeletal muscle, resulting in embryonic death. Based on their data, CD38 expression and endogenous ADP-ribosyl cyclase activity are developmentally regulated during cellular differentiation.

Prenatal and Postnatal Development

The Applicant's Position:

No study or assessment conducted.

The FDA's Assessment:

FDA concurs based on the ICH S9 guidance.

1.1.5. Other Toxicology Studies

The Applicant's Position:

No additional study or assessment was conducted.

The FDA's Assessment:

The in vitro study investigating the compatibility and hemolysis potential of isatuximab with human plasma and blood is summarized below.

Study Title: SAR650984: In vitro compatibility study with human whole blood and plasma (Study #HEM0123; Module 4.2.3.7.7.; GLP compliant: OECD)

Human blood samples were collected from healthy volunteers (3 males and 3 females). For the determination of induced hemolysis, whole blood samples were mixed with isatuximab ((b) (4) batch #650984-F04-024) or the vehicle, with dilution at 1:1 and 9:1 (blood or plasma to isatuximab or vehicle ratio). The final concentrations of isatuximab were 1, 2 and 5 mg/mL. The compatibility of isatuximab with human plasma was conducted following the afore-mentioned procedure. When mixed with human whole blood or human plasma under the conditions of this study, isatuximab formulations at the concentrations tested did not induce hemolysis of human whole blood and were fully compatible with human plasma. The concentrations in the study corresponded to a maximum final isatuximab concentration in blood of 2.5 mg/mL.

In addition to the effects described under reproductive and developmental toxicology studies, based on published articles from CD38 knockout animals, CD38 inhibition may be linked to adverse neurological outcomes and impaired glucose tolerance. See the following articles: 1) "Impaired learning and memory in CD38 null mutant mice" (Kim et al., Mol Brain 9 (1): 16,

2016); 2) "CD38 is required for dendritic organization in visual cortex and hippocampus" (Nelissen et al., Neuroscience 372: 114-125, 2018; 3) "CD38 disruption impairs glucose-induced increases in cyclic ADP-ribose, $[Ca^{2+}]_i$, and insulin secretion" (Kato et al., JBC 274(4): 1869-1872, 1999).

X	X
Shwu-Luan Lee Primary Reviewer	Brenda Gehrke Acting Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Isatuximab (SAR650984) is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that specifically binds CD38. The proposed indication is (b) (4) The proposed dosing regimen is 10 mg/kg weekly (QW) during the first cycle (on Days 1, 8, 15, and 22) followed by every 2 weeks (Q2W) on Days 1 and 15 thereafter until disease progression.

The key registration trial (ICARIA; EFC14335) was an open-label, randomized, parallel-group, two-arm, Phase 3 trial which evaluated the efficacy of Isa-Pd compared with pomalidomide and dexamethasone (Pd; control arm) in 307 patients with relapsed or refractory MM who had received at least 2 prior lines of therapy including lenalidomide and a PI alone or in combination. randomized in a 1:1 ratio. The median PFS was significantly longer in the Isa-Pd arm (11.5 months, 95% CI: 8.94 to 13.9) compared to the Pd arm (6.47 months, 95% CI: 4.47 to 8.28). Isatuximab efficacy and safety are supported by Study TCD14079 Part A.

Isatuximab was administered using a "weight-based" infusion method in pivotal Study ICARIA. A new administration method, "fixed-volume infusion", was introduced in Study 14079 part B in 47 patients and is the recommended administration method. Patients weighing ≥ 100 kg will receive a larger amount of isatuximab administered per unit time with this infusion method compared to the weight-based infusion method. Additional data to assesses the frequency and severity of

IRR of the fixed-volume infusion method in patients weighing ≥ 100 kg will be obtained as part of a PMR.

Exposure-efficacy analysis showed that PFS and the probability of ORR increased with increasing isatuximab exposure. No exposure-safety relationship for infusion-related reactions (IRR), thrombocytopenia, neutropenia, lymphopenia, or respiratory events were observed. Intrinsic factors, including age, gender, renal and hepatic impairment do not have clinically meaningful effect on the PK of isatuximab. Population PK analyses indicated that isatuximab exposure increased with increasing patient weight, supporting the weight-based dosing approach. An average 2-fold lower exposure is predicted in IgG MM patients compared to non-IgG patients; however, no dose adjustment is recommended.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The applicant summarized the pharmacokinetic (PK) and pharmacodynamic (PD) properties of isatuximab based on results from more than 500 patients with MM enrolled in 6 clinical studies that were completed by 15 November 2018, corresponding to the dossier cut-off date. Population PK and population PK/PD analyses were conducted per prespecified analysis plans using pooled data from Phase 1, 1/2, and 3 studies. Two isatuximab drug materials have been used during the clinical development program: (b) (4) hereafter referred to as isatuximab (b) (4)) was used in the initial clinical trials and (b) (4) ((b) (4) hereafter referred to as isatuximab (b) (4)), was introduced in 2015 using the same cell line, and is the drug material intended for commercial use.

The PK and PD data from two single agent Phase 1/2 studies, accounting for approximately half of the overall data, are considered as key information (TED10893 Phase 1, Phase 2 Stages 1 and 2; TED14154 Part A). The PK and PD data of isatuximab administered in combination with Pd in the target population of RRMM were obtained from a 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 included (TCD11863 in combination with lenalidomide and dexamethasone and TCD13983 in combination with bortezomib, cyclophosphamide, and dexamethasone).

No dedicated clinical pharmacology studies were conducted. Because isatuximab is a therapeutic monoclonal antibody, its metabolism is expected to be limited to proteolytic catabolism to small peptides and individual amino acids; hence no metabolism or excretion studies were conducted.

No specific clinical pharmacology studies were conducted on intrinsic factors such as age, gender, race, body weight, or hepatic and renal function. Additionally, specific clinical studies

Reference ID: 4568595

to investigate the effect of these intrinsic factors were not performed as isatuximab is an antibody and its disposition is not expected to be impacted by renal or hepatic impairment. Therefore, all of these intrinsic factors were evaluated using the population PK approach.

Direct drug-drug interaction (DDI) via CYP enzymes or transporters is not expected because isatuximab is a therapeutic monoclonal antibody. However, cytokine levels were extensively monitored after single and repeated administrations of isatuximab in all patients in first in human study, TED10893 Phase 1. Given the extent and transient nature of isatuximab-induced cytokine elevation, its impact on exposures to CYP substrates is likely to be limited. No specific drug-drug interaction studies have been conducted with isatuximab. In Phase 1b combination studies, the effect of other drugs on the PK of isatuximab and vice versa was evaluated based on cross-study comparisons, population PK approach, and literature data.

The FDA's Assessment:

FDA agrees with the applicant's position.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's Position:

The proposed dose regimen of isatuximab when given in combination with Pd in MM patients is 10 mg/kg QW for 4 weeks followed by Q2W.

The applicant explored various isatuximab doses and regimens for treatment of MM in the single agent setting to support dose and schedule selection. Following dose escalation over a wide range (0.0001 to 20 mg/kg, Q2W or QW) in study TED10893 Phase 1, isatuximab doses of 3 to 20 mg/kg were determined to be relevant for dose/schedule finding in Phase 2 of single agent study TED10893. Based on the desire to minimize dosing frequency, two types of regimens were evaluated: Q2W regimens (3 mg/kg, 10 mg/kg) and regimens with an initial loading dose (10 mg/kg Q2W for two 28-day cycles followed by Q4W and 20 mg/kg QW for one 28 day cycle followed by Q2W). Clinical results showed a clear dose response (in terms of ORR) relationship between the 3 mg/kg and doses ≥10 mg/kg, but no clear increase in ORR between 10 and 20 mg/kg. PK/PD modeling and simulations of ORR and serum M-protein showed that intensification of dosing from Q2W to QW in the loading phase provided a better efficacy response as did the higher dose of 20 mg/kg compared to 10 mg/kg in single agent with no clear benefit when extending the loading dose period from 4 to 8 weekly administrations. Based on these results, isatuximab 20 mg/kg QW administration for 4 weeks followed by Q2W (QW/Q2W) was chosen for subsequent Phase 2 single agent studies to maximize the possibility of benefit in single agent therapy.

Combination studies with lenalidomide or pomalidomide and dexamethasone leveraged the

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knowledge gained from the single agent studies for isatuximab dose selection. Phase 1b study TCD11863 of isatuximab in combination with Ld initially evaluated isatuximab administered Q2W in a dose escalation phase and an expansion cohort and then explored the safety, efficacy, and PK of isatuximab 10 and 20 mg/kg QW/Q2W regimens. Later, isatuximab doses of 5, 10, and 20 mg/kg QW/Q2W were assessed in combination with Pd in Phase 1b study TCD14079 Part A. The clinical data from the 2 combination studies showed no difference in responses (ORR) for patients treated with either 10 mg/kg or 20 mg/kg isatuximab. Similarly, PK/PD modeling and simulations of ORR and serum M-protein predicted minimal additional efficacy when increasing the isatuximab dose from 10 to 20 mg/kg. Therefore, 10 mg/kg QW/Q2W was selected for the pivotal Phase 3 study EFC14335 with IPd.

Finally, the proposed isatuximab dose of 10 mg/kg QW/Q2W in combination with standard doses of Pd for the target indication was confirmed based on the results from the pivotal Phase 3 study EFC14335 and supported by exposure-response analyses for safety and efficacy.

The FDA's Assessment:

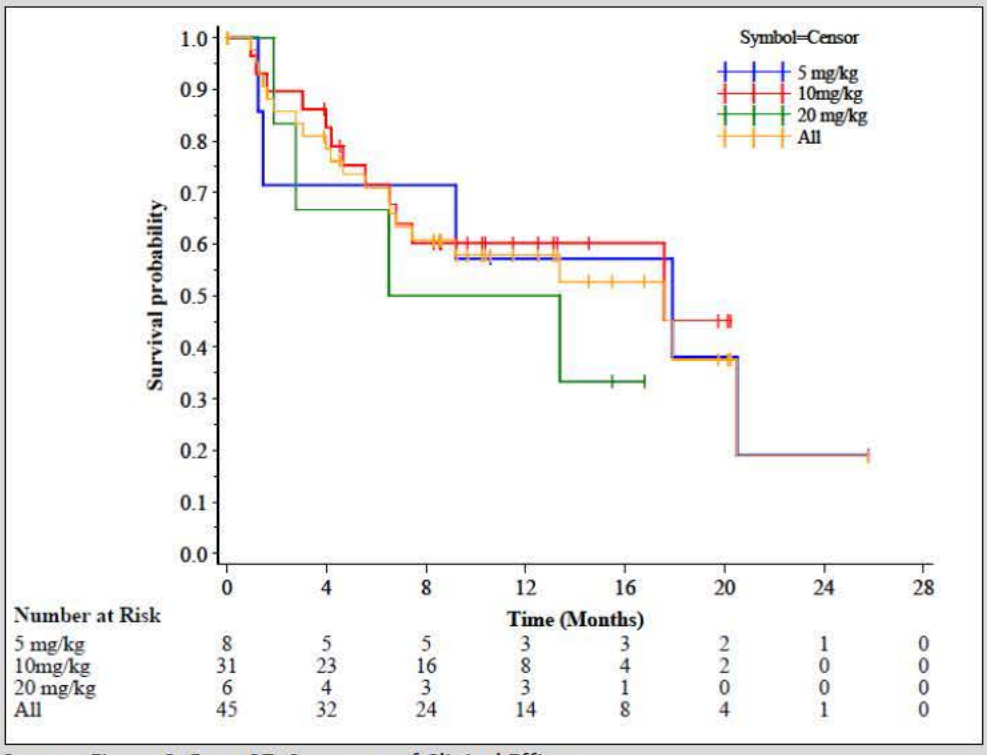
The FDA agrees with Applicant's position. The FDA agrees that a comparison of efficacy between dosage regimens 10 and 20 mg/kg QW/Q2W in Study TCD14079 Part A does not support an increase of the dosage regimen to 20 mg/kg QW/Q2W as summarized in Table 4 and Figure 9.

Table 4. PFS and ORR Summary for All Treated Population in Study TCD14079 Part A.

Study	Dose	ORR %	Median PFS (95% CI)
TCD14079 Part A	10 mg/kg QW/Q2W (n=31)	64.5%	17.6 months (6.80 to NC)
	20 mg/kg QW/Q2W (n=6)	50%	9.9 (2.76 to NC)

Source: Adopted from Table 31, Page 86, and Table 32, Page 88, Summary of Clinical Efficacy.

Figure 9. Kaplan-Meier Plot of PFS by Dosage Regimen in Study TCD14079 Part A.



Source: Figure 9, Page 87, Summary of Clinical Efficacy.

FDA does not agree with the relevance of the data from the Phase 1b Study TCD11863 in which isatuximab is given in combination with lenalidomide and dexamethasone on the dose selection of isatuximab administered in combination with pomalidomide and dexamethasone.

The (b) (4) isatuximab was administered using a "weight-based" infusion method in the pivotal Study ICARIA and most of the isatuximab development program. The fixed-volume infusion method was introduced in Study TCD14079 part B, which evaluated the safety as assessed by incidence of Grade ≥3 IRs of isatuximab in 47 patients. The fixed-volume infusion method employs a varying infusion rate in mL/hour and utilizes a fixed volume of 250 mL for all patients. (b) (4)

The frequency and severity of IRR associated with the fixed-volume infusion method in patients that weigh ≥ 100 kg will be obtained in a PMR. Refer to Section 6.3.2 for additional details on the analyses and rationale for the PMR.

Therapeutic Individualization

The Applicant's Position:

No dose adjustments based on demographic or disease characteristics are recommended. The main sources of intrinsic PK variability identified in patients based on population PK analysis are myeloma type (IgG versus non IgG), β2 microglobulin and body weight. Myeloma type had the

greatest impact: patients producing serum IgG M-protein demonstrated higher linear clearance than patients secreting other types of immunoglobulin or free-light chains (non-IgG myeloma), which translated into a two-fold lower steady-state exposure in IgG patients compared to non-IgG patients. However, this difference in exposure does not impact the efficacy or the safety. Other statistically significant covariates showed limited to moderate effect with a maximal variation in steady state exposure less than 30% compared to the median value. In addition, the impact of weight is considered with weight based dosing of isatuximab. The other demographic characteristics (age, race, or gender) had no to limited effect on the PK of isatuximab.

The FDA's Assessment:

FDA agrees with the applicant's position that no therapeutic individualization is needed based on Ig type multiple myeloma (i.e., IgG vs non-IgG), demographic factors (age, sex), in patients with hepatic, or in patients with renal impairment based on population PK analyses. An effect of age, sex, renal and hepatic impairment is not expected as isatuximab is a monoclonal antibody and its disposition is not expected to be impacted by renal or hepatic impairment. Body weight was identified as a significant covariate in the population PK analysis, with an increase in CL with increasing body weight, which supports the weight-based dosing approach.

Outstanding Issues

The Applicant's Position:

The applicant has identified no outstanding issues.

The FDA's Assessment:

As outlined in Section 6.2.2, the data supporting the use of the fixed volume is limited to frequency and severity of IRR in 47 patients.

A PMR is requested to compare the occurrence and severity of IRR, occurrence of infusion interruptions, infusion rate reductions, and discontinuation during the first two infusions of isatuximab administered via the fixed-volume infusion method in patients weighing ≥ 100 kg. See Section 13 for additional details on the PMR language and timeline.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Isatuximab displays nonlinear PK with target mediated drug disposition (TMDD). Isatuximab exposure increases in a greater than dose proportional manner from 1 to 20 mg/kg following every 2 weeks (Q2W) schedule, while no deviation to the dose proportionality is observed between 5 and 20 mg/kg weekly (QW). These findings are due to a combination of parallel linear and nonlinear elimination pathways. In the range of plasma concentrations achieved

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with a 10 mg/kg QW/Q2W dose and schedule, the linear clearance is the predominant pathway as it represents approximately 90% of total clearance at steady state, elimination indicative of the saturation of the target. Additionally, linear clearance is time dependent with a decrease by 50% from its initial value over the first 8 weeks of treatment predicted for a typical patient based on population PK analysis. This reduction in linear clearance over time is believed to be due to the treatment related reduction in inflammation and IgG M protein, thereby leading to a greater proportion of isatuximab going through the salvage pathways. Isatuximab exhibits a low volume of distribution (8.75 L), which indicates it is primarily distributed into the circulatory system. The typical half-life at steady state associated with the linear clearance is 28 days. The median time to reach steady state is 8 weeks for 10 mg/kg QW/Q2W schedule, with 1.8 (Cmax) to 3.1 (C_{trough}) fold accumulation.

Pharmacodynamic modulation was demonstrated 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 consistently seen in patients treated with isatuximab as a single agent or in combination with Pd.

None of the biomarkers tested on myeloma plasma cells (CD38 receptor density, CD38 mRNA) or in peripheral blood (soluble CD38, immune cell subsets, FCGR3A genotypes) were found to predict response to isatuximab treatment.

The FDA's Assessment:

FDA generally agrees with the applicant's position on general pharmacology and pharmacokinetic characteristics. The general overview of isatuximab ADME and clinical PK information as assessed by FDA are presented in Table 5:

Table 5: Highlights of Clinical Pharmacology for Isatuximab

Physiochemical properties	
Chemical structure and molecular weight	Isatuximab is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody (mAb) produced from a mammalian cell line (Chinese hamster ovary, CHO) using a fed-batch production process. Isatuximab is composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains and has an overall molecular weight of approximately 148 kDa.
Pharmacology	
Mechanism of Action	Isatuximab is an IgG1-derived monoclonal antibody that binds CD38 expressed on the surface of hematopoietic and tumor cells, including multiple myeloma cells. Isatuximab induces apoptosis and activation of immune effector mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Isatuximab inhibits the ADP-ribosyl cyclase activity of CD38. Isatuximab can activate natural killer (NK) cells in the absence of CD38 positive target tumor cells and suppresses CD38-positive T-regulatory cells.
Active Moieties	Isatuximab

QT/QTc Prolongation	Isatuximab is a monoclonal antibody; prolongation of the QT interval is unlikely. No changes were noted in any cardiac parameters evaluated in the safety pharmacology study in cynomolgus monkey. Thorough ECG monitoring was performed in Phase I Study TED10893 (0.3 mg/kg – 20 mg/kg) and did not show clinically relevant changes from baseline for any of the ECG parameters evaluated including QTcF. In Study TED10893, one patient experienced sinus tachycardia which was associated with an infusion-related reaction.
General Information	
Bioanalysis	In the pivotal Study ICARIA, isatuximab was measured using a enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantification (LLOQ) of 0.50 ng/mL (0.0005 µg/mL). The method had adequate sensitivity for assessment of PK of isatuximab as well as acceptable within- and between-run accuracy (-6.6 to 14%) and precision (2.2 to 6.2%). Long term (up to 15 months) stability of isatuximab in frozen human plasma at -20°C and -80°C was demonstrated. Incurred sample reanalysis (ISR) for plasma isatuximab assay was performed on samples from Study ICARIA and met the acceptance criteria. A summary of the method validation reports is included as an appendix.
Healthy Volunteers vs. Patients	Isatuximab was not administered to healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen	In adult patients who received isatuximab 10 mg/kg QW/Q2W in Study ICARIA, the population PK approach derived mean steady-state C_{max} (CV%), $AUC_{0\text{-}2weeks}$, and Ctrough (Cycle 6) were 351 µg/mL (36.0%), 72600 µg.h/mL (51.7%), and 157 (68.1) µg/mL, respectively.
Dose Proportionality	Isatuximab AUC generally increases in a greater than dose proportional manner over a dosage range from 1 mg/kg to 20 mg/kg when administered Q2W; however, no deviation to the dose-proportionality is noted at doses ≥ 5 and up to 20 mg/kg QW or Q2W. Isatuximab total clearance decreased with increasing doses due to target mediated drug disposition (TMDD).
Accumulation	The accumulation ratios (R_{acc}) at steady state following isatuximab 10 mk/kg QW/Q2W is 1.9 for C_{max} and 3.3 for C_{trough}.
Variability	Isatuximab exhibits moderate to large inter-patient variability. Population PK analysis approach-derived variability (CV%) in isatuximab linear CL at steady state, central volume of distribution is 47.5% and 25.7%, respectively. Following administration of isatuximab 10 mg/kg QW/Q2W in combination with pomalidomide and dexamethasone, the inter-subject variability (CV%) of steady state isatuximab AUC_{tau}, C_{max}, and C_{trough} was 36.0%, 51.7% and 68.1%, respectively, based on population PK analysis approach.
Absorption	
Bioavailability	Isatuximab is administered as intravenous infusion; bioavailability is 100%.
T_{max}	Generally, at end of infusion but when it is delayed Cmax values were close to C_{eoi} (Concentrations at the end of infusion).
Distribution	

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Volume of distribution	The population PK approach-derived mean central and peripheral apparent volumes of distribution of isatuximab at steady-state are 5.13 L and 3.62 L, respectively.
Elimination	
Half-life	At steady state, the near elimination (≥99%) of isatuximab from plasma after the last dose is predicted to occur in approximately 2 months.
Clearance	The population PK approach-derived mean linear clearance (%CV) of isatuximab is 0.229 L/day (47.5%).
Metabolism	
Primary metabolic pathway(s)	Since isatuximab is a monoclonal antibody, it is expected to be catabolized by various unsaturable proteolytic enzymes.
Excretion	
Primary excretion pathways (% dose) ±SD	Not applicable as isatuximab is a monoclonal antibody.
Interaction liability	
Inhibition/Induction of Metabolism and Transporter Systems	No formal drug-drug interaction studies have been conducted for isatuximab. Since isatuximab is a monoclonal antibody and is not expected to have immunomodulatory activities, drug-drug interactions through inhibition or induction of metabolizing enzymes or transporter systems are not anticipated.

Source: Prepared by the reviewer.

6.3.2. Clinical Pharmacology Questions

1.1.5.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. The clinical pharmacology data support the proposed dose regimen of 10 mg/kg QW for 4 weeks followed by Q2W when given in combination with Pd in MM patients.

There were a number of factors considered in the isatuximab dose/regimen selection in combination with pomalidomide. These were derived from modeling using data obtained from three primary settings: isatuximab as a single agent, or in combination with either pomalidomide/dexamethasone or lenalidomide/dexamethasone as detailed below:

- An exploratory analysis between isatuximab plasma concentration and CD38 receptor occupancy at one month showed that 99% of plateau for occupancy was reached for plasma concentrations of approximately 30 µg/mL.
- The pharmacokinetic behavior of isatuximab demonstrated substantial TMDD which was evident, especially in individual patients, at doses below 5 mg/kg. Above this dose, specifically at isatuximab doses of 10 mg/kg QW, 20 mg/kg Q2W and QW, TMDD was no

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longer evident, indicative of saturation of the target for these doses/regimens. Coincidentally, 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.

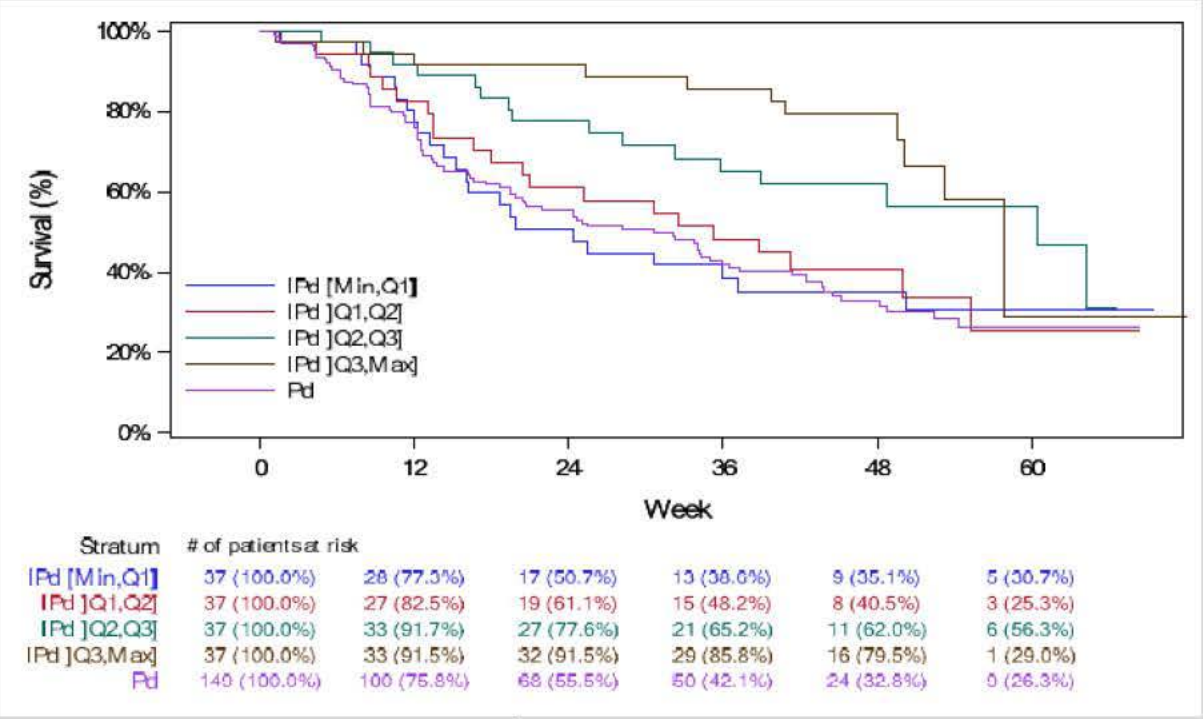
- A clear PK/PD relationship for the impact of isatuximab on serum M-protein was evident but had different characteristics dependent on the therapeutic setting (single agent versus combination setting). In the single agent setting, in patients with measurable serum M-protein, isatuximab produced a dose 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, both with pomalidomide/dexamethasone and lenalidomide/dexamethasone, the overall reduction in serum M-protein was far 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.
- A clear PK/PD relationship for the impact of isatuximab on ORR was evident but had different characteristics dependent on the therapeutic setting. In the combination setting (pomalidomide/dexamethasone), the ORR was far 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.

Considering the totality of the data for receptor occupancy, saturation of the target as indicated by lack of TMDD, dose /concentration relationships for serum M protein and ORR, a 10 mg/kg QW/Q2W dose regimen for isatuximab was chosen for the pivotal Phase 3 study with IPd. Clinical data from the Phase 3 study EFC14335 confirmed the efficacy and safety of this dosing regimen.

The FDA's Assessment:

FDA generally agrees with applicant's position. The exposure-efficacy analysis based on Study ICARIA showed that PFS and probability of ORR increase with increasing isatuximab exposure across the different quartiles of isatuximab CT4W as shown in Figure 10 and Figure 11. The interpretation of effectiveness at the lowest quartile is confounded by baseline risk factors such as disease severity as well as dose modifications occurring due to adverse events and infusion-related reactions after the first infusion as summarized in Section 18. There was no exposure-safety relationship for thrombocytopenia, neutropenia, lymphopenia, or respiratory events within the isatuximab exposure levels between the quartiles. Hence, isatuximab in combination with pomalidomide and dexamethasone has a positive benefit-risk ratio at a 10 mg/kg QW/Q2W dosage regimen.

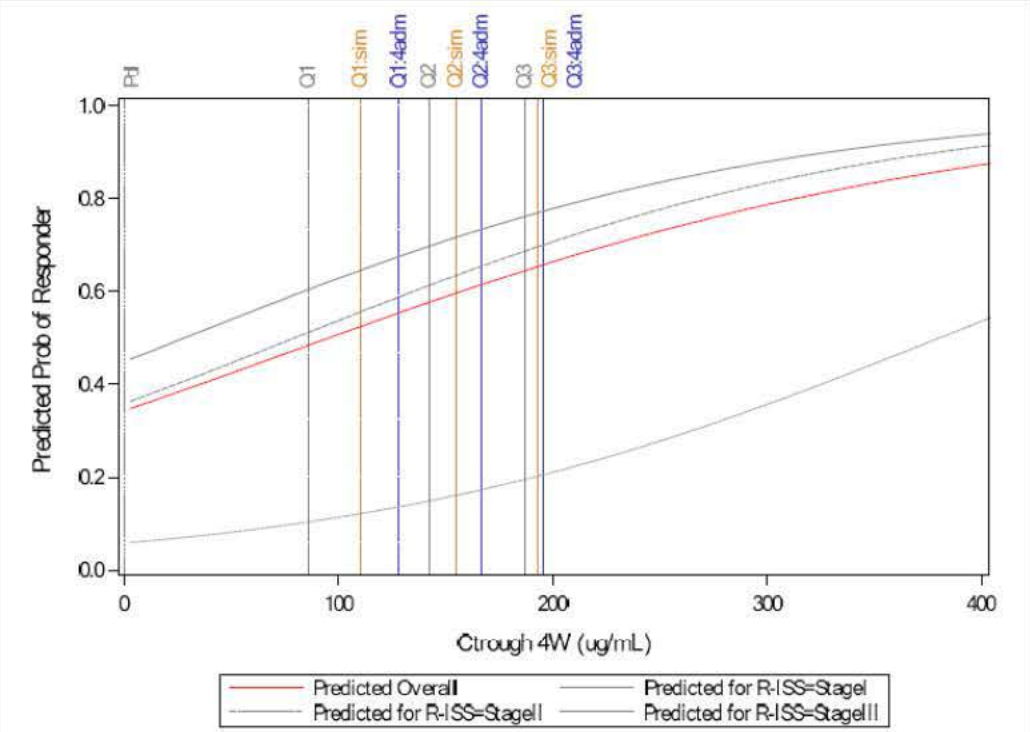
Figure 10. Kaplan-Meier Estimates of PFS by CT4W Quartiles.



Stratum	# of patients at risk					
Pd [Min,Q1]	37 (100.0%)	28 (77.5%)	17 (50.7%)	13 (36.6%)	9 (35.1%)	5 (30.7%)
Pd]Q1,Q2]	37 (100.0%)	27 (82.5%)	19 (61.1%)	15 (48.2%)	8 (40.5%)	3 (25.3%)
Pd]Q2,Q3]	37 (100.0%)	33 (91.7%)	27 (77.6%)	21 (65.2%)	11 (62.0%)	6 (56.3%)
Pd]Q3,Max]	37 (100.0%)	33 (91.5%)	32 (91.5%)	29 (85.8%)	16 (79.5%)	1 (29.0%)
Pd	140 (100.0%)	100 (75.8%)	68 (55.5%)	50 (42.1%)	24 (32.8%)	9 (26.3%)

Source: Figure 13, Exposure-response report poh0648.

Figure 11. Model-Predicted Probability of ORR by Quartiles for 10 mg/kg QW/Q2W.



Q represents the predicted proportion of responders for each quartile of CT4W group for overall population. Qsim represents the predicted proportion of responders for each quartile of CT4W group assuming all patients received 4 weekly administrations. Q 4admin represents the predicted proportion of responders for each quartile of CT4W for patients who completed 4 weekly administrations.

Source: Figure 12, Exposure-response report poh0648.

Based on the clinical results of Study ICARIA as summarized in Section 8.1.2, and a positive risk: benefit assessment, the isatuximab 10 mg/kg QW/Q2W dosage regimen in combination with pomalidomide and dexamethasone is acceptable for approval from a clinical pharmacology perspective. Additional details regarding the efficacy results of Isa-Pd and the Kaplan Meier curves of PFS by treatment group in Study ICARIA can be found in Section 8.1.2.

1.1.5.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The efficacy and safety for IPd 10 mg/kg QW/Q2W which were demonstrated in pivotal study EFC14335 were confirmed by exposure-response analyses for safety and efficacy. In addition, immunogenicity was not a clinical concern and clinical PK, PK/PD, safety, and efficacy analyses confirm the similarity of isatuximab (b) (4) used in the Phase 3 study and intended for commercialization to isatuximab (b) (4) used in earlier studies.

In the exposure-response analyses for efficacy with either single agent or combination therapy, isatuximab C_{trough} at 4 weeks at the end of the loading phase (CT4W) was determined to be the best PK exposure predictor of response (ORR and PFS). A logistic regression model best described the relationship between ORR and log CT4W, with an increase in ORR as log CT4W increased. Predicted ORR at 10 mg/kg QW/Q2W was higher compared to 10 mg/kg Q2W for IPd (67% versus 47%).

In the exposure-response analyses, the Ig MM type was a predictor of the response (ORR), but was no longer significant when C_{trough} at 4 weeks was included in the model. Additionally, Ig MM type was not a significant covariate in the univariate analysis for efficacy. Lastly in the subgroup analyses of clinical data from the Phase 3 study EFC14335, there was no significant difference in treatment effect of the IPd regimen over the Pd regimen on PFS or ORR for IgG patients versus non-IgG patients, with improved response rates in the IPd arm over the Pd arm observed both for IgG patients and non-IgG patients. In conclusion, the impact of Ig MM type (IgG versus non-IgG) on isatuximab exposure does not appear to be clinically meaningful.

For IPd therapy, there was no apparent relationship between isatuximab exposure and the incidence of the safety endpoints of interest including infusion reactions, thrombocytopenia, anemia, neutropenia, lymphopenia, respiratory adverse events, cardiac arrhythmia, cardiac and nervous system disorders and infections except for endpoints related to myeloma disease control (anemia and infections).

In antidrug-antibody (ADA) evaluable patients from all completed studies (N=564), the incidence of treatment emergent ADAs was low (2.3%), with 2 patients having a persistent treatment induced ADA (0.35%). However, since no confirmed positive ADA samples were detected in the pivotal Phase 3 study, the neutralizing ADA status was not determined. No effect of ADAs was observed on PK, safety or efficacy of isatuximab.

The FDA's Assessment:

The FDA agrees with the Applicant's position regarding the proposed dose of isatuximab 10 mg/kg QW/Q2W in combination with pomalidomide and dexamethasone.

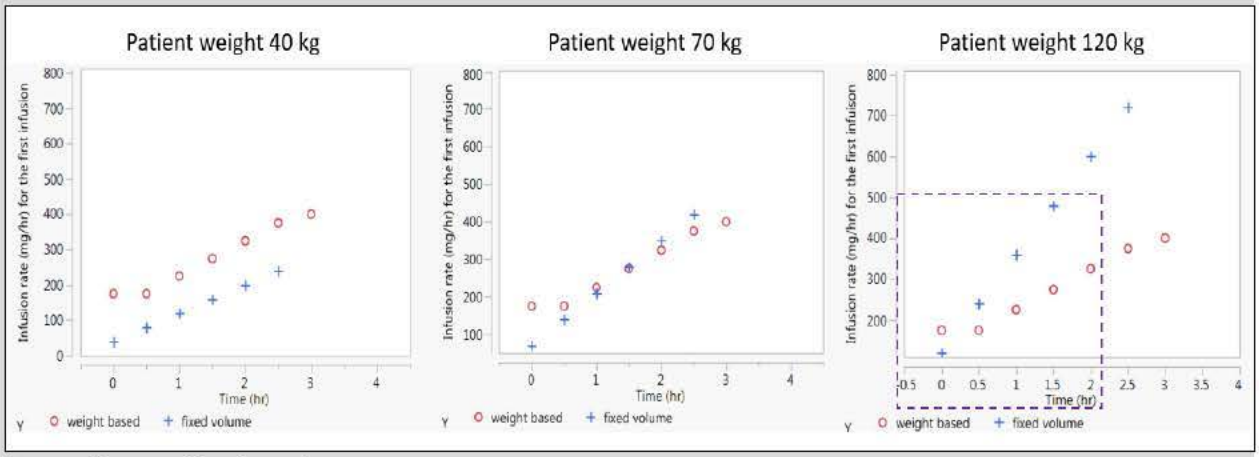
The FDA notes that isatuximab was administered using a weight-based infusion method in the pivotal Study ICARIA and most of isatuximab drug development program. The isatuximab infusion volume using this method depended on the patient's weight; the rate of infusion was prescribed as mg per hour (mg/h) with fixed infusion rate in mg/hour for all patients, and the total infusion volume ranged from 50 to 500 mL. A new administration method, "fixed-volume infusion" method was introduced in Study TCD14079 part B, a Phase 1b trial which evaluated the safety as assessed by incidence of Grade ≥3 IRs of isatuximab in 47 patients with no evaluation of the PK. The fixed-volume infusion method employs a varying infusion rate in mL/hour and utilizes a fixed volume of 250 mL for all patients.

It is important to note that given the use of a fixed volume (i.e., 250 mL infusion bag) in the fixed-volume infusion method, and given that the administration is expressed as volume units per time (i.e., mL/hour), the amount of isatuximab administered per time varies for patients according to

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their weight. A comparison of isatuximab infusion rates (mg/hr) for the first infusion is shown in Figure 12 for representative patients weights of 40, 70, and 120 kg.

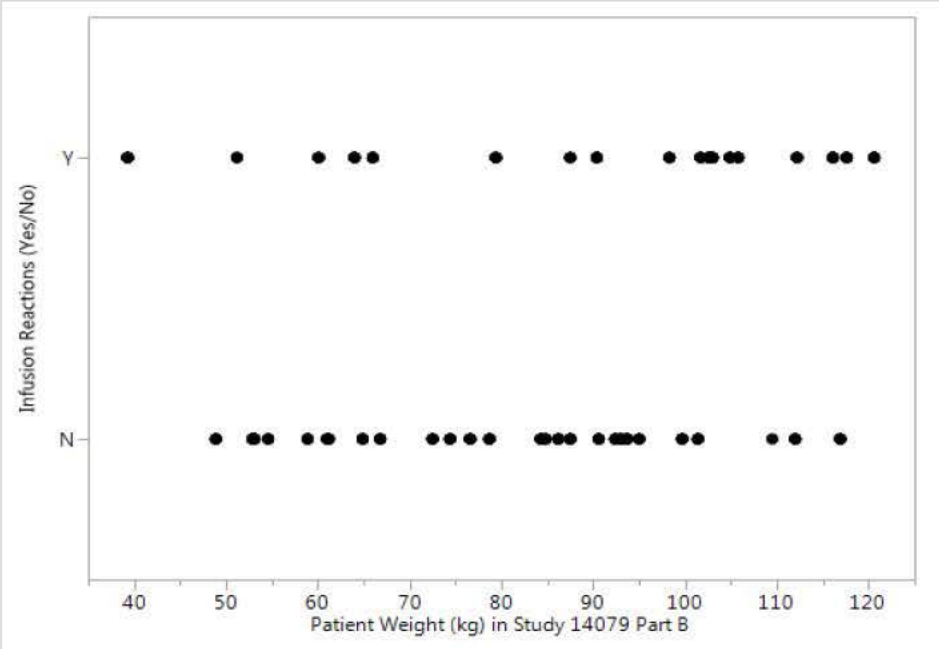
Figure 12. A Comparison of Isatuximab Infusion Rate in mg/hour for the First Infusion for Representative Patient Groups of 40, 70, and 120 kg.



Source: Prepared by the reviewer.

As shown in Figure 12, patients on the upper extreme of the weight distribution have a larger amount of isatuximab administered per time using the "fixed-volume" infusion method compared to the weight-based infusion method. Figure 13 displays the distribution of IRRs across the weight range of patients in Study 14079 Part B and displays comparable frequency of IRRs across the weight range 40-100 kg.

Figure 13. Bubble Plot of IRR Occurrence vs Weight in Study TCD14079 Part B (Fixed-volume Infusion Method).



Source: Prepared by the reviewer.



Table 6. Comparison of IRR Profile between TCD14079 Part B and ICARIA.

Study	**TCD14079 Part B (n=47)**	**ICARIA (n=152)**
Infusion method	Fixed volume	Weight based
Weight range	40-120 kg (Mean 85 kg)	34-110 kg (Mean 74 kg)
% patients with IRR	40.4% (n=20) *1 patient had two episodes (21 IRR occurrences)	38.2% (n=58) *6 patients had two episodes (64 IRR occurrences)
Consequence (%)	Dose interruption (100%)	Dose interruption: 48 patients (83%) Permanent withdrawal: 4 patients (6.8%)
% Grade 1	Zero	10% (n=6)
% Grade 2	100%	83% (n=48)
% Grade 3, Grade 4	Zero	Grade 3: 3% (n=2) Grade 4: 3% (n=2)
% IRR at first infusion	100% of all IRRs (total 21 episodes)	92% of all IRR episodes (total 64 episodes)
% IRR at ≥ 2nd infusion	Zero	7.8% of all IRR episodes (total 64 episodes)

Source: Prepared by the reviewer.

Given the limited number of patients (n=12) at the upper extreme of the weight distribution (≥ 100 kg), and the much larger amount administered per time in these patients using the fixed-volume infusion method compared to the weight-based infusion method, a Post-Marketing Requirement (PMR) is issued to assess the frequency and severity of IRR of the fixed-volume infusion administration method in patients weighing ≥ 100 kg.

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1.1.5.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

Population PK analysis using data from Phase 1 to 3 studies with 476 patients aged 36 to 85 years (14.7% of patients in the dataset were >75 years of age) did not identify age as a significant covariate influencing isatuximab PK. Therefore, no dose adjustments are recommended for elderly patients.

Among the 476 patients in the population PK dataset, 207 (43.5%) were female and 269 (56.5%) were male. Population PK analysis identified gender as a significant covariate influencing isatuximab V1 (i.e., 12% lower in a typical female patient relative to a typical male patient). However, as the impact was limited to V1, it did not translate to a meaningful impact on exposure. Therefore, no dose adjustments are recommended based on gender.

Population PK analysis with data from 377 Caucasian (79% of the population PK data set), 25 Asian (5%), 18 Black (4%), and 33 other race (7%) identified race (Asian versus non-Asian) as a significant covariate influencing isatuximab pharmacokinetics. However, as the impact was limited to V1 (ie, 24% lower in a typical Asian patient compared to a typical non-Asian patient), it did not translate to a meaningful impact on exposure. The steady state post-hoc exposure in Black patients appeared to be lower compared to Caucasian patients (27% at steady state) at 10 mg/kg QW/Q2W, while exposure was comparable at Cycle 1 for the two populations. However, taking into account the small number of patients (N=18) and because the subgroups are not balanced across all covariates in this univariate assessment to allow for a fair comparison, this is not considered to be a true race effect (Black versus non Black). Overall, no dose adjustments are recommended based on race.

Body weight was identified as a significant covariate in the population PK analysis, with a 26% increase in linear CL at steady state and 19% increase in V1, for a body weight of 109.5 kg (95th percentile in the population PK dataset) and a 21% and 17% decrease in linear CL at steady state and V1 respectively, for a body weight of 51.3 kg (5th percentile) compared to 75.6 kg (median weight). Of note, body weight-based dosing allows to slightly reduce the variability.

Population PK analyses did not identify estimated glomerular filtration rate (e-GFR) as a significant covariate influencing isatuximab PK. Among the 476 patients included in the population PK analysis, 192 patients were identified with mild renal impairment (60 mL/min/1.73 m^2 ≤ e GFR <90 mL/min/1.73 m^2), 163 patients with moderate renal impairment (30 mL/min/1.73 m^2 ≤ e GFR <60 mL/min/1.73 m^2) and 12 patients with severe renal impairment (e GFR <30 mL/min/1.73 m^2). Based on these findings, no dose adjustment is recommended in patients with mild to severe renal impairment.

Population PK analyses did not identify bilirubin or transaminases as significant covariates

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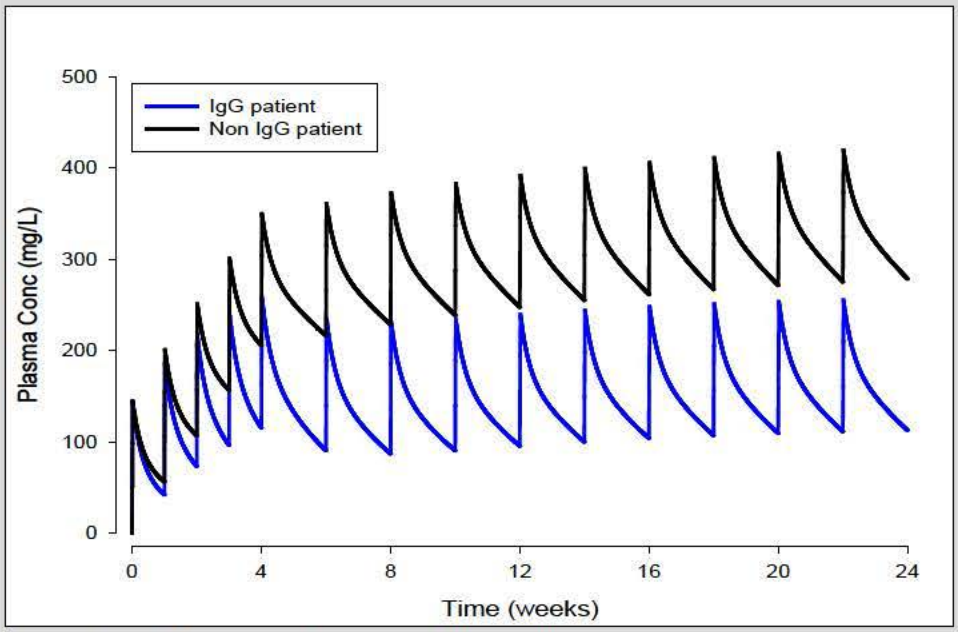
influencing isatuximab pharmacokinetics. Among the 476 patients included in the population PK analysis, 65 patients were identified with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × upper limit of normal [ULN] or AST >ULN), and only 1 patient with moderate hepatic impairment (total bilirubin >1.5 - 3 × ULN and any AST). Therefore, dose adjustment is not recommended for mild hepatic impairment. No conclusion can be drawn for patients with moderate hepatic impairment (N=1 only).

The FDA's Assessment:

FDA agrees with the applicant's position that there is no need for alternative dosing regimen for subpopulations based on the intrinsic factors of age, race, sex, mild, moderate, and severe renal impairment, as well as mild hepatic impairment based on the population PK analysis results.

The FDA acknowledges that patients with IgG-type MM demonstrated higher clearance compared to patients with non-IgG MM resulting in $AUC_{0\text{-}4weeks}$, $C_{troughWeek4}$ and steady state C_{trough} and AUC_{tau} that are approximately 30-60% in IgG MM patients compared to non-IgG MM patients (Figure 14).

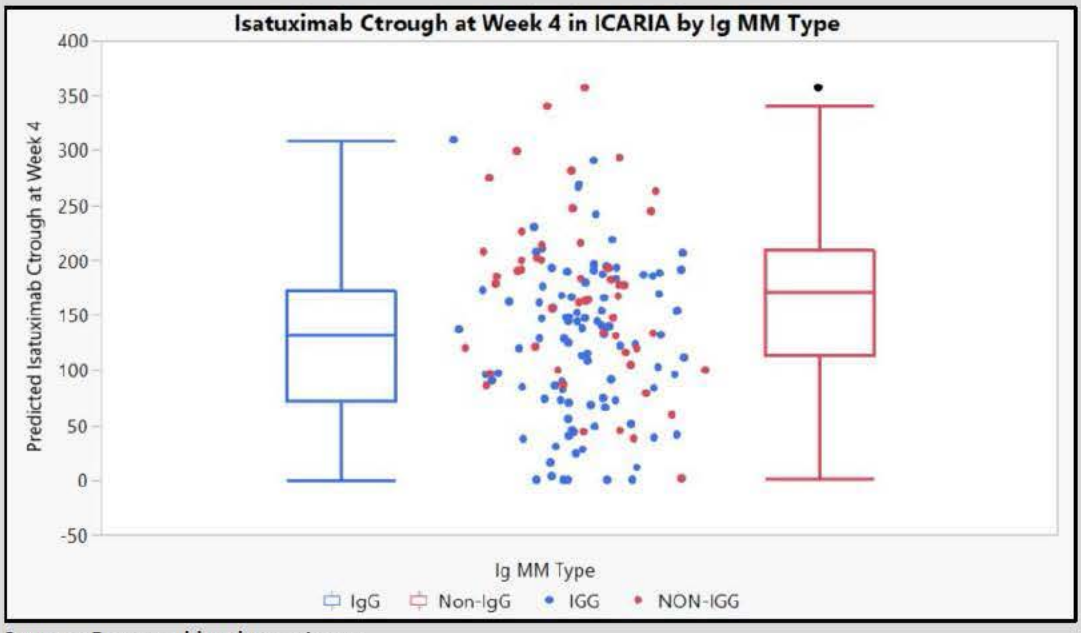
Figure 14. Simulated Mean Concentration-Time Profiles for Isatuximab 10 mg/kg QW/Q2W Dosage Regimen for Typical IgG and non-IgG Patients by the Population PK Analysis.



Source: Figure 24, Page 100, Summary of Clinical Pharmacology.

However, the predicted isatuximab $C_{troughWeek4}$ values between IgG and non-IgG patients in Study ICARIA are overlapping due to moderate/large inherent inter-patient variability of isatuximab despite the difference in central tendencies of exposure parameters (Figure 15). This is not unexpected given that the inter-subject variability (CV%) of steady state isatuximab AUC_{tau}, C_{max}, and C_{trough} was 36.0%, 51.7% and 68.1%, respectively, based on population PK analysis approach, following administration of isatuximab 10 mg/kg QW/Q2W.

Figure 15. Predicted Isatuximab C_{trough} at Week 4 by IgG MM Type in Pivotal Study ICARIA.



Source: Prepared by the reviewer.

In addition, an evaluation of the PFS and ORR results (Table 7 and Table 8) in Study ICARIA do not indicate any remarkable differences between the two categories in PFS and ORR.

Table 7. Evaluation of PFS by Ig Type in Study ICARIA (n=154 Isa-Pd).

Category	Subcategory (n)	N (%) of events	Median PFS (Months) (95% CI)	Hazard Ratio vs Pd (95% CI)
Ig MM Type	IgG (102)	50 (49)	11.57 (8.28 to 14.78)	0.67 (0.46 to 0.98)
	Non-IgG (51)	23 (45.1)	11.40 (6.47 to NC)	0.52 (0.29 to 0.89)

Source: Adopted from Table 17, page 59, Summary of Clinical Efficacy.

Table 8. Evaluation of ORR by Ig Type in Study ICARIA (n=154 Isa-Pd).

Ig MM Type (n)	N of Responders (sCR, CR, VGPR or PR)	ORR % (95% CI)
IgG (102)	64	62.7 (52.6 to 72.1)
Non-IgG (51)	28	54.9 (40.3 to 68.9)

Source: Adopted from Table 19, page 63, Summary of Clinical Efficacy.

1.1.5.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Isatuximab, a monoclonal antibody, is likely to be eliminated by proteolytic degradation, thus drugs that impact CYP or transporter expressions are not anticipated to alter the PK of isatuximab.

The effect of various anti-cancer agents on the PK of isatuximab has been assessed as part of 3 Phase 1 combination studies (TCD14079 Part A, TCD11863, and TCD13983 ICBd) and 1 Phase 3 study (EFC14335).

Combined therapies tested in Phase 1b studies were:

- Standard doses of lenalidomide and low dose of dexamethasone (TCD11863)
- Standard doses of pomalidomide and low dose of dexamethasone (TCD14079)
- Standard doses of CBd (cyclophosphamide, bortezomib and low dose dexamethasone, TCD13983)

Combined therapies tested in Phase 2 studies were:

- Dexamethasone (TED10893, Phase 2 Stage 2)

Combined therapies used in Phase 3 study were:

- Standard dose of pomalidomide and low dose of dexamethasone (EFC14335).

In Phase 1 studies, the effect of combination drugs on the PK of isatuximab was evaluated based on inter-studies comparisons (NCA and modeling approaches). In Phase 2 study, the effect of dexamethasone was evaluated based on an intra-study comparison.

Moreover, the effect of pomalidomide/dexamethasone was also evaluated by population PK analysis approach; by testing it as a potential covariate in the final model.

Inter-study comparisons showed 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.

The effect of isatuximab on various anticancer agents has been evaluated based the comparison of PK data from 3 combination studies (TCD11863, TCD13983 ICBd and TCD14079 Part A) and data published in the literature. It is concluded that isatuximab has no impact on the pharmacokinetics of pomalidomide, lenalidomide, and cyclophosphamide.

The FDA's Assessment:

FDA agrees with the applicant's position. Food-drug interactions are not applicable as isatuximab is administered as an intravenous infusion. No formal in vitro or in vivo Cytochrome P450 and transporter mediated drug-drug interaction studies were conducted for isatuximab as a perpetrator or a victim, since it undergoes proteolytic catabolism and it has no clinically

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significant effect on cytokine levels.

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

The completed studies included in the submission are summarized in Table 9. All studies are relevant to both safety and efficacy. In all studies, patients could remain on treatment until disease progression, unacceptable AEs, patient wish, or any other reason.

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Table 9: Summary of completed company-sponsored studies included in the CTD

Study	Patient population	Study Design and Indication	Treatment, schedule and sample size[a]	Efficacy endpoints
Core studies in combination with pomalidomide and dexamethasone in multiple myeloma				
EFC14335 Pivotal Phase 3 with target combination (NCT02990338)	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. Patients were enrolled at 102 sites in 24 countries.	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 The disease response assessments were evaluated based on radiological and central laboratory assessments by the IRC, which was blinded to treatment group allocation.	Experimental arm: isatuximab (b) (4) (N=152): 10 mg/kg QW/Q2W, pomalidomide, and dexamethasone; Control arm: pomalidomide and dexamethasone (N=149) Randomization ratio: 1:1	Primary: PFS Secondary: ORR, OS, TTP, PFS in HR cytogenetic population, DOR, TT1R, TTBR, patient reported outcomes
TCD14079 Phase 1b with target combination (NCT02283775)	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 Patients were enrolled at 6 sites in 1 country (US).	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 (b) (4) (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 (b) (4) Part A: Expansion isatuximab (b) (4) (N=22): 10 mg/kg QW/Q2W	ORR, DOR, TTR, PFS

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Study	Patient population	Study Design and Indication	Treatment, schedule and sample size[a]	Efficacy endpoints
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 (NCT01084252)	Phase 1: Patients with CD38+ hematological malignancies[b] Patients were enrolled at 13 sites in 3 countries. 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 Patients were enrolled at 17 sites in 3 countries (Stage 1) and at 35 sites in 25 countries (Stage 2).	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 (b) (4) (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 (b) (4) (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 (b) (4) (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 (b) (4) may switch to (b) (4) Phase 2 Stage 2 (N=93): isatuximab (b) (4) 20 mg/kg QW/Q2W, N=63; isatuximab (b) (4) 20 mg/kg QW/Q2W and dexamethasone, N=30; Randomization ratio: 2:1	Phase 1: ORR, DOR, TTR, % change in paraprotein Phase 2: Primary: ORR Additional: DOR, TTR, % change in paraprotein
TED14154 Supportive Phase 1 with single-agent treatment (NCT02514668)	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 Patients were enrolled at 6 sites in 1 country (US).	A dose-escalation/expansion (Part A only) and multi-center study to evaluate the safety, PK and efficacy of isatuximab (b) (4) in patients with relapsed/refractory MM	Part A Dose escalation and expansion cohorts isatuximab: (b) (4) (N=26): 10 mg/kg QW/Q2W, N=12; 20 mg/kg QW/Q2W, N=14	ORR, DOR, TTR, % change in paraprotein

Study	Patient population	Study Design and Indication	Treatment, schedule and sample size[a]	Efficacy endpoints
Supportive combination therapy studies in multiple myeloma				
TCD11863 Supportive Phase 1b with combination therapy[d] (NCT01749969)	Patients with RRMM who have had at least 2 prior anti-MM treatments Patients were enrolled at 5 sites in 1 country (US).	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 (b) (4) (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	ORR, DOR, PFS
TCD13983 Supportive Phase 1b with combination therapy[e] (NCT02513186)	Patients with newly diagnosed MM who are non-eligible for transplant Patients were enrolled at 5 sites in 2 countries.	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 (b) (4) (N=17): 10 mg/kg, N=13; 20 mg/kg, N=4; Ongoing patients may switch to isatuximab (b) (4)	ORR, DOR, TTR, % change in paraprotein

DOR: duration of response, HR: High Risk, IMiD: Immunomodulatory drug, MM: Multiple myeloma, ORR: overall response rate, OS: Overall survival, (b) (4) (b) (4) PD: Pharmacodynamics, PI: Proteasome inhibitor, PK: Pharmacokinetics, PFS: Progression-free survival, TTP: time to progression, TT1R: time to first response, TTBR: time to best response, TTR: time to response, US: United States

a 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.

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

c 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).

d Isatuximab in combination with lenalidomide and dexamethasone

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

The FDA's Assessment:

FDA agrees with the summary of the study EFC14335 as presented in the table above. EFC14335 formed the primary basis of efficacy for the indicated population. TCD14079

Phase 1b study Part A with the target combination enrolled patients at multiple dose levels and supported the dose of isatuximab 10 mg/kg in combination with pomalidomide and dexamethasone.

The Part B portion of the study not shown in the table above evaluated a fixed volume administration of isatuximab. Throughout the drug development, isatuximab was administered using a weight-based infusion method. The Applicant introduced a new administration method "fixed-volume infusion in Study 14079 Part B only and submitted safety data in 47 patients to the BLA during the review of the submission.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study EFC14335 (ICARIA-MM)

The Applicant's Position:

Trial Design

Study EFC14335 is a prospective, multicenter, multinational, randomized, open-label, parallel group, 2-arm Phase 3 study evaluating the efficacy of isatuximab in combination with pomalidomide and low dose dexamethasone compared with standard of care pomalidomide and low dose dexamethasone for the treatment of patients with RRMM who had received at least 2 prior lines of therapy including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) alone or in combination, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Study patients were enrolled at 102 sites in 24 countries, including the US, Canada, Japan, Australia, France, Italy, Belgium, and Turkey.

Pomalidomide in combination with dexamethasone is approved in patients with MM who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. The study population for EFC14335 was defined according to pomalidomide study MM-003, as reported by Miguel JS et al, and referenced in the US product labeling for pomalidomide. Patients 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 function. International standards for inclusion/exclusion criteria, disease staging and response criteria were followed per protocol to ensure consistency and applicability of study results.

Patients with obstructive lung disease or impaired pulmonary function were not excluded from the study and comprised 10% of the study population.

Patients with impaired renal function at baseline (eGFR<60 mL/min/1.73m^2) were included in the study and comprised more than 33% of the study population.

After Investigator confirmation of eligibility criteria, patients were randomly assigned using an interactive response technology (IRT) system in a 1:1 ratio to the IPd (experimental) arm or the Pd (control) arm. Randomization was stratified by age (<75 years versus ≥75 years) and number of previous lines of therapy (2 or 3 versus more than 3). A complete transplant procedure (induction, mobilization, conditioning, transplant, consolidation and maintenance) was considered as one line. Each other regimen was considered as one line, whatever the reason of

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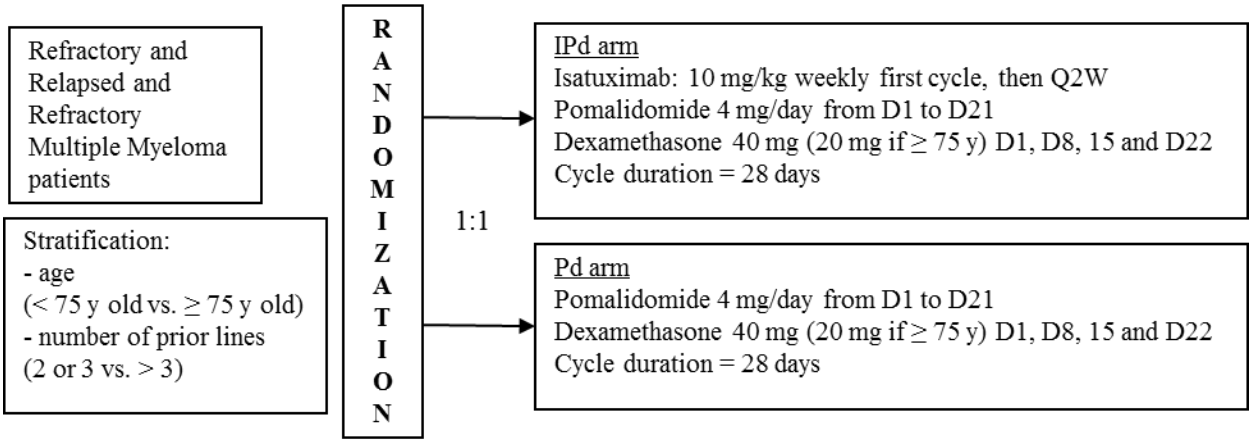
discontinuation (progression, adverse event, or patient request).

The selection of the isatuximab dose in study EFC14335 was based on data from early phase studies of isatuximab given as single-agent or in combination with an IMiD (lenalidomide or pomalidomide) and low-dose dexamethasone that have demonstrated clinical benefit and acceptable safety in patients with RRMM. In study TCD11863, isatuximab 10 and 20 mg/kg administered every week for 4 weeks followed by 10 and 20 mg, respectively, every 2 weeks [QW/Q2W] in combination with lenalidomide and dexamethasone showed similar activity as assessed by ORR and was well tolerated at both doses. The safety profile of the combination was consistent with the individual therapies. Preliminary data from study TCD14079 Part A in patients with RRMM and treated with IPd (isatuximab 10 and 20 mg QW/Q2W) indicated no apparent difference in ORR or tolerability between the 2 doses. No drug-drug interaction was observed between isatuximab and pomalidomide. Based on the results of study TCD14079, the isatuximab 10 mg/kg QW/Q2W dose regimen was selected for this study.

Study EFC14335 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. While the administration of isatuximab was open-label with respect to patients and Investigators, the disease response assessments were evaluated based on radiological and central laboratory assessments by the IRC, which was blinded to treatment group allocation. In addition, blinding rules were defined by the Sponsor to compensate for the lack of blinding and to minimize potential bias resulting from availability of the treatment arm information (Blinding Rules specifications document, see 16-1-9-sap). Team members in charge of validation of the efficacy data had no access to actual treatment received on individual patient basis. No summary tables by treatment arms were produced before the database snapshot.

The study design is summarized in Figure 16.

Figure 16 - Study design – Study EFC14335



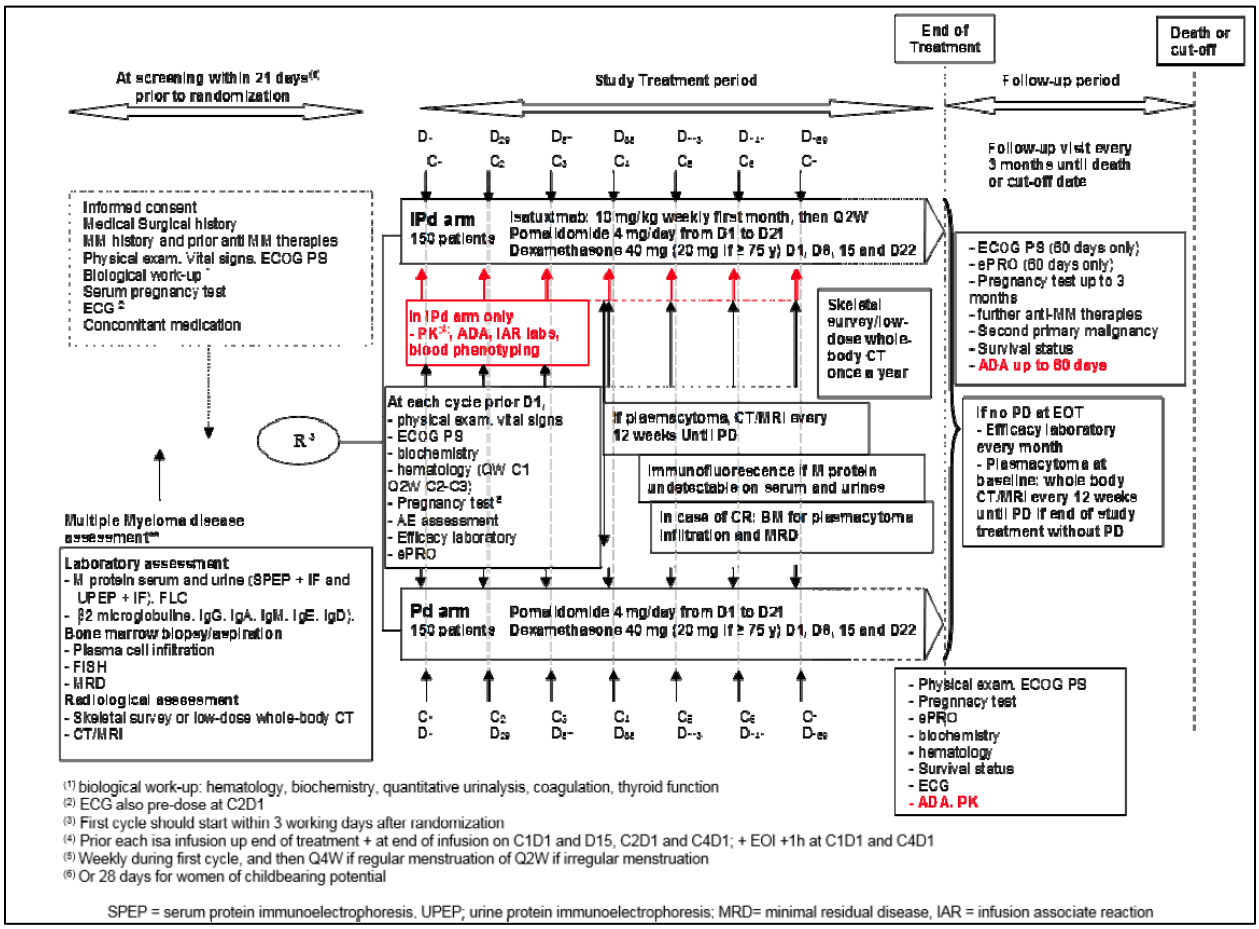
D=study day, y=years; IPd=isatuximab, pomalidomide, and dexamethasone; Pd=pomalidomide and dexamethasone

The FDA's Assessment:

The Reviewer agrees with the Applicant's description of the study design and the patient population. Study EFC14335 is a Phase 3 randomized controlled trial evaluating the addition of isatuximab to a backbone of pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma in the third line setting. The patient population enrolled on the study had measurable disease and received prior treatment with lenalidomide and a proteasome inhibitor. Pomalidomide and dexamethasone is approved in the third line setting for this patient population and is an appropriate comparator. The eligibility criteria did not specifically exclude patients with obstructive lung disease or impaired pulmonary function. However, this patient population comprised only 10% of the EFC14355 study population limiting conclusions on efficacy or safety.

The Applicant did not include a table of trial schedule of events. A graphical chart from the protocol is shown below in Figure 17.

Figure 17 Graphical Study Design and Assessments



Source: 1.1 Graphical Study Design EFC14335 16-1-1 amendment 4

Study Endpoints

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Primary efficacy endpoint

Progression-free survival is an established surrogate endpoint for OS in MM studies and has been used in recent phase 3 trials in MM, leading to the approval of lenalidomide in transplant ineligible patients, carfilzomib and ixazomib in relapsed and refractory patients and monoclonal antibodies like elotuzumab and daratumumab in relapsed and refractory setting.

In study EFC14335, PFS was analyzed based on central laboratory data and central review of radiologic imaging, assessed by an IRC using the IMWG criteria for disease response evaluation. PFS was defined as the time from the date of randomization to the date of first documentation of progressive disease (PD) as determined by the IRC, or the date of death from any cause, whichever occurred first; patients without PD or death before the analysis cut-off or the date of initiation of further anti-myeloma treatment were censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further antimyeloma treatment (if any) or the analysis cut-off date, whichever came first. Patients with no PFS events (death or PD) and without any valid post baseline disease assessments were censored at the day of randomization (Day 1).

Secondary efficacy endpoints

Key secondary endpoints were:

- **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 the IRC using the IMWG criteria. For patients with non-measurable M-protein on Cycle 1 Day 1, the possible responses were CR, non-PD or PD. An additional analysis of ORR using Investigator assessment of response was also performed.

- **OS:** defined as the time from the date of randomization to date of death from any cause. If death was not observed before the analysis data cut-off date, OS was censored at the last date that the patient was known to be alive or at the cut-off date, whichever was first.

Other secondary efficacy endpoints

The following other secondary efficacy endpoints were defined:

- **TTP:** defined as the time from the date of randomization to the date of first documentation of PD (as determined by IRC) excluding PD reported after the analysis cut-off date or the date of initiation of further anti-myeloma treatment. The definition of progression was the same as that used for the PFS endpoint. Censoring followed the same rules as for PFS.

- **PFS in the high risk cytogenetic population:** defined as PFS in the subgroup of patients carrying high risk cytogenetic abnormalities, namely del(17p), t(4;14) or t(14;16) assessed by fluorescence in situ hybridization (FISH). The definition and censoring rules

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were the same as those used for the PFS endpoint.

- **DOR:** defined as the time from the date of the first IRC determined response to the date of first IRC PD or death, whichever occurred first. Duration of response was determined only for patients who achieved a response of ≥PR.

- **BOR:** defined as the best response, using the IRC's assessment of response, from the start of treatment until PD, death, initiation of further anti-myeloma treatment, or cutoff date, whichever occurred first. BOR according to Investigator assessment of response was also provided.

- **Time to first response:** defined as the time from randomization to the date of first IRC determined response (PR or better) that was subsequently confirmed. The time to first response analysis was added per SAP amendment 1.

- **Time to best response:** defined as the time from randomization to the date of first occurrence of IRC determined best overall response (PR or better) that was subsequently confirmed.

Patient-reported outcomes

Health-related quality-of-life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items (EORTC QLQ C30), European Organization for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items (EORTC QLQ-MY20) and the Euro QoL Group self-report questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L) patient-reported outcomes (PRO).

Exploratory efficacy endpoints

Minimal residual disease (MRD) was an exploratory endpoint, assessed by next-generation sequencing in bone marrow samples from patients who achieved CR, to determine the depth of response at the molecular level.

Bone marrow aspirates were collected at baseline/screening, the time of CR confirmation, or if clinically indicated. If the patient presented with CR but was determined to be MRD positive, another bone marrow sample was to be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may have been collected after another 3 months, if the patient remained MRD positive and was still being treated. No more than 3 on-treatment bone marrow samples were to be obtained.

The FDA's Assessment:

PFS, the primary endpoint in EFC14335 is an accepted regulatory endpoint for drug approval in multiple myeloma. The key secondary endpoints, ORR as per IMWG criteria and OS are also

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accepted endpoints that support approval in this disease population. Disease progression and response status of each patient per IMWG were evaluated by a blinded IRC.

Although the trial included PRO outcome evaluation (described above) as secondary endpoints, a clear endpoint definition and formal statistical testing with adjustment for multiplicity was not included for the PRO endpoints. A pre-specified statistical analysis plan (SAP) and a plan to control the type 1 error rate was also not included. PRO findings without a prospectively specified statistical analysis plan are considered descriptive. Additionally, the open label trial design limits interpretability of PRO data. Patients' knowledge of treatment assignment may lead to systematic overestimation of the treatment effect, the magnitude of which is currently unknown. This data was reviewed as part of the totality of submitted information. MRD was an exploratory endpoint on the trial.

Statistical Analysis Plan and Amendments

A general summary of the methods used to analyze efficacy in Study EFC14335 is provided below.

Progressive free survival

All efficacy analyses were performed on the ITT population. All analyses using the stratification factors were performed using the stratification factor as per IRT. A sensitivity analysis of PFS was performed using the stratification factor as per the electronic case report form (eCRF). The primary analysis was a comparison of PFS based on IRC assessment in the IPd group versus the Pd group using a log rank test procedure stratified by stratification factors as entered in the IRT (ie, age and number of previous lines of therapy) and using a 1-sided 0.025 alpha level.

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.

In addition, the following estimates were provided:

- The HR and its 95% confidence interval (CI) were estimated using the Cox proportional hazards model stratified using the stratification factors as per IRT.

- PFS data was analyzed using the Kaplan-Meier method by treatment group:
  - 25th, 50th and 75th percentiles and 95% CIs constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley
  - Kaplan-Meier curves including number of patients at risk at key time points

In addition, the number of patients with events, the type of event (confirmed PD or death), the number of censored patients and the reason and timing of censoring were summarized. The median follow-up duration (months), defined as the time interval from the date of

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randomization to the date of last contact with the patient, estimated using the Kaplan-Meier method was provided. Patients who have died were censored at the date of death.

Sensitivity analyses:
Sensitivity analyses of PFS were performed at a 1-sided 0.025 alpha level.
Five sensitivity analyses were performed:

- PFS analysis 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)
- PFS analysis using Investigator's disease assessment, including symptomatic deterioration (clinical progression with no progression on imaging or M protein per investigator) as an event.
- Initiation of further anti-myeloma treatment considered as PFS 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 - Evaluation of consistency:
The consistency of the results from the primary analysis was evaluated across predefined subgroups shown in Table 10. For each subgroup, the treatment effect HR and its associated 95% CI was estimated. For each predefined demographic/baseline factor, PFS was analyzed 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.

Table 10 - PFS subgroup analyses: covariates investigated - Study EFC14335

Subgroup	**Description**
Age (eCRF)	<65 versus [65 - 75[versus ≥75 years
Number of previous lines of therapy (IRT)	(2 or 3) versus >3
Gender	Male versus female
Race	Caucasian versus Asian versus other
Region of the world (geographical)	Western Europe versus Eastern Europe versus North America versus Asia versus Other countries
Region of the world (regulatory)	Western countries versus Other countries
ECOG PS at baseline	0 or 1 versus 2
ISS staging at diagnosis	I vs II versus III
R-ISS staging at study entry	I vs II versus III
Cytogenetic abnormality (del(17p), t(4;14), t(14;16))	At least one versus none
Cytogenetic abnormality del(17p)	Yes versus No

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MM type at diagnosis	IgG versus non-IgG
Baseline creatinine clearance (MDRD formula)	≥60 mL/min/1.73 m^2 versus <60 mL/min/1.73 m^2
Refractory to PI	Yes versus No
Refractory to lenalidomide	Yes versus No

ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; IRT=interactive response technology; MDRD=Modification of Diet in Renal Disease; MM=multiple myeloma; R-ISS=International Staging System

Note: White and Caucasian are used interchangeably in this document.

Evaluation of confounding factors:

Since the results from the primary analysis could be impacted by confounding factors, any potential issues were examined and, if confirmed, an exploratory analysis of primary endpoint was performed. A multivariate Cox proportional hazards model was used to identify prognostic factors among the demographic and baseline characteristics factors described in the table above using a stepwise selection procedure with a 15% significance level for removing effects. For significant prognostic factors identified in the multivariate model, the balance between treatment groups was assessed. When a major confounding was identified through screening for treatment group imbalances in a prognostic factor at baseline, an exploratory analysis of PFS was done after adjusting for the prognostic factors in the multivariate Cox proportional hazards model.

Other efficacy variables - ORR, BOR, VGPR or better rate and CBR:

Best overall response, ORR, VGPR or better rate, and CBR based on IRC assessments were summarized for the ITT population with descriptive statistics (using data collected up to the PFS analysis cut-off date). Confidence intervals were computed using the Clopper-Pearson method. ORR was compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors as entered in the IRT.

The proportion of patients with BOR≥VGPR (according to IRC assessment) was also compared between the 2 arms using the same test as for ORR (for descriptive purpose only).
Under the VGPR category, two exploratory response categories (near-CR and biochemical CR) were further characterized as part of the IRC response assessment.

OS

The analysis of OS consisted of a comparison between the IPd group versus Pd group using a 1-sided log-rank test procedure stratified by stratification factors as entered in the IRT (ie, age and number of previous lines of therapy). An O'Brien and Fleming α spending function was used to obtain the nominal significance levels for the interim and final analyses of survival. The nominal significance (1-sided) level for the final survival comparisons was expected to be of 0.0244 for 220 death events (corresponding to a HR of 0.767).

In addition, the following were provided for OS: HR and 95% CI estimated using the Cox proportional hazards model stratified by the stratification factors as per IRT; Kaplan-Meier estimates and 95% CIs were provided.

The number of censored patients, the reasons for their censoring (ie, alive at the cut-off date, alive at the last contact before the cut-off date, and lost to follow-up) and the time between the date of last contact and the cut-off date were summarized by treatment group.

In addition, a sensitivity analysis was performed where OS was adjusted for switching to daratumumab as a subsequent treatment using inverse probability of censoring weighting (IPCW) method.

PFS in the high-risk cytogenetic population
PFS was analyzed using Kaplan-Meier methods with the same censoring rules as the primary analysis of PFS.

TTP, DOR, time to first response, duration of follow-up, and time to best response
These time-to-event endpoints were based on IRC assessment and analyzed using Kaplan-Meier methods. Similarly to the primary analysis of PFS, if progression or death (excluding for TTP: only progression) were not observed before the analysis data cut-off date or date of new anticancer therapy, TTP and DOR were censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of further anti-myeloma treatment (if any) or the data cut-off date, whichever occurred first. Time to first response was also analyzed among patients who achieved a response of PR or better only.

If no response (PR or better) was observed before the analysis cut-off date, time to first response, and time to best response were censored at the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti myeloma treatment (if any), or the analysis cut-off date, whichever occurred first.

Analyses of the prespecified secondary endpoints were descriptive only. Any testing procedure carried out on these endpoints was considered exploratory.

<u>Minimal residual disease</u>
The MRD status using next generation sequencing (negative or positive using different thresholds) was summarized by treatment group in the ITT population using descriptive statistics. The timing (study day from first dose) of MRD negative status was also described.

<u>Evaluation of potential isatuximab interference with M-protein assessment</u>
The M-protein interference results, evaluated by mass spectrometry, for patients with near CR (M-protein non-quantifiable and immunofixation positive, bone marrow <5% plasma cells) as best response were summarized and the individual values were listed.

<u>Multiplicity</u>
In the Phase 3 study EFC14335, hypothesis testing of the key secondary efficacy endpoints was carried out. A closed testing procedure was used to control the Type I error rate meaning that

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no further testing was to be performed unless the significance level had been reached for PFS. The hierarchical procedure was then carried out at the 1-sided 2.5% significance level in the following order:

- ORR at the time of the primary analysis on PFS (first cut-off date).
- OS tested both at the time of the primary analysis on PFS (at about 36% information), and at the end of the study (final analysis on OS).

No update of PFS or ORR as per IRC will be provided at the time of final OS analysis.
Since no hypothesis testing was performed in the Phase 1 and 2 studies, no multiplicity adjustments were necessary.

Additional elements of clinical benefit

Patient-report outcomes:
In study EFC14355, analyses of PROs were performed on the Safety population evaluable for C30, MY20 and EQ 5D-5L (randomized and treated patients who completed the C30, MY20 and EQ 5D-5L questionnaires at baseline and at least one post baseline assessment for each).

Evaluation of of anti-isatuximab antibody effect on efficacy:
Anti-isatuximab antibodies (ADA) were evaluated. BOR, ORR, and DOR were summarized for ADA positive patients (patients with at least one treatment-induced or treatment boosted ADA positive sample at any time during the ADA on-study observation period) and patients without ADA positive sample during the ADA on-study observation period.

Evaluation of the impact of hepatic and renal impairment on efficacy:
Further evaluation of the impact of hepatic and renal impairment on efficacy were performed for study EFC14335. BOR and ORR were summarized with descriptive statistics and 95% CIs estimated using the Clopper Pearson method for hepatic and renal impairment categories.

Two changes were made from the protocol to the SAP:

- To avoid possible issues with multiplicity and due to the fact that the study was not powered to detect statistically significant differences in HRQL/PRO endpoints, the population flag for PRO population was adjusted to include the safety population with a baseline and at least one post-baseline PRO assessment. The HRQL analyses were modified to focus on descriptive statistics, more specifically the mean scores at baseline and at each cycle, including end of treatment and follow-up (60 days after end of treatment) and the mean change from baseline scores for each cycle including treatment and follow-up.
- A biomarker population was defined for biomarker analyses.

The statistical analysis plan history table (Table 11) gives the timing, rationale, and key details for major changes to the statistical analysis features presented in the statistical analysis plan. Changes also incorporated in a protocol amendment cross-referenced to Table 12.

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Table 11 - Statistical analysis changes - Study EFC14335

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SAP version number	Date approved	Rationale	Description of statistical changes
2	07 November 2018	Safety analyses were added to better characterize the safety profile and to account for FDA comments on the submission strategy	The following analyses have been added: - Cumulative exposure to treatment in patient-years - Isatuximab dose reductions - Infusions without IR medication - Exposure-adjusted analyses of TEAEs - Indirect antiglobulin test - Neutropenic complications - Thrombocytopenia and hemorrhage - Hemolytic disorders - Autoimmune disorders
2	07 November 2018	Sensitivity analyses for PFS and OS were added to further evaluate the efficacy of study treatments	The following sensitivity analyses have been added: - Analysis of PFS as per Investigator assessment, ignoring symptomatic deterioration has been added - Analysis adjusting OS for switch to subsequent anti-cancer treatment therapy
2	07 November 2018	Additional exploratory endpoints were added to further characterize the efficacy of study treatments	The following analyses have been added: - Time to first response - Time to best response - Overall response rate based on Investigator assessment - Proportion of patients with VGPR or better as best overall response
2	07 November 2018	Subgroup analyses were added to further evaluate the efficacy in specific subgroups	The following subgroup analyses have been added: - Age as per eCRF - Regulatory region - Refractory to lenalidomide
2	07 November 2018	Some subgroup variables were removed because not deemed relevant based on number of patients and/or further clinical evaluation	The following subgroup analyses have been removed: - Age per IRT - Previous allogenic transplantation - Previous therapy with anti-CD38 mAb - Existing plasmacytomas - Refractory to lenalidomide in last previous regimen - Refractory to IMiD

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SAP version number	Date approved	Rationale	Description of statistical changes
2	07 November 2018	Based on clinical consideration, death due to PD occurring within 45 days after first documentation of PD were used to confirm PD (including death occurring after initiation of further therapy)	- Death due to PD occurring within 45 days after a first documentation of PD based on M-protein is considered as confirmation of PD
2	07 November 2018	The following data handling conventions were added to account for cases not described in the previous version of the SAP and that were reported in the database	The following conventions have been added: - Patients who received only one prior therapy will be classified in the "2 or 3 prior lines" stratum as per eCRF. - Convention for missing/partial death dates
2	07 November 2018	To clarify some definitions and analyses	The following definitions have been updated: - Baseline value - Intolerance to lenalidomide and/or PI - Overall number of cycles started - Isatuximab infusion interruption - Planned dose intensity of pomalidomide - Persistent and indeterminate ADA The following analyses have been updated: - Evaluation of confounding for primary analysis (following FDA comment) - Analysis of cytogenetic abnormalities - Analysis of MRD - Analysis of PK parameters - Analyses of PROs
2	07 November 2018	Due to issues in data collection	Removal of analysis of thyroid function parameters

ADA=anti-drug antibody; eCRF=electronic case report form; FDA=Food and Drug Administration; mAB=monoclonal antibody; IMiD=immunomodulatory drug; IR=infusion reaction; IRT=interactive response technology; MRD=minimal residual disease; OS= overall survival; PD=disease progression; PFS=progression-free survival; PI=proteasome inhibitor; PK=pharmacokinetic; PRO=patient-reported outcome; SAP=statistical analysis plan; TEAE=treatment-emergent adverse event; VGPR=very good partial response

Protocol Amendments

There were 3 global amendments to the protocol, of which one was introduced before the inclusion of any patients. There were 2 country-specific amendments, one for the UK that was introduced before inclusion of any patients in the UK and one for Japan. The amendments are summarized in Table 12. Amendment 4 protocol was submitted prior to the database cutoff for the CSR, but the changes had not been implemented at all sites.

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Table 12 - Summary of protocol amendments - Study EFC14335

No.	Date	Purpose of amendments
Amendments approved prior to inclusion of first patient		
1	01 Nov 2016 (all countries)	• Study was given a name: ICARIA-MM • ECG assessments added at Cycle 2 Day 1 (pre-dose) and at end of treatment • Fasting requirement prior to pomalidomide administration removed • Specified 2 options for assessment of bone disease: skeletal survey and low-dose whole-body CT scan • Specified patients excluded due to amyloidosis included those with evidence of end organ damage or receiving treatment for amyloidosis • 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 • Clarified that after Cycle 1 Day 1, FLC was analyzed by central laboratory only to confirm and document CR • Modified text for analysis cytogenetic abnormalities to include others that may be identified from emerging data • IMWG criteria were updated to most recent guidance • Removed of PK sampling on Day 15 after Cycle 4 • For patients who discontinued due to PD, PRO assessments were added at end of therapy and 60 days post-treatment instead of every 30 days • 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 • Specified the treatments considered equivalent to ranitidine and diphenhydramine to prevent IRs • The definition of renal dysfunction was updated from a creatinine clearance of <45 mL/min to <30 mL/min • Guidance on resumption of treatment after Grade 2 Infusion reactions was updated • Pomalidomide was not to be provided through POMALYST REMS program • Procedures for patients still on treatment at the PFS cut-off date were added • Updated definitions for treatment exposure variables • PFS, OS, and DOR censoring text was harmonized • Added women of childbearing potential should wear gloves when touching pomalidomide capsules or bottles • Added possibility to modify ADA sampling based on updated information on isatuximab immunogenicity
2	24 Feb 2017 (UK only)	• 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 (eg, systemic infection unless anti-infective therapy is employed) or patient unable to comply with the study procedures. • Added reference to expected AE table in IB

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No.	Date	Purpose of amendments
3[a]	18 May 2017 (all countries)	• Added changes from Amendment 2 (UK only above) • 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 • Screening window for women of childrearing potential extended to 28 days • Pregnancy testing requirements were clarified to be consistent across documents with Pomalidomide Pregnancy Prevention Plan • Since it was known that daratumumab could cause interference with red blood cell antibody screening for blood transfusions, an antibody screening test was added after 4 infusions of isatuximab or anytime a red blood cell transfusion was needed • Clarified that Day 1 laboratory assessments and physical examinations could be performed the day before first treatment administration • IRC no longer needed to assess patients for extramedullary disease at baseline to determine whether they required radiologic follow-up • Added the missing benefit/risk assessment in the protocol rationale section • 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 • If a patient could not tolerate dexamethasone during study treatment, methylprednisolone 100 mg IV could have been administered as premedication only, but both drugs could not be used at the same time. • Clarified wording for dose reductions and cycle delay • Clarified how to determine maximum interval for resumption of isatuximab administration following dosing interruption • Clarified patient management and pregnancy testing for patients still receiving treatment at the OS cut-off date • Added instructions for overdose of non-investigational medicinal product • Number of OS events to be observed before interim analysis was updated because enrollment window was reduced • ECOG PS was updated with most recent version and a new reference was added • Clarifications and edits to IMWG response criteria • Guidance for notification of early trial termination was added • Clarified that if study personnel administered medications, they (not patient) were to record them • Clarified concentration of dexamethasone solution • Added that patients would be followed for second primary malignancies during the follow-up • Removed collection of blood samples for TLS during infusion reactions • Blood phenotyping variables specified • Harmonization/clarification of post-study assessments • Specified that all IRs would be collected, but only IRs Grade ≥3 were considered AESIs • Clarification of Investigator decision to continue study treatment based on local laboratory results

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No.	Date	Purpose of amendments
3	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 text to clarify how data will continue to be collected to evaluate efficacy both as per Investigator and as per IRC • Added an Appendix with details of country specific requirements for Japan as per the new template requirements • Added an Appendix with details of past protocol amendment changes as per the new template requirements
4	25 Oct 2018 (all countries)	• Clarified in Schedule of Assessments that minimal residual disease assessment to be performed in case of CR at end of treatment EOT, ie 30 days after last study treatment administration and post treatment follow-up period, ie 60±5 days and every 3 months (±7 days) after last study treatment administration • Clarified Day 1 time window was ±2 days to allow time for reporting in the electronic case report form • 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 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/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. • Added details about various body parts (skull, spine, all long bones, pelvis, and chest) to be assessed during skeletal survey, for clarity. • Clarified contraception details for FCBP and partner on Day 1 and thromboprophylaxis. • Clarified that when there is a negative result for urine M-protein at Screening and Cycle 1 Day 1 then a repeat assessment should be performed at every 3 cycles (Cycle 4, Cycle 7, Cycle 10, etc). • Added details of bone marrow aspirate or biopsy as a parameter for MRD assessment. • Added second primary malignancies in the table of AESI category for consistency with the protocol body.

ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group Performance Scale; FCBP=females of childbearing potential; FLC=free light chain; IR=infusion associated reaction; IB=investigator's brochure; IMWG=International Myeloma Working Group; MM=multiple myeloma; MRD=minimal residual disease; PD=disease progression; PRO=patient-reported outcome; UK=United Kingdom

a There were 7 patients randomized and 10 who had signed consent for the study when protocol amendment 3 was signed off (18May2017).

The FDA's Assessment:

The FDA agrees with the Applicant's summary of the protocol and SAP amendments for Study EFC14335.

The portions of the Assessment Aid completed by the Applicant are ambiguous in reporting the one-sided level of significance and p-values. The FDA reports all p-values at the two-sided level of significance. In general, to get the equivalent two-sided value, the estimate should be multiplied by two.

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Study EFC14335 was designed to have approximately 90% power to detect a hazard ratio of 0.60 (median PFS 6.67 months versus 4 months) with a two-sided type I error of 5%. The primary PFS analysis was planned to be performed when approximately 162 events had occurred. There were no planned interim PFS analyses. The OS analyses had 80% power to detect a HR of 0.685 with 220 deaths. There was one planned interim analysis for OS timed to coincide with the analysis of PFS and using the O'Brien Fleming boundary condition for controlling of the type I error. A hierarchical testing strategy was employed in which PFS was tested first followed by the key secondary endpoint of ORR and then OS. No multiplicity adjustments were made for other secondary or exploratory endpoints.

8.1.2. Study Results

The Applicant's Position:

Compliance with Good Clinical Practices

This study was performed in compliance with Good Clinical Practices, including the archiving of essential documents. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996.

The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted. The protocol and amended protocols were submitted to Independent Ethics Committees and/or Institutional Review Boards for review and written approval. The list of all committees consulted, with the name of the committee chair, is provided in the CSR appendices.

Financial Disclosure

Study EFC14335: EFC14335: A Phase 3 randomized, open-label, multicenter study comparing isatuximab (SAR650984) in combination with pomalidamide and low-dose dexamethasone versus pomalidamide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma is the covered clinical study for BLA 761113.

Questionnaires were completed by investigators participating in the covered clinical trials, in conformance with 21 CFR 54, whereby investigators self-disclosed financial arrangements including the value of any compensation received that could influence the outcome of the study, significant payments of other sorts made to them by the sponsor, any proprietary or financial interests in the test product, and any significant equity interests in the sponsor of the study. In addition, the applicant performed internal due diligence to discover and quantify possible multiple sources of significant payments of other sorts to clinical investigators participating in the subject trials by means of queries to representatives in the sponsor's

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finance, clinical, marketing, legal, regulatory, and project direction departments.

The applicant submitted a financial disclosure certification document in Module 1.3.4 showing there were no clinical investigators with disclosure financial interest and/or arrangements in the study EFC1433.

FDA's Assessment:
The Applicant was unable to obtain complete financial disclosure information for 2 clinical sub-investigators. The two sub-investigators left the trial prior to obtaining the required information. The Applicant submitted a certification of due diligence for the two sub-investigators. The FDA agrees that the Applicant exercised due diligence in obtaining financial disclosures.

Patient Disposition

A total of 387 patients were screened and 307 patients were randomized at 102 sites in 24 countries in this study (154 patients in IPd arm and 153 patients in Pd arm) between 10 January 2017 and 01 February 2018. The countries with the largest enrollment (ie, randomized patients) were France (49 patients, 16.3%), Turkey (36 patients, 11.7%), Czech Republic (28 patients, 9.3%), and Italy (24 patients, 8.0%).

Six of the 307 randomized patients (4 patients in the Pd arm and 2 patients in the IPd arm) did not receive study treatment (Table) due to: AE, 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.

As of the data cutoff date, 65 (42.2%) patients in IPd arm and 35 (22.9%) patients in the Pd arm were still on treatment.

Definitive discontinuation was defined as discontinuation of all study treatments or discontinuation of the last ongoing study drug. Premature discontinuation was defined as discontinuation of at least 1 treatment while at least 1 treatment is continued. At the time of the data cutoff for the primary analysis, 87 (56.5%) patients in the IPd arm and 114 (74.5%) patients in the Pd arm had definitively discontinued treatment. The main reasons for definitive treatment discontinuation were as follows:

- PD: 42.9% and 57.5% in the IPd and Pd arms, respectively
- AE: 7.1% and 12.4% in the IPd and Pd arms, respectively
- Patient decision: 3.2% and 3.9% in the IPd and Pd arms, respectively
- "Other": 4 patients in the IPd arm (3 due to Principal Investigator decision based on FLC increase and 1 due to Principal Investigator decision to switch treatment to daratumumab/Pd); 1 patient in the Pd arm (physician decision).

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A total of 9.2% of patients and 2.0% of patients in the IPd and Pd arms, respectively, have prematurely discontinued at least 1 treatment, all due to AE. Four (2.6%) patients in the IPd arm prematurely discontinued isatuximab due to AE; all were due to Grade ≥3 TEAEs of infusion related reaction. In the IPd arm, 5.3% of patients prematurely discontinued pomalidomide due to AEs. Premature discontinuations of dexamethasone occurred in 1.3% and 2.0% of patients in the IPd and Pd arms, respectively, all due to AE.

Table 13 - Disposition of patients – randomized population - study EFC14335

	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)

PGM=PRODOPS/SAR650984/EFC14335/CIR/REPORT/PGM/dis dispo r t.sas OUT=REPORT/OUTPUT/dis dispo r t i rtf (19FEB2019 18:37)

The FDA's Assessment:

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The reviewer, in general concurs with the Applicant's analysis and report of patient disposition events. Treatment discontinuation due to progressive disease and toxicity were lower in the IPd arm compared to the Pd arm. "Personal reason" was the most common reason reported under "other" reasons for withdrawal by subject.

The first patient began treatment on (b) (6) and the last patient enrolled began treatment on (b) (6)

There were two different data-cutoffs in the data submitted for review of Study EFC14335. The cut-off date for PFS and all other efficacy analyses was 11 October 2018 and the cut-off date for data included in safety analyses was 22 November 2018. This results in 99 death events in the OS analyses and 113 deaths in the safety analyses. An additional 120 safety day update was provided after the submission of the application that had 127 deaths.

Protocol Violations/Deviations

Major deviations reported in more than 1 patient included enrollment when progression occurred ≥60 days after the end of the last line immediately before ICF 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.

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, respectfully). Fewer than 3% of patients received prohibited concomitant treatments, all of which were due to inappropriate use of or not receiving thromboprophylaxis (2 and 4 patients in the IPd and Pd arms, respectively). Two patients in the Pd arm had ICF procedural issues. For Patient 014335-(b) (6) (b) (6) the Investigator used an incorrect version of the eligibility criteria, although there was written evidence that the criteria were properly reviewed. Patient 014335-(b) (6) (b) (6) was a screen failure and later rescreened and assigned a new patient ID. The patient had signed the ICF at the initial visit, but because another patient ID was assigned, needed to sign the ICF again. When noted, the patient signed the ICF again.

Twenty-two patients (12 and 10 in the IPd and Pd arms, respectively) deviated from Inclusion Criterion 4. Although these patients had received prior therapy with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib), they had not failed treatment with both. These deviations were considered to be minor because this was consistent with the approved indication for the pomalidomide and dexamathasone combination in the US and EU (ie, patients must have received prior treatment with lenalidomide and a proteasome inhibitor).

Thirty-one patients (16 and 15 in the IPd and Pd arms, respectively) received ciprofloxacin for treatment of infections or the management of febrile neutropenia. Ciprofloxacin being a

CYP1A2 inhibitor was to be avoided as a concomitant medication. As ciprofloxacin is widely used for the treatment and prophylaxis for febrile neutropenia and neutropenia and is part of the recommendations of American Society of Clinical Oncology (ASCO), these deviations were considered as minor.

The FDA's Assessment:

Details of the protocol deviations in EFC14335 are shown above. Major protocol deviations as defined by the Applicant were small (<5%). A common cause of protocol violations (major or minor) was use of prohibited medications and not failed treatment with both lenalidomide and proteasome inhibitor. The protocol deviations were generally balanced between the two arms. The FDA agrees with the applicant's assessment that the overall pattern and nature of protocol deviations would not alter the conclusion of the benefit-risk relationship for use of isatuximab, pomalidomide and dexamethasone in the indicated population.

Table of Demographic Characteristics

Demographic characteristics were similar between the 2 treatment arms, with the exception of geographic region and gender (Table 14). While the 2 arms were similar for the age stratification factor (<75 years versus ≥75 years) and median age, there was difference in age group ≥65 years. Overall, the median age was 67 years (range 36 to 86) and 19.9% of the population was ≥75 years of age; more patients were ≥65 years of age in the IPd arm than in the Pd arm (64.9% versus 54.2%). Slightly more than half (51.8%) of all patients were male, but there were more males in the IPd arm than in the Pd arm (57.8% versus 45.8%). The majority of patients were White (79.5%) or Asian (11.7%). Information on race could not be obtained in 20 (6.5%) patients due to local legal restrictions. Most patients had an ECOG PS score of 0 (40.4%) or 1 (49.2%); 10.4% of patients had ECOG PS of 2. There were fewer patients in the IPd arm as compared with the Pd arm from Western Europe (35.7% versus 49.7%) and more patients from Eastern Europe (18.2% versus 13.1%) and Asia (13.6% versus 9.8%). The inclusion of a relevant proportion of elderly patients and of patients with low performance status and the geographic distribution are indications that the study population was representative of the global RRMM population.

Table 14 - Demographic characteristics - Randomized 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

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	Pd (N=153)	IPd (N=154)	All (N=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

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The FDA's Assessment:

The reviewer agrees that a relevant proportion of elderly patients and of patients with low performance status were enrolled but there was a severe underrepresentation of African American's in Study EFC14335. African Americans comprised <2% of the study population in Study EFC14335 . Less than 5% were enrolled and randomized in North American sites which may have contributed to the underrepresentation of racial minorities. However, the reviewer notes that the available data (biological or treatment related) does not indicate that either geographic region or race representation should limit applicability of the results of study EFC14335.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Overall, the most frequent conditions reported in the patients' medical history (>10% of the patients) consisted of hypertension (44.8% and 40.5% in the IPd and Pd arms, respectively), menopause (20.1% and 25.5%), peripheral sensory neuropathy (24.7% and 19.6%), back pain (15.6% and 13.7%), and pathological fracture (11.7% and 11.8%). Differences in the incidences between the 2 arms did not appear to be meaningful.

A medical history of neoplasm was present in 17.5% and 26.1% of patients in the IPd and Pd arms, respectively, and cardiac history was present in 22.1% and 19.6 % of patients, respectively. A history of diabetes mellitus and type 2 diabetes mellitus was reported in 10.4% and 8.4% of patients in the IPd arm, respectively, and in 5.9% and 5.2% in the Pd arm, respectively.

Sixteen patients in each treatment arm had a history of COPD or asthma. A total of 24.5% of patients were past smokers and 7.2% were current smokers. More patients were former smokers in the IPd arm than the Pd arm (28.1% versus 20.9%).

Disease characteristics at initial diagnosis were similar between the 2 arms. The median time from initial MM diagnosis to randomization was 4.23 years (range 0.5 to 20.5 years) and 28.0% of patients had ISS Stage III.

Overall, MM subtype at study entry was similar to the one collected at diagnosis. At study entry, the ISS criteria were classified as Stage I and II in 73.0% of the patients and stage III in 25.1% of patients. Disease characteristics were as expected in this heavily treated population of patients with RRMM and similar between the treatment arms.

The term creatinine clearance rather than eGFR was used to qualify renal function, although the estimation of renal function was performed with the MDRD formula to establish the eGFR. Renal function at baseline was estimated for 287 patients who had baseline creatinine values and race reported in the eCRF. A total of 36.2% of patients entered the study with renal function impairment (creatinine clearance [MDRD] <60 mL/min/1.73m^2), with a trend toward more patients with renal impairment in the IPd arm (IPd 38.7% and Pd 33.8%). All patients with

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renal function impairment had creatinine clearance (MDRD) between 30 60 mL/min/1.73m^2 except one patient in the IPd arm who had creatinine clearance levels <30mL/min/1.73m^2. All patients had Grade ≤2 baseline values for laboratory hepatic parameters

At baseline, 30.6% of patients had ≥50% bone marrow plasma cell infiltration; the median was 27.0% (range 0-100%). At study entry according to IRC assessment, soft tissue plasmacytomas were present in 7.8% of patients and bone lesions in 67.5% of patients, and these parameters were well balanced between treatment groups. Bone lesion incidence based on eCRF as assessed by Investigator (72.1% and 76.8% in the IPd and Pd arms, respectively) was higher when compared with incidence per IRC (67.3% and 67.8%).

At baseline, 9 (2.9%) patients had non-measurable M-protein by central laboratory assessment. Of note, 1 of these patients (Pd arm) had non-measureable M protein at screening and was noted as having a protocol deviation. The other 8 patients had measurable M protein at screening.

Cytogenetic risk was characterized by central laboratory FISH testing of purified CD138+ plasma cells from baseline bone marrow aspirate. A bone marrow aspirate for FISH was obtained and interpretable in 78.5% of patients. The main reasons for missing results were samples not provided for the test or poor sample quality. Overall, 19.5% of patients had high-risk chromosomal abnormalities (CAs) with del(17p) and t(4;14) being the most frequent abnormalities. The percentage of patients with high-risk CAs was lower in the IPd arm compared with the Pd arm (15.6% versus 23.5%). Eight (2.6%) patients (3 in the IPd arm and 5 in Pd arm) had 2 high-risk CAs, which is a patient population with very poor prognosis.

Per protocol, all patients had received at least 2 prior lines of treatment including prior lenalidomide and proteasome inhibitor. All patients were previously treated with IMiD (100% received lenalidomide), PI, and steroid, and 93.5% of patients had also been treated with an alkylating agent. The median number of prior lines was 3 (range 2 to 11), with 107 (34.9%) patients having received 4 or more prior lines of treatment. The number of prior lines and class of therapies were well-balanced between the treatment arms.

Nearly all patients had received at least 1 regimen containing ≥3 drugs (90.9% and 94.8% in the IPd and Pd arms, respectively).

Overall, 25.4% of patients received prior carfilzomib, 10.4% ixazomib/ ixazomib citrate, and 97.7% bortezomib, and 1 (0.3%) patient (IPd arm) was previously treated with pomalidomide. Three (1.0%) patients received elotuzumab and one (0.3%) patient received daratumumab. During prior MM treatment, 7.2% of patients were intolerant to lenalidomide, 13.0% to proteasome inhibitor, and 2.6% to both.

During prior therapy, 94.8% of patients were refractory to IMiD; 92.5% were refractory to lenalidomide; 75.9% to proteasome inhibitor, and 72.6% to both. Nearly all patients (98.0%) were refractory to their last regimen and all patients (100%) were considered “relapsed and

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refractory".

Overall, prior anti-myeloma treatments and refractory status to prior treatments were generally well balanced between treatment arms.

The last treatment regimen for MM prior to first study treatment administration most frequently included an immunomodulatory agent (66.8%) and/or proteasome inhibitor (48.9%). The median duration of last regimen was 7.87 months in the IPd arm, and 6.64 months in the Pd arm.

Overall, last prior anti-myeloma treatments, best response to, and reason for discontinuation of last treatment were generally well balanced between treatment arms. One hundred seventy-three (56.4%) patients had a PR or better response to last regimen given prior to study entry (57.8% and 54.9% in the IPd and Pd arms, respectively) and 13.7% had PD as best response to last regimen (14.3% and 13.1% in the IPd and Pd arms, respectively).

Most patients (85.7%) discontinued the last treatment due to PD (87.0% and 84.3% in the IPd and Pd arms, respectively). The time from last treatment to first dose of investigational treatment was 1.31 months, which was similar in the IPd and Pd arms (1.33 and 1.31 months, respectively).

Over half of patients (56.4%) had received a prior stem cell transplant, and 16.0% had received a double stem cell transplant. The incidence of a double stem cell transplants was similar in both arms.

The study population was representative of the global RRMM patient population, including important subgroups of patients with poor prognosis characteristics (ISS Stage III [25.1%], renal function impairment [36.2%], high-risk cytogenetics [19.5%], elderly ≥75 years [19.9%], ECOG PS 2 [10.4%], and high levels of LDH [32.2%]). Patients were heavily pretreated (median of 3 prior lines) and all were relapsed/refractory to their last regimen.
Baseline demographics and disease characteristics were generally well balanced between treatment arms. Among relevant prognostic factors, a trend was observed toward fewer patients in the IPd arm than in the Pd arm including high risk cytogenetics (15.6% versus 23.5%), more patients in the IPd arm ≥65 years (64.9% versus 54.2%), and patients in the IPd arm had a greater incidence of renal function impairment, ie creatinine clearance <60 mL/min/1.73m^2 (38.7% versus 33.8%).

<u>The FDA's Assessment:</u>
The reviewer agrees with the analysis of the baseline disease characteristics presented by the Applicant. In addition to a trend towards fewer patients with high risk cytogenetics in the IPd arm as stated above, the IPd arm also enrolled fewer patients with ISS Stage III at study entry (34/154, 22.1%) compared to the Pd arm (43/153,28.1%).

Study EFC14335 enrolled a heavily pretreated population with nearly 1/3 of the population had

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received 4 or more lines of prior therapies. Additionally, all patients had received prior treatment with lenalidomide and a proteasome inhibitor. Nearly 100% had received bortezomib as a prior proteasome inhibitor and additional 1/4 had also received carfilzomib. The number of patients who had received prior carfilzomib was higher in the PD arm (44/153, 28.8%) compared to the IPd arm (34/154, 22.1%). As stated above in the section on protocol deviations, not all patients had failed both PI and lenalidomide. The differences in relevant prognostic factors and type of therapies were taken into consideration for interpreting efficacy results from Study EFC14335

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Isatuximab was administered IV under the supervision of the Investigator or appropriate member of the study center staff. Dosages and infusion times were recorded on each patient's eCRF. The patient diary was used to document all oral pomalidomide and dexamethasone drug administrations (except when administered by study personnel).

No patients in the Pd treatment arm discontinued treatment due to non-compliance and 1 subject (0.6%) in the IPd arm discontinued due to non-compliance.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Primary efficacy endpoint

Adding isatuximab to Pd treatment significantly increased PFS (based on IRC assessment) compared to Pd. At the cutoff date, 73 (47.4%) and 89 (58.2%) PFS events had occurred in the IPd in Pd arms, respectively. Median PFS was significantly longer in the IPd arm (11.53 months, 95% CI: 8.936 to 13.897) than in the Pd arm (6.47 months, 95% CI: 4.468 to 8.279), respectively. The stratified HR was 0.596 (95% CI: 0.436 to 0.814) corresponding to a reduction of 40.4% in risk for disease progression or death with IPd compared to Pd. The 1-sided stratified log rank test resulting from the comparison of PFS between the 2 arms was statistically significant with a p-value of 0.001, which met the prespecified efficacy boundary of 0.025 (Table 15, Figure 18)

- Consistent improvement in PFS was demonstrated for IPd over Pd across all prespecified patient subgroups including poor prognosis subgroups such as the high risk cytogenetics population, elderly patients, renal function impairment, heavily pretreated patients (>3 prior lines), and relapsed/refractory patients. (Table 16)

- The results for sensitivity analyses were consistent with the primary analysis, demonstrating robustness of the results. Investigator-assessed PFS, based on local laboratory M-protein results and Investigator assessment of radiologic imaging, was consistent with the IRC assessment of PFS. Median PFS (95% CI) in the IPd arm was 11.14 months (7.491 to 14.784) and was longer than compared with 6.54 months (4.468 to 7.885) in the Pd arm (HR 0.602; p=0.0009). (Table 18)

- The HR for PFS adjusted in multivariate analyses for demographic and baseline

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characteristics defined in the SAP was 0.484 (95% CI [0.334 to 0.702]). This lower adjusted HR when compared to the primary analysis of PFS provides further evidence of the robustness of the results of the primary analysis PFS and suggests there may have been some confounding factors among the analyzed covariates that influenced the treatment effect in the primary analysis in favor of the Pd arm.

The FDA's Assessment:

Several demographic characteristics listed in Table 10 were tested in a step-wise selection procedure before arriving on the final selection of the covariates. The final set of covariates included in the multivariate analysis are : Race (Asian versus White), Race (Other versus White), Regulatory region (Western countries versus other countries), R-ISS staging at study entry (II versus I), R-ISS staging at study entry (III versus I), refractory to lenalidomide (Yes versus No) and number of previous lines of prior therapy (>3 vs 2 or 3).

The statistical reviewer notes that one of the benefits of study randomization is that unmeasured confounders are balanced across the two treatment arms. There are several covariates that could be added in the multivariate model for example age and gender. When adjusted for age in the multivariate model along with the other covariates mentioned above, the point estimate of the HR for PFS is 0.50, implying that the point estimates for the HR of PFS in a multivariate analysis are subject to change based on the variables adjusted for in the model.

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Table 15 - PFS - Primary analysis based on disease assessment by the IRC by treatment group – ITT population in Study EFC14335

	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

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Figure 18 – PFS - Primary analysis based on disease assessment by the IRC - Kaplan-Meier curves by treatment group – ITT population in Study EFC14335



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.

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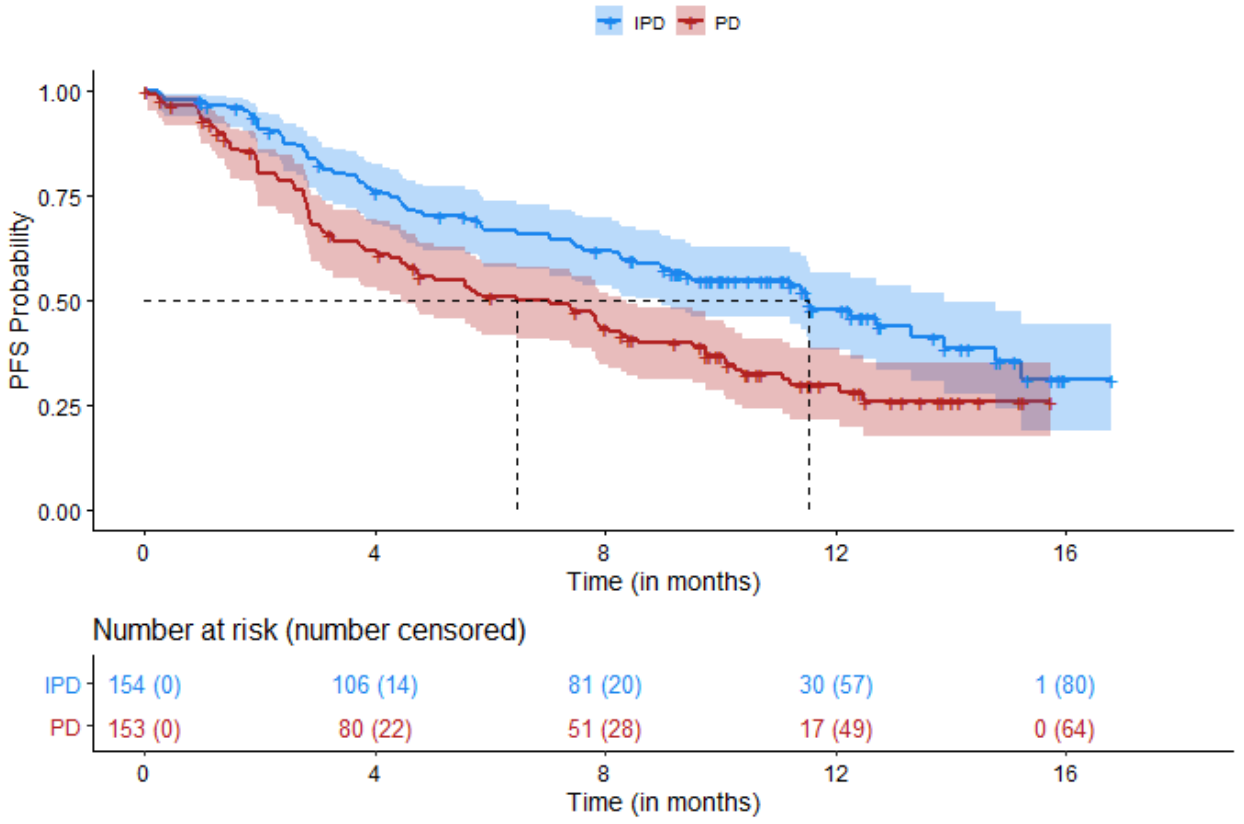
The FDA's Assessment:

The FDA agrees with the applicant's results presented in Table 15 and notes that the PFS comparison at the two through 16-month time points is arbitrary and was not pre-specified. No conclusions should be drawn, nor any efficacy claims made, based upon differences in PFS at these two-month time-point intervals. Also, the FDA notes that the corresponding two-sided p-value is 0.001.

The FDA agrees with the applicant's KM curves. The KM plot with the 95% CI are provided in Figure 19 below.

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Figure 19 Kaplan-Meier Plot of Progression Free Survival in the ITT Population



Source: FDA statistical reviewer generated using the adtte.xpt dataset

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Table 16 – PFS: Summary of subgroup analyses in Study EFC14335

	Pd (N=153)			IPd (N=154)				
	N	N(%) of Events	Median (Months) (95% CI)	N	N(%) of Events	Median (Months) (95% CI)	Hazard Ratio (95% CI) vs Pd	P-value for interaction[a]
All patients	153	89 (58.2)	6.472 (4.468 to 8.279)	154	73 (47.4)	11.532 (8.936 to 13.897)	0.596 (0.436 to 0.814)	
Age (eCRF)								
Age <65	70	41 (58.6)	5.027 (3.285 to 8.279)	54	26 (48.1)	11.532 (4.567 to 14.784)	0.656 (0.401 to 1.074)	0.5952
Age [65-75[	54	29 (53.7)	8.575 (4.567 to 12.057)	68	32 (47.1)	11.565 (8.279 to NC)	0.638 (0.385 to 1.059)	
Age ≥75	29	19 (65.5)	4.468 (2.595 to 7.754)	32	15 (46.9)	11.400 (4.435 to NC)	0.479 (0.242 to 0.946)	
Gender								
Male	70	41 (58.6)	6.472 (3.745 to 11.072)	89	43 (48.3)	11.499 (8.246 to 14.784)	0.667 (0.435 to 1.024)	0.5454
Female	83	48 (57.8)	7.392 (3.811 to 8.575)	65	30 (46.2)	12.715 (7.031 to 15.211)	0.553 (0.349 to 0.877)	
Race								
White	126	74 (58.7)	6.472 (4.468 to 9.528)	118	56 (47.5)	11.532 (8.969 to 14.784)	0.585 (0.413 to 0.830)	0.9780
Asian	15	8 (53.3)	7.852 (2.891 to NC)	21	8 (38.1)	NC (5.815 to NC)	0.517 (0.192 to 1.393)	
Number of prior lines of therapy (IRT)								
2 or 3	101	57 (56.4)	7.819 (5.027 to 10.086)	102	44 (43.1)	12.255 (8.969 to NC)	0.590 (0.397 to 0.878)	0.9583
>3	52	32 (61.5)	4.271 (2.563 to 8.575)	52	29 (55.8)	9.396 (4.830 to 14.784)	0.590 (0.356 to 0.977)	
Baseline creatinine clearance (MDRD)								
≥60 mL/min/1.73m2	96	55 (57.3)	7.885 (5.651 to 10.086)	87	36 (41.4)	12.715 (8.936 to NC)	0.576 (0.378 to 0.877)	0.7575
<60 mL/min/1.73m2	49	29 (59.2)	3.745 (2.760 to 6.472)	55	30 (54.5)	9.495 (7.031 to 13.897)	0.502 (0.297 to 0.847)	
ISS staging at study entry								
I	51	28 (54.9)	9.758 (7.754 to 12.485)	64	25 (39.1)	13.306 (11.203 to NC)	0.657 (0.383 to 1.128)	0.7901
II	56	32 (57.1)	5.027 (2.858 to 10.053)	53	23 (43.4)	11.532 (5.782 to NC)	0.541 (0.315 to 0.929)	
III	43	27 (62.8)	3.285 (1.971 to 5.585)	34	24 (70.6)	6.472 (2.760 to 9.495)	0.635 (0.363 to 1.110)	
R-ISS staging at study entry								
I	31	17 (54.8)	10.382 (7.754 to NC)	39	13 (33.3)	14.784 (11.203 to NC)	0.584 (0.283 to 1.205)	0.9871

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	Pd (N=153)			IPd (N=154)				
	N	N(%) of Events	Median (Months) (95% CI)	N	N(%) of Events	Median (Months) (95% CI)	Hazard Ratio (95% CI) vs Pd	P-value for interaction[a]
II	98	57 (58.2)	6.472 (4.041 to 9.528)	99	47 (47.5)	11.499 (7.491 to 15.211)	0.587 (0.398 to 0.868)	
III	24	15 (62.5)	1.971 (1.248 to 3.285)	16	13 (81.3)	2.793 (1.840 to 9.495)	0.605 (0.280 to 1.307)	
MM type at diagnosis								
IgG	100	56 (56.0)	7.754 (4.567 to 9.758)	102	50 (49.0)	11.565 (8.279 to 14.784)	0.670 (0.457 to 0.982)	0.3980
Non-IgG	52	32 (61.5)	4.764 (2.858 to 9.528)	51	23 (45.1)	11.400 (6.472 to NC)	0.517 (0.299 to 0.892)	
Baseline ECOG PS								
0 or 1	137	80 (58.4)	7.031 (4.698 to 9.528)	138	62 (44.9)	11.532 (8.969 to NC)	0.578 (0.415 to 0.806)	0.5468
2	16	9 (56.3)	4.041 (2.595 to 8.575)	16	11 (68.8)	5.881 (1.708 to 13.897)	0.827 (0.328 to 2.085)	
Refractory to PI								
Yes	115	67 (58.3)	5.585 (3.713 to 8.049)	118	57 (48.3)	11.400 (7.622 to 14.784)	0.578 (0.405 to 0.824)	0.6518
No	38	22 (57.9)	7.852 (4.731 to 12.485)	36	16 (44.4)	12.255 (8.115 to NC)	0.671 (0.351 to 1.280)	
Refractory to lenalidomide								
Yes	140	82 (58.6)	5.585 (3.811 to 7.885)	144	72 (50.0)	11.400 (8.246 to 13.306)	0.593 (0.431 to 0.816)	0.3006
No	13	7 (53.8)	10.053 (6.472 to NC)	10	1 (10.0)	NC (2.168 to NC)	0.182 (0.022 to 1.485)	
Geographical region								
Western Europe	76	39 (51.3)	7.754 (3.811 to 10.251)	55	24 (43.6)	11.532 (3.943 to NC)	0.684 (0.411 to 1.139)	0.9308
Eastern Europe	20	14 (70.0)	5.585 (2.825 to 10.382)	28	15 (53.6)	12.715 (4.830 to 13.306)	0.605 (0.291 to 1.254)	
Asia	15	8 (53.3)	7.852 (2.891 to NC)	21	8 (38.1)	NC (5.815 to NC)	0.517 (0.192 to 1.393)	
Other countries[b]	37	26 (70.3)	4.698 (2.595 to 8.378)	43	23 (53.5)	11.203 (7.031 to NC)	0.527 (0.300 to 0.925)	
Regulatory region								
Western countries	97	52 (53.6)	7.031 (4.041 to 9.758)	77	36 (46.8)	11.499 (7.491 to 14.784)	0.636 (0.414 to 0.978)	0.7207
Other countries[c]	56	37 (66.1)	6.472 (3.285 to 8.575)	77	37 (48.1)	12.255 (7.622 to NC)	0.555 (0.352 to 0.877)	

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	Pd (N=153)			IPd (N=154)				
	N	N(%) of Events	Median (Months) (95% CI)	N	N(%) of Events	Median (Months) (95% CI)	Hazard Ratio (95% CI) vs Pd	P-value for interaction[a]

CI=Confidence interval, ECOG PS=Eastern Cooperative Oncology Group Performance Status, eCRF=electronic case report form, IRT=interactive response system, ISS=International staging system, MDRD=Modification of Diet in Renal Disease, PFS= progression-free survival, R-ISS=Revised International staging system
Cutoff date = 11OCT2018
Note: Only subgroups with >10 patients in any treatment arm are included.
a Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction
b Other countries=Australia, New Zealand, Turkey and Russia
c Other countries=Czech Republic, Hungary, Poland, Slovakia, Japan, Korea, Republic of Taiwan (Province of China), Turkey and Russia
Source: eff_pfs_subgrp_strat_i_t_i.rtf, eff_pfs_subgrp_dis_i_t_i rtf, eff_pfs_subgrp_dem_i_t_i rtf, eff_pfs_subgrp_pamt_i_t_i

The FDA's Assessment:

The FDA agrees with the applicant's subgroup analyses presented in Table 16 and notes that the p-values have not been adjusted for multiplicity. No alpha has been allocated to the subgroup analyses, therefore, all results should be considered exploratory. There were insufficient African American patients for any comparative analyses.

Key secondary endpoints

- An improvement in ORR was shown in patients who received IPd compared with Pd (60.4% versus 35.3%). The 1 sided stratified CMH p-value was <0.0001, demonstrating a significant difference in ORR between the two arms in favor of IPd at the 1-sided 0.025 level. A consistent improvement in ORR was observed across the prespecified subgroups.

- At a median duration of follow-up (11.56 and 11.73 months in the IPd and Pd arms, respectively), a trend toward longer OS was observed in patients who received IPd compared with Pd (HR 0.687), but median OS had not been reached in either treatment arm. At the time of the analysis, the probability of surviving (95% CI) 12 months was 0.720 (95% CI: 0.636 to 0.787) in the IPd arm and 0.633 (95% CI: 0.545 to 0.709) in the Pd arm. Further follow-up is ongoing.

Other secondary endpoints

- The addition of isatuximab to Pd improved median time to progression (12.71 months in IPd arm versus 7.75 months in Pd arm)

- Duration of response was longer with IPd than Pd treatment (13.27 months versus 11.07 months).

- Responses in the IPd arm occurred more rapidly, with the median time to first response 1.94 months and 3.02 months in the IPd and Pd arms, respectively. Among responders, the median time to first response was 35 and 58 days in the IPd and Pd arms, respectively. Median TTBR was similar in the IPd and Pd arms (76 and 85 days).

Among patients in the high-risk cytogenetic population, adding isatuximab to Pd treatment improved median PFS based on the IRC assessment (7.491 versus 3.745 months). The stratified HR was 0.655 (95% CI: 0.334 to 1.283), corresponding to a reduction of 34.5% in the risk of progression or death with IPd compared to Pd.

Health-related quality-of-life endpoints

- Overall quality of life as measured by EORTC-QLQ-C30 GHS score was sustained over time and similar in both treatment groups.

Additional evidence of clinical benefit

- The addition of isatuximab to Pd delayed the need for subsequent therapy. The median time to next anti-myeloma treatment was not reached in the IPd arm and was 9.10 months in the Pd arm (HR 0.538), with fewer patients in the IPd arm receiving subsequent therapy (39.0% versus 54.2%).

- Among patients with creatinine clearance <50 mL/min/1.73 m2 at baseline, more patients

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in the IPd than the Pd arm showed complete renal response (71.9% versus 38.1%) and sustained complete renal response also occurred more frequently in the IPd arm than the Pd arm (31.3% versus 19.0%). In addition, overall, progression to severe or end stage renal disease occurred less frequently in the IPd arm than in the Pd arm overall (12.1% versus 18.6%), which was due to fewer patients developing end stage disease in the IPd arm than the Pd arm (2.9% versus 7.9%).

- The incidence of MRD negativity at the sensitivity level of 10-5 was greater in patients who received IPd (8 patients, 5.2%) compared with Pd (0 patients).

The FDA's Assessment:

The FDA agrees with the numerical results of the OS data presented above and that the median OS has not been reached in either arms. No detriment in OS with addition of isatuximab to Pom-Dex is apparent at this time. However, the results of the OS data at the first interim analysis of OS are immature. The FDA issued a PMC to request the final report of OS per Post marketing Commitment (PMC) #1.

The "other secondary endpoints", Health related quality of life endpoints, and "measures of clinical benefit" were not included in the statistical testing strategy and were not adjusted for multiplicity. Additionally, the analysis of Health-Related Quality of life endpoints was not adequately powered to support a non-inferiority conclusion (i.e. a finding of no difference between the two arms). It is not possible to exclude a detrimental effect of isatuximab on global health status or quality of life for patients enrolled in the EFC14335 trial. The results should be considered hypothesis generating and exploratory. No efficacy conclusions can be made based on the results of these endpoints.

MRD assessment in Study EFC14335

• MRD assessments were not performed consistently across the two arms.
• There was a high rate of failure to detect a baseline diagnostic clone in the pomalidomide-dexamethasone (Pd) arm patients who achieved CR or sCR.

The above issues limit interpretability of the MRD results.

The summary of the ORR results is provided in the Table 17. There were seven and two patients with CR on the IPd and Pd arms respectively. Although the ORR was higher in the IPd arm, 32 (34%) of the 93 responders had a disease progression/death event comparable to 19 (35%) events of the 54 responders on the Pd arm.

The FDA does not agree with the applicant's promotional language characterization that "the duration of response was longer" on the IPd arm although the point estimates might differ. In an analysis that considers only the responders without appropriate statistical tests, such analyses are considered exploratory.

Similarly, the FDA disagrees with the promotional language "responses occurred more rapidly" used to characterize the time to response. These analyses were conducted only in the responders and is considered exploratory.

Table 17 Best Overall Response for Patients in Study EFC14335

Endpoint	**IPd N=154**	**Pd N=153**
Overall Response Rate Responders (sCR+CR+VGPR+PR) n(%) [95% CI]	93 (60.4) [52.2%-68.2%]	54 (35.3) [27.8%-43.4%]
Complete Response (CR) n(%)	7 (4.5)	2 (1.3)
Stringent Complete Response (sCR) n(%)	0	1 (0.7)
Very Good Partial Response (VGPR) n(%)	42 (27.3)	10 (6.5)
Partial Response (PR) n(%)	44 (28.6)	41 (26.8)
Stable Disease (SD)	33 (21.4)	45 (29.4)
Disease Progression (PD)	6 (3.9)	14 (9.2)

Source: Statistical reviewer generated from ADRS.XPT dataset

Exploratory analyses

- The addition of isatuximab to Pd resulted in an improvement in PFS as well as a higher ORR across the different genotype subgroups for FCGR3A gene polymorphism.

- M-protein interference by isatuximab impeded the CR assessment in the IPd arm. Mass spectrometry analysis indicated that, in 11 of 22 patients with near-CR tested in IPd arm, the residual immunofixation-positivity was due to M-protein interference.

The FDA's Assessment:
The FCGR3A polymorphism assay and M protein interference testing by mass spectrometry reported above have not been evaluated by the FDA. These are considered exploratory and the FDA cannot confirm the validity of the assay or the accuracy of the results based on these tests. FDA notes that isatuximab similar to daratumumab can interfere with serum protein electrophoresis and immunofixation and the determination of CR. The interference with serum protein electrophoresis and immunofixation tests in patients treated with isatuximab will be included in the USPI. FDA issued a post marketing commitment (PMC) to develop and submit a validated assay to detect interference of isatuximab and facilitate determination of CR in patients treated with isatuximab .

Sensitivity analyses

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To assess the robustness of the primary PFS results, 4 sensitivity analyses of PFS were performed at a 1-sided 0.025 alpha level. All 4 PFS sensitivity analyses were consistent with the primary PFS analysis results, showing consistent HRs ranging from 0.568 to 0.602, consistent median PFS results both for the IPd arm (range 8.97 to 11.53 months) and Pd arm (range 4.60 to 6.47 months), and statistically significance difference in favor of IPd over Pd for p-value (range 0.0002 to 0.0009) (Table 18).

Investigator-assessed PFS, based on local laboratory M-protein results and Investigator assessment of radiologic imaging, was consistent with the IRC assessment of PFS. Median PFS (95% CI) in the IPd arm was 11.14 months (7.491 to 14.784) and was longer than 6.54 months (4.468 to 7.885) in the Pd arm (HR 0.602; p=0.0009). As observed for the primary analysis of PFS, based on the Investigator assessment, there was an early separation observed between the IPd and Pd arms.

An additional analysis of PFS was performed based on IRC disease assessments, but using stratification factors as entered in the eCRF, since there were small differences in the 2 treatment arms between the IRT (used for the primary analysis of PFS) and eCRF for the stratification factor distribution for the number of prior lines of treatment (Table 14). In this analysis, the stratified HR was 0.568 (p=0.0004), which was consistent with the results of the primary analysis.

The FDA's Assessment:
The Agency agrees that the sensitivity analyses performed on PFS indicate that the results from the primary analyses are robust.

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Table 18 - 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
Source: eff_km_pfs_i_t_x.rtf, eff_km_pfs_scrf_i_t_x.rtf, eff_km_pfsnfat_i_t_x.rtf, eff_km_pfsinvns_i_t_x.rtf, eff_km_pfsinv_i_t_x.rtf, eff_km_pfsfat_i_t_x.rtf

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Data Quality and Integrity

Regular site monitoring ensured the quality of trial conduct. Monitoring of Investigator sites was performed by Sanofi in all countries according to Sanofi procedures, except in the US (b) (4) (b) (4), Canada (b) (4) (b) (4) and Japan, Taiwan and Korea (b) (4) according to Sanofi monitoring procedures.

Management of clinical trial data was performed according to the following rules and procedures. Data entry and validation were carried out using standard validated remote data capture computer software (RAVE version 2018.1.3). Data were stored in a SQL server database. Data entry was performed directly from the Investigator site from the data source documents and signed electronically by the authorized site personnel. Moreover, any modification in the database was traced using an audit trail.

Sanofi conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, case report form, and study procedures, in compliance with GCP.

Dose/Dose Response

Clinical results from single agent study TED10893 showed a clear dose response (in terms of ORR) relationship between the 3 mg/kg and doses ≥10 mg/kg, but no clear increase in ORR between 10 and 20 mg/kg. PK/PD modeling and simulations of ORR and serum M-protein showed that intensification of dosing from Q2W to QW in the loading phase provided a better efficacy response as did the higher dose of 20 mg/kg compared to 10 mg/kg in single agent with no clear benefit when extending the loading dose period from 4 to 8 weekly administrations.

Combination studies with lenalidomide or pomalidomide and dexamethasone leveraged the knowledge gained from the single agent studies for isatuximab dose selection. Phase 1b study TCD11863 of isatuximab in combination with Ld initially evaluated isatuximab administered Q2W in a dose escalation phase and an expansion cohort and then explored the safety, efficacy, and PK of isatuximab 10 and 20 mg/kg QW/Q2W regimens. Later, isatuximab doses of 5, 10, and 20 mg/kg QW/Q2W were assessed in combination with Pd in Phase 1b study TCD14079 Part A. The clinical data from the 2 combination studies showed no difference in responses (ORR) for patients treated with either 10 mg/kg or 20 mg/kg isatuximab. Similarly, PK/PD modeling and simulations of ORR and serum M-protein predicted minimal additional efficacy when increasing the isatuximab dose from 10 to 20 mg/kg. Therefore, 10 mg/kg QW/Q2W was selected for the pivotal Phase 3 study EFC14335 with IPd.

The proposed isatuximab dose in combination with Pd for the target indication was confirmed

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based on the results from the pivotal Phase 3 study EFC14335 and supported by exposure-response analyses for safety and efficacy.

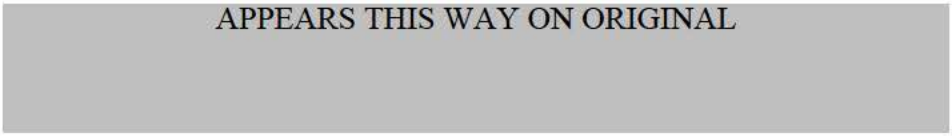
Durability of Response/Persistence of Effect

The primary endpoint of pivotal study EFC14335 is PFS, which demonstrates sustainability of efficacy over time on treatment. Follow-up in the study was robust, with median duration of 11.56 months. The addition of isatuximab resulted in prolonged PFS when added to a Pd regimen, with median PFS (95% CI) of 11.53 months (8.936 to 13.897) in the IPd arm, compared with 6.47 months (4.468 to 8.279) in the Pd arm (HR = 0.596, p value=0.0010).

At the analysis cutoff date, a clear trend toward prolonged OS was also observed in study EFC14335 patients who received IPd compared with Pd (hazard ratio 0.687), while median OS had not been reached in either treatment arm. At the time of the analysis, the probability of surviving 12 months (95% CI) was 0.720 (95% CI: 0.636 to 0.787) in the IPd arm and 0.633 (95% CI: 0.545 to 0.709) in the Pd arm.

Figure 20 – Overall survival – Kaplan-Meier curves by treatment group – ITT population in Study EFC14335

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154 145 127 116 51 15

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.

PGM=PRODOPS/SAR650984/EFC14335/CIR/REPORT/PGM/eff km i f.sas OUT=REPORT/OUTPUT/eff km os i f i rtf (07MAR2019 15:02)

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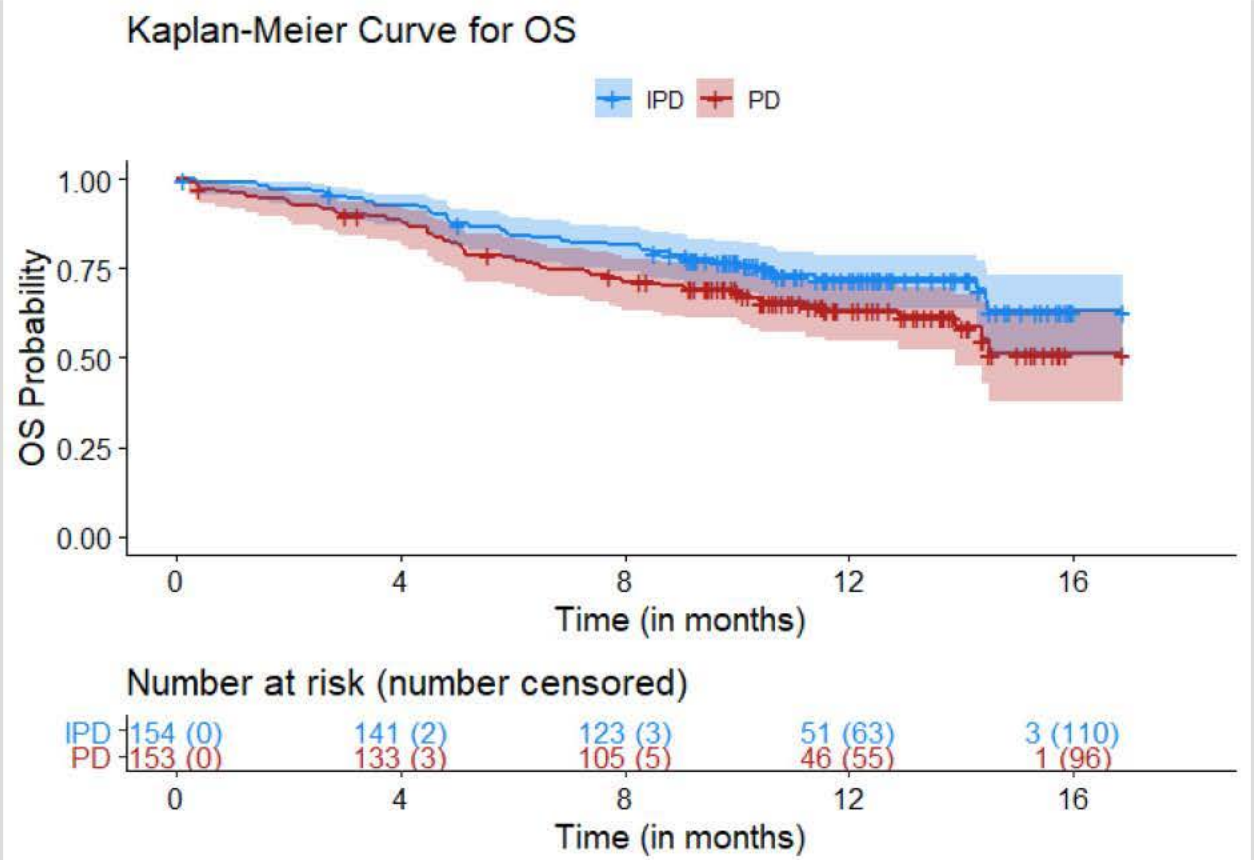
In study EFC14335, evidence of long-term benefit is also provided by time to next treatment and duration of response. The addition of isatuximab to Pd delayed the need for subsequent therapy. The median time to the next anti-myeloma treatment was not calculable in the IPd arm and was 9.10 months in the Pd arm (HR 0.538; p value=0.0003), with fewer patients in the IPd arm receiving subsequent therapy (39.0% versus 54.2%). Persistence of efficacy was also demonstrated by a duration of response of 13.27 months with IPd. In addition, the duration of exposure was longer in the IPd arm compared with the Pd arm. A median of 10 cycles were initiated in the IPd arm and 6 cycles in the Pd arm. The median duration of exposure was 41 weeks (range 1.3 to 76.7) in the IPd arm and 24 weeks (range 1.0 to 73.7) in the Pd arm. At the cut-off date, 100 patients (65 in the IPd arm and 35 in the Pd arm) were still on treatment, and 55 patients in IPd arm and 38 patients in the Pd arm received ≥12 cycles.

The FDA's Assessment:

The FDA agrees that the OS data at the first interim analysis of OS are immature. There was a total of 99 deaths, 43 (28%) on IPd and 56 (37%) on the Pd arm. No detriment in OS with isatuximab is apparent at this time. The KM plot for the OS analysis with the 95% CI is presented in Figure 13 below. The estimated HR at the interim OS analysis is 0.69 (95% CI: 0.46,1.02, stratified log-rank p-value=0.06). The result was not statistically significant when compared to the 0.0016 significance level (calculated from the O'Brien-Fleming alpha spending function at 45% of the targeted 220 events). The final report of OS is expected in 2021 per Post marketing Commitment (PMC) #1.

Figure 21 Kaplan-Meier Plot for Overall Survival in the ITT population

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Source: FDA statistical reviewer generated using the adtte.xpt dataset

Integrated Review of Effectiveness

The FDA's Assessment:

The FDA found Applicant's sensitivity analyses adequate and did not conduct additional sensitivity analyses.

8.1.3. Assessment of Efficacy Across Trials

The Applicant's Position:

Phase 1b TCD14079 Part A study serves as a supportive study for BLA 761113, as it also evaluates isatuximab in combination with Pd for RRMM patients.

Study TCD14079 Part A

Study TCD14079 Part A was a US, multicenter, open label, non-comparative, Phase 1b study in which isatuximab was evaluated in combination with standard doses of pomalidomide and dexamethasone (given at the respective approved doses of pomalidomide [4 mg] and dexamethasone [40 mg; 20 mg for patients aged ≥75 years]) in patients with RRMM who had

received at least 2 previous therapies and that have been previously exposed to proteasome inhibitors and lenalidomide and progressed during or after the most recent therapy.

The key eligibility criteria in this study were similar to those in the pivotal study EFC14335. As per Amendment 2, patients previously exposed to pomalidomide and non-refractory to the last line were allowed in the trial. Study TCD14079 Part A consisted of a dose escalation phase followed by an expansion cohort of 22 patients that was initiated after determination of the recommended dose.

Patients could continue treatment in the study until unacceptable AEs, disease progression, withdrawal of consent, Investigator's decision, Sponsor decision to stop the study, and/or availability of study drug.

The standard 3+3 design was used during the dose escalation phase of the study. The following dose levels of isatuximab administered QW/Q2W were sequentially evaluated:

- Dose Level 1: 5 mg/kg (QW/Q2W)
- Dose Level 2: 10 mg/kg (QW/Q2W)
- Dose Level 3: 20 mg/kg (QW/Q2W)

After the dose escalation phase, where there were no differences in overall response and safety profile between the doses of 10 mg/kg and 20 mg/kg, PK simulations, and the results of the trial in combination with lenalidomide and dexamethasone (study TCD11863) where there was no difference in response rate and safety profile between the dose of 10 mg/kg and 20 mg/kg, the dose of isatuximab 10 mg/kg QW/Q2W was defined as the recommended dose in combination with Pd and was further assessed in an expansion phase in 22 patients to further characterize safety and explore evidence of efficacy.

The primary endpoint of study TCD14079 was safety, with efficacy of isatuximab assessed with BOR as per the IMWG 2014 response criteria (Table 19), ORR, PFS, DOR, TT1R, and OS. Responses were assessed by the investigator based on local laboratory M-protein results, local bone marrow and local radiology imaging assessment.

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Table 19 - Best overall response, overall response rate and clinical benefit rate – All-treated population in Study TCD14079

	Isatuximab (dose level) + pomalidomide/dexamethasone			
	5 mg/kg (N=8)	10 mg/kg (N=31)	20 mg/kg (N=6)	All (N=45)
Overall Response Rate (≥PR)	5 (62.5%)	20 (64.5%)	3 (50.0%)	28 (62.2%)
95% CI[a]	(24.5% to 91.5%)	(45.4% to 80.8%)	(11.8% to 88.2%)	(46.5% to 76.2%)
- Stringent Complete Response (sCR)	0	1 (3.2%)	0	1 (2.2%)
- Complete response (CR)	1 (12.5%)	0	0	1 (2.2%)
- Very Good Partial Response (VGPR)	2 (25.0%)	6 (19.4%)	2 (33.3%)	10 (22.2%)
- Partial response (PR)	2 (25.0%)	13 (41.9%)	1 (16.7%)	16 (35.6%)
Minimal response (MR)	0	4 (12.9%)	1 (16.7%)	5 (11.1%)
Stable disease (SD)	1 (12.5%)	3 (9.7%)	2 (33.3%)	6 (13.3%)
Progressive disease (PD)	1 (12.5%)	2 (6.5%)	0	3 (6.7%)
Not evaluable	1 (12.5%)	2 (6.5%)	0	3 (6.7%)
Clinical benefit rate (≥MR)	5 (62.5%)	24 (77.4%)	4 (66.7%)	33 (73.3%)
95% CI[a]	(24.5% to 91.5%)	(58.9% to 90.4%)	(22.3% to 95.7%)	(58.1% to 85.4%)

a estimated by Clopper-Pearson Exact method
PGM=PRODOPS/SAR650984/TCD14079/CSR/REPORT/PGM/eff_oresp_s_t.sas OUT=REPORT/OUTPUT/eff_oresp_s_t_i.rtf (09MAY2018 - 17:16)

Duration of follow-up, duration of response, and time to first response

DOR was assessed using Kaplan-Meier method in 28 responders. All responding patients who did not have an event of PD or death at the time of the DOR analysis were censored (N=17) at last disease assessment. The median DOR was 18.7 (95% CI 12.45 to NC) months overall. Median DOR was not reached for the 10 mg/kg and 20 mg/kg groups. Overall, the median duration of follow-up was 8.61 (range 0 to 25.8) months . Among the 3 dose groups, the median duration of follow-up was 11.19 months in the 20 mg/kg group, and lower in the 5 mg/kg group (10.35 months) and the 10 mg/kg group (8.54 months); note that the 10 mg/kg expansion group was the last enrolled, and therefore the duration of follow-up was shorter.

Overall, in responder patients, the median time to first response was 0.95 months (range 0.9 to 5.1 months) and was similar between all dose levels.

Progression-free survival

At the time of analysis, 21 (46.7%) patients were reported to have had a PFS event (ie, confirmed PD, symptomatic deterioration or death), and 24 (53.3%) patients were censored. The median PFS was 17.6 months (95% CI: 6.80 to 20.50) overall. In the 10 mg/kg group, the median PFS was 17.6 months (95% CI: 6.80 to NC) and the estimated PFS rate at 24 months was 45.2% (95% CI: 16.1 to 74.2%). (**Figure 22**)

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In subgroup analyses, patients who had received >3 prior lines of therapy appeared to have longer PFS versus patients who had received 1-3 prior lines of therapy, before the survival curves cross around 17 months; the reason for the finding is unclear. However, these results should be interpreted with caution because of the small sample size.

At the time of analysis, 19 patients were still ongoing treatment and the median duration of exposure was 41.7 weeks.

Figure 22 - Kaplan-Meier curves of progression free survival - Studies EFC14335 and TCD14079

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Pd: pomalidomide and dexamethasone; IPd: isatuximab in combination with pomalidomide and dexamethasone
PGM=PRODOPS/SAR650984/OVERALL/SCE_MM_SUB_1/REPORT/PGM/eff_km_pfs_f.sas
OUT=REPORT/OUTPUT/eff_km_pfs_f_x rtf (19FEB2019 8:24)

The FDA's Assessment:

Study TCD14079 was a single arm, dose-finding trial with safety as the primary endpoint. Various dose-levels were evaluated as part of the '3+3' design before selecting the dose of isatuximab 10 mg/kg QW/Q2W for further development. This trial is not designed to support regulatory conclusions regarding efficacy of the Isa-Pd combination in the indicated patient population.

The FDA does not agree in evaluating time to event endpoints like PFS and OS in a single arm trial without a comparative control arm.

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The statistical reviewers do not agree with the characterization of data in the KM plot in **Figure 22** for the following reasons.

a) This plot ignores the key fact that the patients in Study TCD14079 were treated at different dose levels and combines them into a single cohort in the plot.

b) Superimposing the results from a single arm trial with the results from a randomized trial could imply inferential comparison which is misleading.

The FDA disagrees (b) (4)

8.1.4. Integrated Assessment of Effectiveness

The Applicant's Position:

The overall efficacy results across studies are summarized below.

Isatuximab 10 mg/kw QW/Q2W, when added to a Pd regimen, led to prolonged PFS, induced deep and durable responses, and provided evidence of disease control and longer OS in patients with relapsed/refractory multiple myeloma, including heavily pretreated and refractory patients, and patients with adverse disease characteristics.

The efficacy of the IPd regimen was demonstrated in the pivotal study EFC14335 in comparison with a Pd control group. The efficacy data from the IPd arm of the pivotal study were consistent with the data from Phase 1b study TCD14079 Part A in the same combination in a similar population. These studies, combining isatuximab with pomalidomide and dexamethasone, built on earlier evidence of antitumor activity as a single agent in heavily pretreated relapsed/refractory multiple myeloma (overall response rate of 24.3% in 111 patients treated with isatuximab at the dose level of 10 mg/kg in single agent studies).

The EFC14335 study population was representative of the global population with RRMM, including important subgroups of patients with poor prognosis characteristics (ISS Stage III [25.1%], renal function impairment [36.2%], high-risk cytogenetics [19.5%], elderly ≥75 years [19.9%], ECOG PS 2 [10.4%], and high levels of LDH [32.2%]). Patients were heavily pretreated (median of 3 prior lines) and almost all were refractory to their last regimen.

In study EFC14335, the addition of isatuximab to Pd led to a statistically significant and clinically meaningful improvement in PFS as compared to Pd. The estimated hazard ratio was 0.596 (95% CI: 0.436 to 0.814), corresponding to a reduction of 40.4% in the risk of progression or death with IPd compared to Pd (1-sided, p=0.001). Median PFS (95% CI) in the IPd arm was 11.53 months (8.936 to 13.897) and was longer than the 6.47 months (4.468 to 8.279) in the Pd arm. In study TCD14079 Part A, the median PFS was 17.6 months at the 10 mg/kg QW/Q2W dose. The observed improvement in PFS in study EFC14335, as determined by IRC, was consistent

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with the assessment per investigator using local data and was consistent with all sensitivity analyses, with hazard ratios within the 0.5 and 0.6 range, demonstrating its robustness. Analyses of PFS by the investigator and of time to next treatment provided real-life confirmation of the improved disease control for the IPd combination.

Improvement in PFS was shown for IPd over Pd across patient subgroups in study EFC14335, including the high risk cytogenetics population, elderly patients, renal function impairment, heavily pretreated patients (>3 prior lines), and highly refractory patients. A multivariate analysis of PFS adjusted for demographic and baseline characteristics (adjusted HR of 0.484 versus 0.596 for the primary analysis stratified by stratification factors) suggested that there could have been some confounding factors among the analyzed covariates that may have influenced the treatment effect in the primary analysis in favor of the Pd arm.

An improvement in the rate and depth of responses (PR or better) was shown for patients who received IPd compared with Pd (60.4% versus 35.3%). The 1-sided stratified CMH p-value was <0.0001, demonstrating a significant difference in ORR between the two arms in favor of IPd at the 1-sided 0.025 level. Results of subgroup analyses were consistent with the overall ORR analysis. The VGPR or better rate was significantly higher in the IPd arm (31.8%) compared to Pd arm (8.5%) (p<0.0001). Results of subgroup analyses were consistent with the overall ORR analysis. In Phase 1b study TCD14079 Part A, the ORR was 64.5% at the 10 mg/kg QW/Q2W dose. The VGPR rate was higher in study EFC14335 (31.8%) versus study TCD14079 Part A (22.6%).

The responses observed with IPd were fast and durable. In an ITT analysis, the time to first response (TT1R) was shorter in the IPd arm than in the Pd arm of study EFC14335: median TT1R (95% CI) was 1.94 months (1.31 to 2.00) and 3.02 months (2.83 to 5.06), in the IPd and Pd arms, respectively. In patients obtaining a response, the median time to first response was 35 days on the IPd arm and 58 days on the Pd arm. In study TCD14079 Part A, the median time to response in the responder population was 30 days at 10 mg QW/Q2W (consistent with EFC14335). In study EFC14335, the median duration of response (95% CI) was 13.27 months [10.612 to NC] with IPd and 11.07 months [8.542 to NC] with Pd. In study TCD14079 Part A, the median duration of response was not calculable for the 10 mg QW/Q2W dose at a median of 8.5 months of follow-up; the 25% quantile was 5.9 months (4.6 to NC).

In the IPd arm, 8 patients were MRD negative (10-5) and neither of the 2 patients tested in the Pd arm reached the threshold for negativity. An exploratory mass spectrometry analysis indicated that, in 11 of 22 patients who achieved near-CR (a VGPR subcategory) in the IPd arm, the residual immunofixation-positivity was due to M-protein interference. This provides evidence that the CR rate in the IPd arm was likely underestimated due to the interference of isatuximab with M-protein assessment, particularly immunofixation.

In study EFC14335, a trend toward longer OS was observed in patients who received IPd compared with Pd (hazard ratio 0.687). At a median duration of follow-up of 11.56 months in the IPd arm and 11.73 months in the Pd arm, median OS had not been reached in either

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treatment arm; the 25% quantile for median OS (95% CI) was 10.64 months (7.688 to 14.456) for IPd and 6.60 months (5.027 to 10.086) for Pd. This improvement was observed despite the potential to switch patients to a daratumumab containing regimen as next therapy (10% in the IPd arm versus 54.2% in the Pd arm of patients received subsequent daratumumab therapy). In study TCD14079 Part A, the 25% quantile for median OS (95% CI) was 17.6 months (6.2 to NC). Disease control with IPd was also demonstrated in study EFC14335 by a delay in the need for subsequent treatment, evidence regarding positive benefit on renal function on treatment, and maintenance of quality of life. The median time to next myeloma treatment was not reached in the IPd arm and was 9.10 months in the Pd arm, with fewer patients in the IPd arm receiving subsequent therapy (39.0% versus 54.2%).

There was greater improvement in renal function and a trend toward less renal function deterioration in the IPd arm in patients who entered the study with renal impairment. These benefits are in addition to the overall efficacy seen in the subgroup of IPd patients with eGFR <60 mL/min/1.73m^2: median PFS of 9.50 months (HR 0.502) and ORR of 56.2%. The addition of isatuximab to Pd did not negatively impact quality of life. The QLQ-C30 global health score was maintained throughout treatment and was similar in both treatment groups.

In conclusion, the addition of isatuximab to the pomalidomide-dexamethasone regimen provided a clinically meaningful efficacy benefit in Phase 3 study EFC14335. The improvements in efficacy were consistent between endpoints, between IRC and investigator assessment, between subgroups, and between the Phase 3 EFC14335 and the Phase 1b study TCD14079 Part A. They were further supported by the prior observations of single agent antitumor activity of isatuximab in relapsed/refractory multiple myeloma.

The FDA's Assessment:

Study EFC14335 was a well-controlled and well-conducted randomized clinical trial. The FDA agrees that study EFC1433 provided evidence of effectiveness in terms of PFS of the IPd arm over the Pd arm in treatment of multiple myeloma patients. This was further substantiated by the evaluation of ORR. The OS analyses at this interim analysis had 45% of the 220 death events and a final analysis is requested as part of a PMC to rule out any long term detriments from the addition of isatuximab to the Pd backbone.

The Applicant also provided data from Study TCD14079 which was designed an early phase dose finding trial with an expansion cohort of patients treated at the recommended dose level. With 31 patients treated at the 10mg/kg dose level, the study results provided sufficient evidence of the appropriate dose selection. Due to the single-arm nature of the trial, no comparative statistical inference could be conducted. The approval of isatuximab was based mainly on the efficacy demonstrated in Study EFC14335.

The FDA has the following comments regarding the characterization of results by the Applicant in this section:

1. The FDA disagrees with the Applicant's promotional language *"The EFC14335 study population was representative of the global population..."*. The study EFC14335 population was selected based on specific inclusion/exclusion criteria, and the current sampling mechanism does not guarantee to have the study EFC14335 population to represent the global population in all aspects.
2. Although the ORR was higher in the IPd arm, 32 (34%) of the 93 responders had a disease progression/death event comparable to 19 (35%) events of the 54 responders on the Pd arm. The FDA does not agree with the applicant's promotional language characterization that *"the duration of response was longer"* on the IPd arm although the point estimates might differ. In an analysis that considers only the responders without appropriate statistical tests, such analyses are considered exploratory.
3. The FDA disagrees with the promotional language *"responses occurred more rapidly"* used to characterize the time to response. These analyses were conducted only in the responders and is considered exploratory.
4. The applicant's analysis of PFS and ORR in the various subgroups is exploratory as no alpha was allocated for these comparative analyses.
5. There was no pre-specified testing procedure and analysis plan for the QoL endpoints. Also, there was no formal statistical testing done to claim that *"the addition of isatuximab to Pd did not negatively impact quality of life"*. The QoL endpoints were not evaluated to show a difference in the two treatment arms.
6. The *"improvement in renal function"* was tested in a very small subgroup of patients who had creatinine clearance (MDRD) <50ml.min/1.73m2 at baseline, 21 and 32 patients on the Pd and IPd arm, respectively. These conclusions are not based on pre-planned subgroup analyses. No efficacy conclusions can be made based on this analysis.
7. MRD was an exploratory endpoint. MRD assessments were not performed consistently across the two arms. There was a high rate of failure to detect a baseline diagnostic clone in the Pd arm patients. These issues limit interpretability of the MRD results.
8. Patients in Study TCD14079 were treated at different dose levels and this single-arm study was not designed to show the efficacy of IPd combination. The efficacy results from this study presented in the assessment is only descriptive and considered exploratory.

8.2. Review of Safety

The Applicant's Position:

The safety profile of isatuximab in combination with pomalidomide and dexamethasone (IPd) has been evaluated compared to pomalidomide and dexamethasone (Pd) in patients with RRMM in study EFC14335, supported by a Phase 1b study with the same combination (TCD14079 Part A). Although some TEAEs were more frequent in the IPd arm, the overall safety profile is generally favorable. When serious TEAEs were adjusted for the longer duration of exposure in the IPd arm, their overall incidence rates in patient-years were similar (1.36 and 1.30 in the IPd and Pd arms, respectively). No dose dependency in the isatuximab safety profile was seen through the analyses of the single-agent isatuximab studies.

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From a total of 576 patients treated with isatuximab as single agent or in a number of combinations, the vast majority of whom being patients with RRMM, the safety profile of IPd consists mainly of infusion reactions (IRs) and an increase of neutropenia and infections compared to Pd, which did not interfere with the treatment duration or the overall quality of life as assessed by the Global Health Score of EORTC QLQ-C30 and the clinical benefit. Overall, the safety profile of IPd was well manageable and consistent through the pooled data analyses in RRMM population.

The pivotal study EFC14335 is the first controlled, randomized trial that has investigated a regimen consisting of an anti-CD38 monoclonal antibody used in combination with the backbone therapy consisting of pomalidomide plus dexamethasone in patients with RRMM. The findings from this study, supported by TCD14079 Part A (the Phase 1b study with the same combination), allow the careful evaluation of the safety profile of isatuximab added to pomalidomide and dexamethasone, compared to pomalidomide and dexamethasone alone, in this patient population. As a result, the overall safety profile of this active triplet is well characterized and is generally manageable with supportive care and dose modifications of pomalidomide and dexamethasone, adding a significant clinical benefit through the proposed product labelling.

The FDA's Assessment:

The FDAs independent analysis demonstrated the safety profile of IPd at the dosing regimen used in Study EFC14335. Infusion related reactions, neutropenia and infections are important safety concerns with the addition of isatuximab to pomalidomide and dexamethasone. In addition to the safety profile described above, the FDA analysis also noted higher rates of second primary malignancies in the IPD arm (3.9%) compared to the Pd arm (0.7%). FDA agrees with Applicant's assessment that the overall safety profile of this active triplet is well characterized and is generally manageable with supportive care and dose modifications of isatuximab in addition to pomalidomide and dexamethasone. The FDA does not agree with the Applicant's conclusions that the safety profile did not interfere with the treatment duration or the overall quality of life as assessed by the Global Health Score of EORTC QLQ-C30 and the clinical benefit. The study was not designed to answer these questions the results of these analysis should be considered exploratory. FDA did not independently analyse safety data from the other IPd studies and the other pooled populations.

8.2.1. Safety Review Approach

The Applicant's Position:

Safety was primarily assessed by integrating safety data from the completed MM studies or study parts into a common safety database. In total, safety data from 6 completed studies involving 576 patients treated with isatuximab were combined into 4 data pools: the IPd core studies, single agent studies, other isatuximab combination studies, and totality of the

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isatuximab treated patients (from the other 3 pools). This safety database is informative for the proposed indication as most safety data are obtained within the target disease (571 patients with MM, 554 patients with RRMM) and provide relevant exposure with the targeted IPd combination (197 patients) and with isatuximab as single agent (305 patients). An analysis of all the reported serious adverse events (SAEs) in all ongoing MM studies is also provided. In addition, interim results are provided from the ongoing study TCD14079 Part B regarding the use of a fixed infusion volume method and optimized rate for the administration of isatuximab in mL/h.

The safety review focuses on the IPd pooled analysis (Pool 1, defined below), particularly on the comparison between treatment arms in pivotal study EFC14335, supported by the single agent pooled analysis (Pool 2). Where relevant, the pooled analysis of all isatuximab treated patients (Pool 4) is also summarized. When discussing Pool 1, the analyses focus on study EFC14335, as the Pd control group allows a direct comparison and the pooled IPd safety data were generally very similar to the data obtained on the IPd regimen in the pivotal study.

Clinical studies

At the time of the dossier cutoff date (15 November 2018), the following 6 company-sponsored studies had been completed and their data were integrated in a common safety database: the pivotal Phase 3 MM trial (EFC14335) and 5 supportive studies (TCD14079 Part A, TED10893, TED14154 Part A, TCD11863, TCD13983 ICBd). In these 6 studies, a total of 576 patients were treated with isatuximab.

As described, the core studies of IPd in patients with RRMM consist of the pivotal Phase 3 EFC14335 study and the Phase 1b TCD14079 Part A study, as these 2 studies were conducted with the Pd regimen.

- EFC14335 is a prospective, multicenter, multinational, randomized, open-label, parallel group, and 2-arm Phase 3 study evaluating the clinical benefit of IPd as compared to Pd for the treatment of patients with RRMM who have received at least two lines of therapy including lenalidomide and a PI (bortezomib, carfilzomib, or ixazomib) given alone or in combination and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
- Study TCD14079 Part A is a Phase 1b, multicenter, open label, dose escalation study of isatuximab in combination with Pd in patients with RRMM who have received at least two previous therapies including a PI and immunomodulatory drugs (IMiD) and have demonstrated disease progression on therapy or after completion of the last therapy (ie, a patient population similar to that of the pivotal Phase 3 study EFC14335). This trial enrolled patients in the United States only.

Supportive safety data are provided by 2 single-agent studies and 2 studies of isatuximab in combination with other myeloma regimens. Single-agent Phase 1-2 studies in patients with MM and other hematological malignancies include:

- TED10893 (Phase 1, Phase 2 Stage 1, and Phase 2 Stage 2), dose escalation and expansion safety, pharmacokinetic and efficacy study of multiple intravenous administrations of isatuximab in patients with selected CD38+ hematological

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malignancies. The data from study TED10893 Phase 2 Stage 2 are based on an interim safety report.

- TED14154 (Part A), A dose-escalation/expansion and multi-center study to evaluate the safety, PK, and efficacy of isatuximab (b) (4) in patients with relapsed/refractory MM.

Combination Phase 1b studies in patients with MM include:

- TCD11863 ILd, dose escalation and expansion study of isatuximab in combination with lenalidomide and dexamethasone (ILd) for the treatment of relapsed/refractory MM
- TCD13983 ICBd, 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 not eligible for transplantation.

In addition to the completed studies, fourteen studies were ongoing at the dossier cutoff date:

- 7 MM company-sponsored studies or parts of studies (TCD14079 Part B,TED14095, TED14154 Part B, TCD13983 IBLd, TCD14906, EFC12522, and EFC15246)
- 2 non-MM company-sponsored studies (ACT15319 and ACT15377)
- 5 MM investigator-sponsored trials (TCD12795, IIT15379, IIT14801, IIT15403, and IIT14272)

Among the ongoing studies, TCD14079 Part B is a Phase 1b study, where the feasibility of isatuximab, in combination with pomalidomide and dexamethasone, administered in a fixed infusion volume was evaluated using the occurrence of Grade ≥3 IRs as primary endpoint in patients with RRMM. Interim safety results of the TCD14079 Part B are presented in addition to the SAEs (cutoff 02 January 2019, n=34).

Safety parameters and conventions

All adverse events (AEs) were graded according to NCI-CTCAE v4.03 and coded according to MedDRA version 21.0. AEs, regardless of their seriousness or causal relationship to study treatment, were recorded from the time of signed informed consent until the end of the treatment period (30 days after the last dose of study treatment). During the post-treatment period, only treatment-related AEs or SAEs regardless of causal relationship were reported in the eCRF.

Adverse events were defined by observation period, as follows:

- Pre-treatment adverse events are any AEs reported during the pre-treatment period, which is defined as the time from the signed informed consent date up to the first dose of study treatments.
- Treatment-emergent adverse events (TEAEs) are AEs that developed or worsened or became serious during the treatment period, which is defined as the time from the first dose of study treatments administration to the last dose of study treatments + 30 days.
- Post-treatment adverse events are AEs that developed or worsened or became serious during the post-treatment period, which is defined as the period of time starting the day after the end of the treatment period up to the end of the study (as defined in the protocol).

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Treatment-related TEAEs are defined as TEAEs for which, according to the reporting investigator, there was a reasonable possibility that it was caused by isatuximab in monotherapy studies, or at least one of the study treatments in drug combination studies.

Other significant adverse events included TEAEs leading to treatment discontinuation and TEAEs leading to dose modifications. In addition, to further evaluate potential risks, the following other significant AEs were assessed: IRs (including cytokine release syndrome [CRS]), second primary malignancies (SPMs), respiratory AEs (lower respiratory AEs and respiratory infections), neutropenia and neutropenic complications, infection, thrombocytopenia and hemorrhages, tumor lysis syndrome (TLS), hemolytic disorders and blood cell (red blood cells and platelet) transfusions, autoimmune disorders, anti-drug antibodies (ADAs), and long term adverse events. IRs were reported as adverse events of special interest (AESI), and SPMs were reported as AESIs in combination studies TCD11863, TCD14079, and TCD13983.

Data pooling strategy

The pooling strategy is defined according to the use of isatuximab in combination with Pd, as a single-agent (with or without dexamethasone), or in combination with other MM regimens. The integrated safety database has been generated based on the 6 company-sponsored studies that were completed, at least in one of their parts (Table 9). The four data pools were defined as follows:

- Data Pool 1: Core IPd combination studies (EFC14335 and TCD14079 Part A). Tables contain data from study EFC14335 by arm and pooled with data from study TCD14079 Part A at the isatuximab10 mg/kg dose group and for all patients treated with IPd.
- Data Pool 2: Supportive single-agent isatuximab studies (TED10893 and TED14154 Part A). Tables are presented for the isatuximab dose groups <10 mg/kg, 10 mg/kg, 20 mg/kg, 20 mg/kg + dexamethasone, and all together, based on the absence of dose dependency across the dose groups, as concluded in the individual CSRs.
- Data Pool 3: Supportive studies of isatuximab in combination with other regimens (TCD11863 and TCD13983 ICBd). The data from each of these 2 studies are tabulated side by side for full disclosure. In addition, they provide information on (1) the role of the infusion rate in association with the incidence and severity of IRs, (2) the long duration of drug exposure, and (3), a different but related population of patients with NDMM.
- Data Pool 4: All patients exposed to isatuximab in Data Pools 1, 2, and 3 are included in Data Pool 4. Tables are presented by combination category (IPd, single agent isatuximab [+/- dexamethasone], and other combinations).

Statistical analyses

The safety population includes all patients who gave informed consent and were exposed to at least one dose or a partial dose of the study treatments. In addition:

- In randomized studies, patients are analyzed in the treatment arm actually received. In particular, a randomized patient who received at least 1 isatuximab dose (even if by

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error) during the trial, was analyzed in the isatuximab arm. Any patient treated but not randomized was excluded from the safety population.

- In non-randomized studies, patients enrolled and treated are analyzed according to their intended treatment and dose assignment.

The ADA population includes isatuximab treated patients in the safety population with at least one ADA reportable result during the on-study ADA observation period.

For continuous variables, descriptive statistics include the number of observations, mean, standard deviation, median, and range (minimum and maximum). For categorical variables, descriptive statistics include the frequency and percentage. Percentages are calculated using the number of patients with non-missing data as a denominator, unless otherwise stated. All confidence intervals (CIs), statistical tests, and resulting p-values are reported as 2 sided and are assessed at the 5% significance level, unless otherwise stated. As there is no adjustment for multiplicity, p values are reported for informational purposes only.

AEs and laboratory findings are presented using different incidence thresholds, based on severity, clinical relevance, and the number of patients.

The primary focus of AE analyses is on TEAEs. For patients with multiple occurrences of the same adverse event, the maximum (worst) grade by period of observation was used.

Statistical analysis details are described in greater detail in the Summary of Clinical Safety.

The FDA's Assessment:

The FDAs assessment of safety focused primarily on results from the randomized Phase 3 study EFC 14335. The safety population from this trial included a total of 301 patients (IPd=152; Pd=149). The FDA independently confirmed the safety results from Study EFC 14335. The FDA assessment focused on the analysis from Study EFC14335 only as this trial was the only trial that included the Pd control group and allows a direct comparison of safety results. The Applicant's assessment of the other studies included in the Pool 1 and the other pooled populations was reviewed but FDA did not independently confirm the numerical values reported, as the patient population and backbone differed across these studies and results from the pooled analysis may not be applicable to the patient's population covered in the requested indication.

The FDA also used grouped terms to calculate rates of TEAEs for adverse events of "pneumonia", "upper respiratory tract infections", "dyspnea" and cough as these events were captured under different adverse event terms in the AE dataset.

Grouped Terms:
Pneumonia: atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenzal, pneumonia pneumococcal, pneumonia streptococcal,

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pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jirovecii pneumonia.

Upper Respiratory Tract Infections: bronchiolitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenzae virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial
Dyspnea: Dyspnea, dyspnea exertional, and dyspnea at rest.
Cough: Cough and productive cough.

Additional differences in the FDA's and Applicant's assessment of safety are noted under the respective safety categories in this safety section.

Review of the Safety Database

Overall Exposure

The Applicant's Position:

Pool 1 (core IPd combination studies)
The safety population in Pool 1 includes 149 patients and 152 patients in the Pd and IPd arm of study EFC14335, and 183 and 197 pooled patients in Group IPd 10 mg/kg and Group All IPd doses, respectively (34 and 45 additional patients from study TCD14079 Part A).

The extent of overall treatment exposure in study EFC14335 was greater in IPd compared to Pd in terms of the median number of cycles started (10 versus 6, respectively) and the median duration of exposure (41 versus 24 weeks); overall, the extent of isatuximab exposure was similar among the 3 IPd groups in Pool 1. Comparing Groups IPd 10 mg/kg and Pd in the pivotal Phase 3 study EFC14335, group IPd had more patients still ongoing in treatment at the cutoff date (42.8% versus 23.5%) and had fewer patients who discontinued treatment due to disease progression (43.4% versus 59.1%) or due to AE (7.2% versus 12.8%), which were the most frequent reasons for discontinuing treatment. The 2 pooled IPd groups were similar to Group EFC14335 IPd 10 mg/kg regarding the percent of patients ongoing treatment and the reasons for treatment discontinuation (incidence values differed by <3%). The median RDI of isatuximab was 92.3%. While the median RDI of pomalidomide (85.1% in the IPd arm versus 93.3% in the Pd arm) and dexamethasone (87.8% in IPd am and 96.3% in Pd arm) were affected by dose reductions and omissions for the management of neutropenia and infections, it was without impact on the extent of the treatment duration and therefore on the clinical benefit from the therapy.

The duration of overall treatment exposure was almost twice as long in the IPd arm compared to the Pd arm, 41 weeks versus 24 weeks (the median duration of isatuximab exposure in group All IPd doses was 41 weeks). The incidence of dose reductions and dose omissions of

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pomalidomide and dexamethasone (and dose delays of dexamethasone) was greater in IPd than Pd. Groups pooled IPd 10 mg/kg and pooled All IPd doses were similar to group EFC14335 IPd 10 mg/kg in terms of median duration of isatuximab exposure, median isatuximab RDI, and the number of patients with at least 1 isatuximab infusion delayed, interrupted, or omitted.

Pool 2 (supportive single-agent isatuximab studies)

The safety population in Pool 2 included 305 patients: 48 patients received isatuximab <10 mg/kg, 111 received isatuximab 10 mg/kg, and the majority, 146 patients, received isatuximab 20 mg/kg with or without dexamethasone. The median total duration of isatuximab exposure was 12 weeks (range 1 to 120.4), and the median RDI was 99.9%.

Pool 3 (supportive isatuximab combination studies)

For Studies TCD11863 ILd and TCD13983 ICBd, respectively, the median number of cycles started was 9 and 12, the median total duration of isatuximab exposure was 36.3 and 52.3 weeks, with a maximum of approximately 3 years (152 weeks) of isatuximab treatment exposure in the TCD11863 ILd study. The median RDI was ≥93% in both studies. The percent of patients having at least 12, 18, and >24 months of treatment, respectively, in study TCD11863 ILd was 31.6% (18 patients), 14.0% (8 patients), and 7.0% (4 patients); and in study TCD13983 ICBd was 52.9% (9 patients), 23.5% (4 patients), and 0%. Overall, the median number of cycles started and the duration of exposure for lenalidomide (in study TCD11863 ILd) and for cyclophosphamide and bortezomib (in study TCD13983 ICBd), were both similar to isatuximab. The median RDI for lenalidomide was 83.4%, and for cyclophosphamide and bortezomib was 94.75% and 92.97%, respectively.

Pool 4 (all patients exposed to isatuximab)

Pool 4, which includes all isatuximab-treated patients, includes 576 patients: 197 patients from Pool 1, 305 patients from Pool 2, and 74 patients from the other combination studies in Pool 3. Of all patients treated with isatuximab, 31.3% were still ongoing treatment at the cutoff date. The median total duration of isatuximab exposure was 20 weeks (range 1 to 152.4), and the median RDI was 96.9%. The most frequent reasons for definitive or premature discontinuation of isatuximab were disease progression in 54.0% and AEs in 7.6% of patients. There were 99 patients (17.2%) who have been treated with isatuximab for ≥12 months (50 patients with IPd), 23 patients (4.0%) treated for ≥18 months (7 patients with IPd), and 8 patients (1.4%) treated for ≥24 months (1 patient with IPd). The overall extent of exposure in all-isatuximab treated patients is summarized in Table 20.

Table 20 - Extent of isatuximab exposure - Data Pool 4 - safety population

	Isatuximab*			
	IPd (N=197)	**Isa(+/-Dex) (N=305)**	**Other combo (N=74)**	**All (N=576)**
Total number of cycles started	1847	1447	812	4106
Number of cycles started by patient				
Number	197	305	74	576

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	Isatuximab*			
	IPd (N=197)	**Isa(+/-Dex) (N=305)**	**Other combo (N=74)**	**All (N=576)**
Mean (SD)	9.4 (5.4)	4.7 (4.9)	11.0 (8.9)	7.1 (6.2)
Median	10.0	3.0	10.5	5.0
Min ; Max	1 ; 28	1 ; 28	1 ; 37	1 ; 37
Number of cycles started by patient [n(%)]				
At least 1 cycle	197 (100)	305 (100)	74 (100)	576 (100)
At least 2 cycles	185 (93.9)	234 (76.7)	63 (85.1)	482 (83.7)
At least 3 cycles	174 (88.3)	181 (59.3)	58 (78.4)	413 (71.7)
At least 4 cycles	160 (81.2)	128 (42.0)	55 (74.3)	343 (59.5)
At least 5 cycles	147 (74.6)	104 (34.1)	50 (67.6)	301 (52.3)
At least 6 cycles	139 (70.6)	77 (25.2)	49 (66.2)	265 (46.0)
At least 7 cycles	128 (65.0)	65 (21.3)	44 (59.5)	237 (41.1)
At least 8 cycles	123 (62.4)	56 (18.4)	43 (58.1)	222 (38.5)
At least 9 cycles	117 (59.4)	48 (15.7)	43 (58.1)	208 (36.1)
At least 10 cycles	106 (53.8)	37 (12.1)	39 (52.7)	182 (31.6)
At least 15 cycles	31 (15.7)	20 (6.6)	22 (29.7)	73 (12.7)
At least 20 cycles	6 (3.0)	4 (1.3)	12 (16.2)	22 (3.8)
At least 25 cycles	1 (0.5)	3 (1.0)	5 (6.8)	9 (1.6)
Duration of isatuximab exposure (weeks)				
Number	197	305	74	576
Mean (SD)	38.44 (22.61)	18.85 (20.28)	44.97 (37.11)	28.90 (26.16)
Median	41.00	12.00	41.93	19.86
Min ; Max	1.0 ; 113.0	1.0 ; 120.4	1.0 ; 152.4	1.0 ; 152.4
Duration of isatuximab exposure [n(%)]				
At least 6 months	130 (66.0)	68 (22.3)	44 (59.5)	242 (42.0)
At least 12 months	50 (25.4)	22 (7.2)	27 (36.5)	99 (17.2)
At least 18 months	7 (3.6)	4 (1.3)	12 (16.2)	23 (4.0)
More than 24 months	1 (0.5)	3 (1.0)	4 (5.4)	8 (1.4)
Total cumulative dose (mg/kg)				
Number	197	305	74	576
Mean (SD)	196.19 (119.29)	141.88 (144.61)	240.26 (206.01)	173.09 (150.25)
Median	202.76	100.09	201.07	139.60
Min ; Max	0.6 ; 813.2	0.0 ; 760.2	0.2 ; 762.7	0.0 ; 813.2
Actual dose intensity (mg/kg/week)				
Number	197	305	74	576
Mean (SD)	5.37 (1.59)	8.50 (5.75)	5.91 (3.90)	7.10 (4.75)
Median	5.10	6.73	4.93	5.11
Min ; Max	0.6 ; 13.7	0.0 ; 20.7	0.2 ; 21.0	0.0 ; 21.0
Relative dose intensity (%)				
Number	197	305	74	576
Mean (SD)	89.72 (13.81)	100.41 (40.09)	87.48 (23.87)	95.10 (31.93)
Median	92.61	99.92	95.39	96.89
Min ; Max	5.6 ; 111.5	1.5 ; 525.6	1.1 ; 114.4	1.1 ; 525.6

Data Pool 4: EFC14335 (IPd arm only), TCD14079 Part A, TED10893, TED14154 Part A, TCD11863, and TCD13983 ICBd
IPd: isatuximab, pomalidomide, and dexamethasone; ILd: isatuximab in combination with lenalidomide and dexamethasone; ICBd: isatuximab in combination with cyclophosphamide, bortezomib, and dexamethasone, Isa: isatuximab, Dex: dexamethasone.

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	Isatuximab*			
	IPd (N=197)	Isa(+/-Dex) (N=305)	Other combo (N=74)	All (N=576)

* 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.
PGM=PRODOPS/SAR650984/OVERALL/POOL_MM_SUB_1/REPORT/PGM/cdc_extent_s_t.sas
OUT=REPORT/OUTPUT/cdc_extent_isa_p4_s_t_i.rtf (28MAR2019 7:54)

The FDA's Assessment:

The FDA does not agree with the presentation of the exposure data in Table 20. as it does not include the exposure from the Pd arm on Study EFC14335 for comparison. Additionally, the IPd arm includes patients from all IPd arms regardless of dose. FDA analysis of exposure of each drug in the combination in the individual arms of Study EFC14335 is shown in Table 21.

The FDA agrees with the Applicant's assessment of treatment exposure of the IPd arm and Pd arm in the EFC14335 study as stated in the text. The median number of cycles (10 versus 6, respectively) and the median duration of exposure (41 versus 24 weeks) was higher in the IPd arm compared to the Pd arm. This was consistent with the treatment exposure reported by the Applicant in the pooled Isa-Pd population (Pool 1). The RDI of pomalidomide (85.1% in the IPd arm versus 93.3% in the Pd arm) and dexamethasone (87.8% in IPd am and 96.3% in Pd arm) in the Pd arm on EFC 14335 study was >93% indicating that patients had adequate treatment exposure in the Pd arm. The exposure data from the studies evaluating single isa, isa-dex, and isa with other combinations were not confirmed independently by the FDA because these results are not applicable to the assessment of the IPd regimen.

Table 21 Exposure of Isatuximab, Pomalidomide and Dexamethasone – Study EFC14335

	IPd N=152			Pd N=149	
	Isa	Pom	Dex	Pom	Dex

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Median Number of Cycles Started **Min, Max**	10.0 1.0,19.0	10.0 1.0,18.0	10.0 1.0,19.0	6.0 1.0,18.0	6.0 1.0,18.0
Median Duration of Exposure (weeks) **Min, Max**	40.93 1,75.1	40.36 1.3,75.1	40.86 1.0,76.7	24.0 0.9,73.7	24.0 1.0,73.7
Median Actual Dose Intensity (mg/wk.) **Min, Max**	5.11 2,10	17.9 4.8,21.8	33.1 6.4,52.0	19.6 7.8,24.9	37.3 9.0,60.0
Median Relative Dose intensity (%) **Min, Max**	92.3 19.7,111.1	85.1 22.9,103.7	87.7 15.9,130.0	93.3 37.2,118.5	96.3 30.3,300.0

Source: FDA Analysis

Relevant characteristics of the safety population:

The Applicant's Position:

Pool 1 (core IPd combination studies)

The demographic characteristics at baseline of the patients in Data Pool 1 are representative of patients with RRMM. The IPd and Pd groups in study EFC14335 had similar demographic characteristics, including for median age (68 [range 36-83] versus 66 [range 41-86] years, respectively), patients aged ≥75 years (21.1% versus 18.8% of patients), and ECOG performance score of 0 or 1 (89.4% versus 90.6%), although the proportion of men was lower in the Pd group (57.9% versus 45.6%). The demographic characteristics of the 2 pooled IPd groups were similar those of the IPd group in study EFC14335, except for region, because TCD14079 Part A enrolled only patients in the US.

Groups IPd and Pd in study EFC14335 were similar for the median time from initial MM diagnosis to the study reference start date (4.38 [range 0.6 to 18.4] versus 4.07 [range 0.5 to 20.5] years) and for the percent of patients classified at study entry as ISS criteria Stage I, Stage II, Stage III, and unknown or missing, respectively (41.4%, 34.9%, 21.7%, and 2% versus 34.2%, 36.9%, 26.8%, and 2%), and the incidence of high risk of cytogenetic abnormality in 15.1% and 22.8%. The 2 pooled IPd groups were similar to the IPd group in study EFC14335 for these disease related characteristics. Among the prior treatments, alkylating agents, PIs, IMiDs and corticosteroids were each reported in 88.8% to 100% of patients. For the 4 groups in Pool 1, prior transplants (either autologous or allogenic) was reported in 53.3% to 59.1% of patients and 2 prior transplants were reported in 14.1% to 17.1%. Prior surgery and prior radiotherapy were generally balanced in groups IPd and Pd of EFC14335.

Comparing the IPd and Pd groups in study EFC14335, the overall use of systemic antibacterial

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agents was 91.4% versus 84.6%, respectively. More specifically, the concomitant curative use of antibacterial agents was higher in the IPd arm compared to Pd arm (80.9% versus 66.4% of patients), and the use of granulocyte colony stimulating factor (G-CSF) was also higher in the IPd arm (64.5% versus 45.0%). The two groups were similar for erythropoietin and blood transfusions. The overall use of antiviral agents was 79.6% versus 75.2% in the IPd and Pd arms, respectively, with a higher use as a prophylactic in both arms, 72.4% and 68.5% respectively, compared to the curative use.

In the three IPd groups in Data Pool 1, infusion reaction premedication's (paracetamol, corticosteroid or antihistamines [H1 only]) were used in 95% to 100% of all infusions. In EFC14335, montelukast was not included as a systematic premedication agent. It was allowed and was used per the investigator's decision. Montelukast was used in only 8 (5.3%) patients in group IPd, primarily as prophylaxis (6 patients).

Pool 2 (supportive single-agent isatuximab studies)
The demographic characteristics at baseline for the patients in Data Pool 2 are representative of patients with RRMM. Overall, the median age was 64 years (range 37 to 85) with about half of patients aged ≥65 years and 12.5% aged ≥75 years. The proportion of male and female was about 50% each. Nearly 90% of patients had a baseline ECOG performance score of 0 or 1.

At baseline, 300 of 305 patients (98.4%) had RRMM, 2 patients had chronic lymphocytic leukemia, and 3 patients had non-Hodgkin lymphoma. The median time from initial MM diagnosis to reference study start date was 5.79 years (range 0.7 to 24.1 years). At study entry, 28.5% of MM patients had a ISS criteria Stage III with a poor prognosis and 28% had a high risk cytogenetic abnormality. Patients from Data Pool 2 were heavily pretreated with an overall median 5 (range 1 to 14 lines) prior therapy lines. Among the prior treatments, PIs, IMiDs, and alkylating agents were each reported in ≥97% of patients. Prior transplants (either autologous or allogenic) reported in 74.8% of patients and at least 2 prior transplants were reported in 25.2% of patients.

Overall, among concomitant medications administered prophylactically or therapeutically, systemic antivirals were used in 65.2% of patients and systemic antibacterials in 59.7%.

Pool 3 (supportive isatuximab combination studies)
For Studies TCD11863 (ILd) and TCD13983 (ICBd) respectively, the median age was 61 and 71 (range 42 to 80 years) and the proportion of patients with age ≥65 years was 35.1% and 100% (in the latter study, transplant ineligibility was an inclusion criterion). In study TCD13983 (ICBd), approximately a quarter of the patients were aged ≥75 years. More than 80% of the patients in each study had an ECOG performance score of 0 or 1.

The median time from initial MM diagnosis to study start date in Studies TCD11863 and TCD13983 was 4.31 years (range 1.1 to 16.6 years) and 0.07 years (range 0 to 2.6 years), respectively. Of note, the population of patients in TCD13983 were newly diagnosed MM. In study TCD11863 ILd at baseline,19.3% of patients had a ISS criteria Stage III with a poor

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prognosis and 26.3% had a high risk cytogenetic abnormality.

In study TCD11863 ILd, the patients were heavily pretreated with a median number of prior therapy lines of 5 (range 1 to 12 lines) and prior treatments with PIs, IMiDs, and alkylating agents were reported in >95% of patients. Prior transplants were reported in 94.7% of patients, with 15.8% of patients having at least 2 prior transplants. Study TCD13983 only enrolled patients with newly diagnosed multiple myeloma who were not eligible for transplant, and had not received prior MM treatment.

Pool 4 (all patients exposed to isatuximab)

For all 576 patients treated with isatuximab (Pool 4), the median age was 65.0 years (range 36 to 85), 14.2% of patients were aged ≥75 years, 55.9% were male, and 88.9% had an ECOG performance score of 0 or 1. Groups Isa(+/- Dex) and Other combo had similar demographic characteristics to group IPd, although differences (5% to 13% versus group IPd) are noted for the following: both groups had fewer patients aged ≥75 years and fewer patients that were male, and group Other combo had more patients with an ECOG performance score of 2. While the median age was slightly higher in IPd versus the Isa(+/- Dex) and Other combo groups (68.0 versus 64.0 and 64.5 years, respectively), the other characteristics at baseline were generally balanced among the groups, and were substantially reflective of the RRMM patient population.

For all 576 patients treated with isatuximab, 571 (99.1%) had MM (including 17 from TCD13983 with NDMM) and 5 (0.9%) had other hematological malignancies. The median time from initial MM diagnosis to study reference start date was 5.03 years (range 0 to 24.1), and the percent of patients classified at study entry as ISS criteria Stage I, Stage II, Stage III, and unknown or missing, respectively, was 35.2%, 30.9%, 23.4%, and 10.4%. The median number of prior lines of anti-myeloma therapy was 4 and 99.0% of patients had at least 2 prior lines; 92.4% were previously pretreated with lenalidomide and 95.8% were previously treated with a PI

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the demographics of the safety population from Study EFC14335. The overall use of systemic antibacterial agents, specifically the concomitant use of antibacterial agents was higher in the IPd arm compared to Pd arm (80.9% versus 66.4% of patients), and the use of granulocyte colony stimulating factor (G-CSF) was also higher in the IPd arm (64.5% versus 45.0%). The FDA did not independently confirm the demographics, baseline disease characteristics and concomitant medications from the other 5 studies included in the pooled analysis above. The FDA did review the Applicant's analysis and notes that Study TCD TCD14079 Part A enrolled patients only in the US. The FDA also noted that despite enrolling all the patients in the US, no African Americans were enrolled on Part A of Study 14079.

Adequacy of the safety database:

The Applicant's Position:

The Applicant considers that study EFC14335 (a global trial) with support from study TCD14079

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(a US trial) represents the real world RRMM patient population who have received 2 prior therapies.

The FDA's Assessment:
The FDA agrees that the safety assessment from the pivotal trial Study EFC14335 provides adequate primary evidence to support approval of isatuximab in combination with pomalidomide and dexamethasone in patients with multiple myeloma who have received at least two previous therapies including lenalidomide and a proteasome inhibitor. The FDA disagrees with the Applicant's statement that this represents the real world RRMM patient population. The trial enrolled patients based on specific inclusion and exclusion criteria. The Applicant's assessment of safety from other trials and pooled population was not independently confirmed by the FDA.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
The Applicant considers the data to be well organized and of quality that allows a complete review of the safety of isatuximab.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Categorization of Adverse Event

The Applicant's Position:
All adverse events were graded according to NCI-CTCAE v4.03 and coded according to MedDRA.

Adverse events, regardless of their seriousness or causal relationship to study treatment, were recorded from the time of signed informed consent until the end of the treatment period (30 days after the last dose of study treatment). During the post-treatment period, only treatment-related AEs or SAEs regardless of causal relationship were reported in the eCRF.

Treatment-related TEAEs are defined as TEAEs for which, according to the reporting investigator, there was a reasonable possibility that it was caused by isatuximab in monotherapy studies, or at least one of the study treatments in drug combination studies.

Infusion reaction reporting. Throughout the isatuximab development program different rules have been used across clinical studies for the reporting of IRs in the electronic case report forms (eCRFs) and for the analysis of IRs in individual CSRs:

- In the pivotal study EFC14335, a specific AE eCRF page (ie, "Adverse events IR") was designed to collect the most appropriate diagnosis of the IR as per investigator judgment. In addition, symptoms related to IRs were to be reported in another specific

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page to allow a complete characterization of the IR. The diagnosis of the IRs is part of the TEAE analyses, while symptoms were analyzed separately.

- In all the supportive studies, the investigators were instructed to report a generic diagnostic term (ie, infusion related reaction) and each individual symptom of the IR in the same AE page of the eCRF. The generic diagnostic term of infusion related reaction and symptoms associated with the IRs were both part of the TEAE analyses in the individual CSRs.

To ensure that the data from the supportive studies are consistent with the pivotal EFC14335 study, only the generic term of "infusion related reaction" was kept in the TEAE analyses from the supportive studies, while other adverse events were analyzed as part of the symptoms of IRs in the SCS/ISS.

Further analyses of IRs were performed using the following CMQ that includes TEAEs from the following AE grouping: 'Hypersensitivity' and 'Cytokine release syndrome'.

The FDA's Assessment:
FDA agrees with the Applicant's reporting of the assessment of the categorization of adverse events on Study EFC14335. See the FDA assessment regarding limitations in the characterization of adverse events of infusion related reactions in the Significant Adverse Events section.

Routine Clinical Tests

The Applicant's Position:
Clinical laboratory parameters were assessed at baseline and through-out the study. Clinical laboratory abnormalities were recorded as AEs only if they were serious or led to study treatment modification or discontinuation.

Hematology parameters included:

- Red blood cells (RBC): hemoglobin, hematocrit, RBC count
- White blood cell (WBC): WBC count with differential, ANC
- Platelet count
- Indirect anti-globulin test (IAT), for the IPd arm only.

Biochemistry parameters included:

- Metabolism: fasting glucose, total protein, albumin
- Electrolytes: sodium, potassium, chloride, calcium, corrected serum calcium, bicarbonate/carbon dioxide, magnesium, phosphate
- Renal function: serum creatinine, estimated creatinine clearance by MDRD formula, urea or blood urea nitrogen (BUN), uric acid
- Liver parameters: ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total and direct bilirubin
- Pregnancy test: female patients of childbearing potential

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- β2-microglobulin

Coagulation parameters included

- Prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time (aPTT)

Other safety parameters included physical examination, vital signs, ECG, other laboratory assessments and immunogenicity.

Anti-isatuximab antibodies were measured using a validated polyethylene glycol precipitation and acid dissociation assay (PandA) assay method.

- ADA pre-treatment period: defined as the time from signed informed consent to the first isatuximab administration.
- ADA on-study observation period: defined as the time from first isatuximab administration until the end of the study.

ADA attributes:

- Pre-existing ADA: ADA present in samples drawn during the pre-treatment period.
- Treatment boosted ADA: pre-existing ADA that increased at least 2 titer steps between pre-treatment and post-treatment; assuming a 2 fold serial dilution schema was used for the analysis, the increase was ≥4-fold.
- Treatment induced ADA: defined as ADAs that developed at any time during the ADA on-study observation period in patients without pre-existing ADA, including patients without pre-treatment samples.
- Transient ADA response: Treatment-induced ADA detected only at one sampling time point during the ADA on study observation period (excluding the last sampling time point) or detected at 2 or more sampling time points during the ADA on study observation period, where the first and last ADA-positive samples (irrespective of any negative samples in between) were separated by a period <16 weeks and the patient's last sample was ADA-negative.
- Persistent ADA response: treatment-induced ADA detected at 2 or more sampling time points during the ADA on-study observation period, where the first and last ADA-positive on-study samples were separated by a period of ≥16 weeks (irrespective of any negative samples in between).
- Indeterminate ADA response: treatment induced ADA detected only in the last sample with all prior samples being negative, or the last 2 samples were ADA-positive and separated by a period of <16 weeks.

The FDA's Assessment:

The FDA agrees with the Applicant's collection of routine clinical tests and monitoring for safety parameters in Study EFC14335 Figure 17. See FDA clinical pharmacology and biopharmaceutics reviewer comments regarding adequacy of ADA testing.

8.2.3. Safety Results

Deaths

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The Applicant's Position:

Pool 1 (core IPd combination studies)

A summary of the causes of death by study period in Pool 1 is presented in Table 22. Comparing the IPd and Pd arms in study EFC14335, the incidence of death during the treatment period was similar between the two arms (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%) of the patients, and "Other" causes in 2 (1.3%) of the patients in both arms.

Table 22 - Number (%) of deaths by study period and cause of death - Data Pool 1 - Safety population

	EFC14335		Pooled[a]	
n(%)	Pd (N=149)	IPd 10 mg/kg (N=152)	IPd(10 mg/kg) (N=183)	All IPd doses[b] (N=197)
Death during the treatment period	13 (8.7)	11 (7.2)	15 (8.2)	16 (8.1)
Disease progression	5 (3.4)	6 (3.9)	9 (4.9)	10 (5.1)
Adverse Event	6 (4.0)	3 (2.0)	4 (2.2)	4 (2.0)
Other	2 (1.3)	2 (1.3)	2 (1.1)	2 (1.0)
Death during post-treatment period	44 (29.5)	34 (22.4)	36 (19.7)	39 (19.8)
Disease progression	33 (22.1)	24 (15.8)	26 (14.2)	29 (14.7)
Adverse Event	0	0	0	0
Other	11 (7.4)	10 (6.6)	10 (5.5)	10 (5.1)
Death within 60 days from first dose	8 (5.4)	3 (2.0)	3 (1.6)	3 (1.5)
Disease progression	4 (2.7)	3 (2.0)	3 (1.6)	3 (1.5)
Adverse Event	2 (1.3)	0	0	0
Other	2 (1.3)	0	0	0

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

a Data Pool 1: EFC14335 and TCD14079 Part A

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

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

PGM=PRODOPS/SAR650984/OVERALL/POOL_MM_SUB_1/REPORT/PGM/ae_death_s_t.sas OUT=REPORT/OUTPUT/ae_death_p1_s_t_i rtf (01APR2019 9:45)

The FDA's Assessment:

The reviewer concurs with the Applicant's analysis of rates of treatment emergent deaths and post treatment deaths in the pivotal trial and the pooled population. FDA notes that CRFs captured 12 and 14 patients with any TEAE leading to death during the treatment period in the IPd and Pd arms, respectively. However, upon further review the Applicant noted that 1 patient in each treatment arm was counted as having died during the treatment period (patients with any grade 5 TEAE) because of a data entry error, although the patients had previously discontinued treatment period and died due to disease progression during the post-treatment period. Patient 014335-(b) (6) (IPd arm) discontinued isatuximab treatment and subsequently received daratumumab and died 42 days after the last dose of IMP due to PD. Patient 014335-(b) (6) (Pd arm) definitively discontinued treatment due to disease progression and died 77 days after the last dose of IMP. These 2 patients were excluded from

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Table 22 by the Applicant. These 2 deaths were however, included in the FDA analysis of fatal AEs in Table 24.

Higher death rates in the Pd arm in the safety population on the pivotal trial were primarily due to greater deaths occurring during the post treatment period and early study deaths (≤60 days from start of first dose). Note: The difference in death rates reported in this safety section compared to death events included in the analysis of efficacy is due to different data cut-off dates for the analysis. The cut-off date for PFS and all other efficacy analyses was 11 October 2018 and the cut-off date for data included in all other analyses (safety, disposition, demographics, and baseline characteristics) was 22 November 2018. The Applicant submitted 120 day safety report with a DBL 3-May-2019. A total of 127 patients have died during the on treatment or post-treatment periods. Deaths continued to remain higher in the PD arm compared to the IPd arm: 58 (38.2%) and 69 (46.3%) patients in the IPd and Pd arms, respectively. Only one additional Grade 5 TEAE on treatment was reported in the IPd arm (Source: 120 Day Safety Update Version 1 June 25, 2019).

Overall, disease progression was the most common reported cause of death for both arms during treatment and post treatment.

Comparing the IPd and Pd arms in study EFC14335, the incidence of fatal TEAEs not in the context of disease progression was similar (8 [5.3%] and 10 [6.7%] patients, respectively). Across all fatal TEAEs the incidence was similar for both arms, and most TEAEs occurred in only 1 patient (Table 23), with the exception of septic shock, which occurred in 2 (1.3%) patients in the Pd arm and none in the IPd arm. Overall, there was a higher incidence of deaths due to infections in both arms (4 [2.6%] patients in IPd arm and 6 [4.0%] in Pd arm) compared to other system organ classes (SOCs).

One patient in the IPd arm with a history of hypertension developed general physical health deterioration leading to treatment withdrawal, followed by renal injury, and the patient died of unrelated cardiac failure and atrial fibrillation 41 days after last dose of study treatment. Sudden death occurred in 1 patient in the Pd arm.

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

Table 23 - Summary of fatal AEs or Grade 5 post-treatment AEs not 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	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)

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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

a Data Pool 1: EFC14335 and TCD14079 Part A

b 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. Grade 5 post-treatment AEs are defined as AEs with grade 5 that occurred during the post-treatment period (thus, with the exclusion of fatal TEAEs)
Note: this table includes deaths with fatal TEAEs and with cause of death not equal to disease progression, or deaths with grade 5 post-treatment AEs and caused by an adverse event
Note: Table sorted by the internationally agreed SOC order and decreasing frequency of PTs (all grades) in the pooled IPd arm.
PGM=PRODOPS/SAR650984/OVERALL/POOL MM SUB 1/REPORT/PGM/ae death socpt s t.sas
OUT=REPORT/OUTPUT/ae_death_socpt2_p1_s_t_i rtf (01APR2019 9:52)

Pool 2 (supportive single-agent isatuximab studies)

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

Overall, of 305 patients in Pool 2, 15 (4.9%) died during the treatment period, and the cause of death was disease progression in 10 (3.3%) and AE in 5 (1.6%, 0% related). During the treatment period the incidence of death due to disease progression was higher in the <10 mg/kg dose group (8.3% of patients) compared to the 3 higher dose groups (0.9% to 3.4%). These incidences are consistent with the lower overall response rate seen at the dose groups of <10 mg/kg versus the higher doses (6.3% versus >20%). One (0.3%) death during the post-treatment period was caused by an AE, which was reported as not related to treatment.

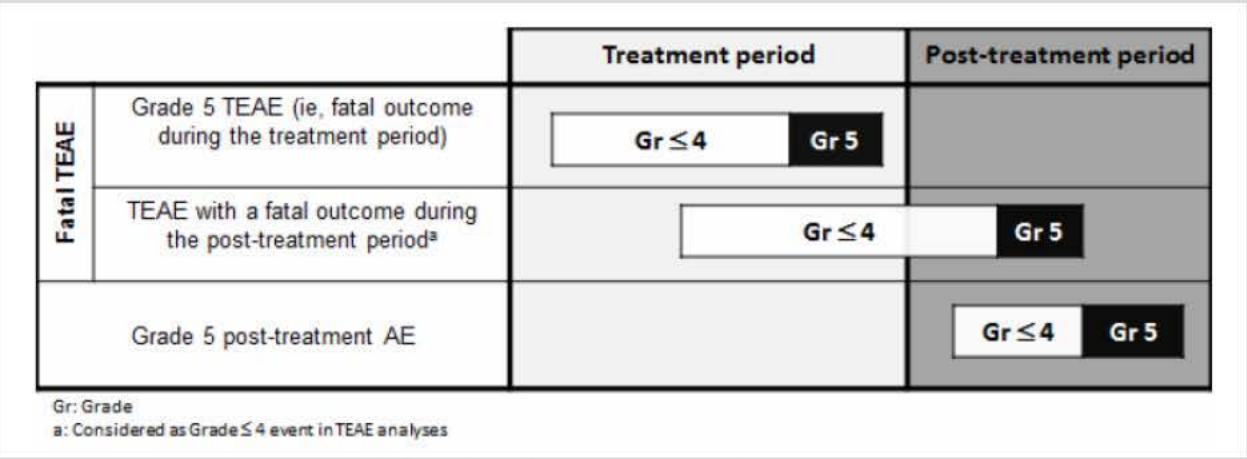
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Overall, 2.3% of patients (7 of 305) had fatal TEAEs or Grade 5 post-treatment AEs that did not occur in the context of disease progression, and similar rates were observed throughout all the dose levels. Two of the deaths were related to infection (bacterial meningitis and pneumonia), and two other deaths occurred as a consequence of nervous system disorders (cerebral hemorrhage and ischemic stroke). Other AEs occurred in 1 patient (sudden death, atrial fibrillation, and acute kidney injury). None of the AEs leading to death were reported as treatment-related.

The FDA's Assessment:

The Applicant categorized and reported rates of fatal TEAE that included Grade 5 TEAE (AEs leading to death during treatment or within 30 days after the last dose) and any TEAES that started during the treatment period and worsened to grade 5 during the post-treatment period in Study 14335 (Figure 23).

Figure 23 Assessment of Fatal TEAEs



Source: Figure 2. Summary of Clinical Safety Section 3.1.2

This reviewer disagrees with the Applicant's presentation of the causes of fatal AEs from the pivotal Study EFC14335 in Table 23 . The table does not include fatal AEs that were assessed as related to disease progression. Additionally, the FDA does not agree with the Applicant's assertion that only AE reported in more than 1 patient was sepsis. The FDA analysis of fatal TEAEs are shown in Table 24. Fatal AEs as defined above were reported in 11% of patients. Grade 5 TEAEs were reported in 7.9% (12 patients) in the IPd arm and 9.4% (14 patients) in the Pd arm. Fatal AEs were most commonly reported in the Infections and infestations SOC (7 patients in the IPd arm and 5 in the Pd arm). Pneumonia (grouped term) was the most common fatal TEAE in the IPd am reported in 4 patients.

Table 24 Fatal TEAEs* - Study EFC14335

AEDECOD	IPd N=152		Pd N=149	
	N	(%)	N	(%)

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Total	16	10.5	17	11.4
Disease progression	6	3.9	4	2.7
Pneumonia#	4	2.6	1	0.7
Death	2	1.3	1	0.7
Renal failure	1	0.7	1	0.7
Sepsis	1	0.7	1	0.7
Septic shock	0	0.0	2	1.3
Urinary tract infection	1	0.7	1	0.7
Acute kidney injury	0	0.0	1	0.7
Atrial fibrillation	1	0.7	0	0.0
Cauda equina syndrome	0	0.0	1	0.7
Cerebral hemorrhage	0	0.0	1	0.7
Hemorrhage intracranial	0	0.0	1	0.7
Hepatic enzyme increased	1	0.7	0	0.0
Hepatic failure	1	0.7	0	0.0
Lymphangitis	1	0.7	0	0.0
Multiple organ dysfunction syndrome	1	0.7	0	0.0
Neutropenia	1	0.7	0	0.0
Sudden death	0	0.0	1	0.7
Upper respiratory tract infection	0	0.0	1	0.7

*Grade 5 TEAE (AEs leading to death during treatment or within 30 days after the last dose) and any TEAES that started during the treatment period and worsened to grade 5 during the post-treatment period]
#Includes Grouped PT Terms
Source: FDA Analysis

Narratives

Patient (b) (6) was a 68 year old with history of chronic ischemia disease, hepatic steatosis, persistent of atrial fibrillation, and hypertension with MM relapsed after 3 prior lines of therapy. On Cycle 10, Day 25 (Day 278), the patient died at his house 'death from unknown cause' (**death**); no autopsy was performed, and the cause of death was unknown. No additional details were included in the narrative. Cause of death cannot be determined.

Patient (b) (6) was a 68 year old ECOG 2, non-contributory past medical history received Isa-Pd. The patient had received three platelet transfusions for thrombocytopenia on

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D-7 and D 1 and D2 of Cycle 1 and red blood cell transfusion on D2. On Cycle 1, Day 6 (Day 6), the patient was diagnosed with serious 'increased hepatic enzymes due to progressive disease'. Alanine aminotransferase (ALT) was 185 IU/L (Grade 1, baseline value: 17 IU/L [Grade 0]), aspartate aminotransferase (AST) was 471 IU/L (Grade 3, baseline value: 113 IU/L [Grade 2]), alkaline phosphatase (ALP) was 371 IU/L (Grade 2, baseline value: 114 IU/L [Grade 0]), and bilirubin was 40 µmol/L (Grade 2, baseline value: 7 µmol/L [Grade 0]). AST increased to 2037 (Grade 4) on Cycle 1 D9 and patient died the next day. Abdominal ultrasound was normal. An information request was sent to the Applicant requesting additional details of Hepatitis virus testing and testing for infection. However, additional details were not available. Given the time course of the hepatic enzyme elevation (after only 1 dose), temporal relation to transfusions and the progressive disease, the hepatic enzyme elevations does not appear to be related to isatuximab infusion. The multiple blood transfusions and progressive disease are confounding factors.

Patient (b) (6) was a 75 year old with history of diabetes, heart failure, hypercholesterolemia, renal failure, hypertension, prostatic hypertrophy, and Hepatitis B. The patient was randomized to ISA-Pd arm. On Cycle 2, Day 11 (Day 39), the patient developed nonserious 'haemophilus influenzae pneumonia'. No treatment was reported until the Grade 3 **pneumonia** became serious on Cycle 2, Day 16 (Day 44) leading to hospitalization. A sputum culture revealed presence of *Haemophilus influenzae*, and a blood culture was negative. The patient's condition improved, and the last reported action with isatuximab was dose omission and delayed, and with pomalidomide and dexamethasone was dose delayed and reduced because of the haemophilus pneumonia. The patient was discharged from the hospital, recovered according to the narrative. On Cycle 3, Day 13 (Day 83), the patient died at home because of 'death from unknown cause' . The cause of death could not be identified in the absence of an autopsy. Recurrent pneumonia as a cause of death cannot be completely ruled out.

Patient (b) (6) was a 74 year old history of type II diabetes, dyslipidemia, hypertension, ischemic cardiomyopathy, and acute pulmonary edema started treatment with IPd on (b) (6). Patient experienced Grade 3 infusion reaction and treatment with isatuximab was discontinued after Cycle 1. Patient continued pomalidomide and dexamethasone only. Subsequently patient also experienced hyperglycemia and catheter related infection and was treated. Patient started treatment with daratumumab in combination with pomalidomide and dexamethasone 8 days after the last dose of isatuximab and after device related infection resolved. On follow-up 1 (29 days after the last dose of investigational medicinal product isatuximab and while on treatment with daratumumab-pom-dex, the patient developed serious lymphangitis, pneumonia bacterial, urinary tract infection, severe renal failure due to disease progression, and neutropenia and subsequently died. The patient received only one dose of isatuximab and the event occurred while on treatment with daratumumab-pom and dex; death unlikely related to isatuximab.

Patient (b) (6) was a 79 year old with past medical history of hypertension, hyperuricemia, hyperkalemia and peripheral neuropathy. Patient developed adverse event of

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new onset atrial fibrillation Grade 2 and was managed medically and resolved. On Cycle 16, Day 15, (Day 483) if IPd, the patient had serious Grade 3 'general physical health deterioration' with malaise and difficulty of taking food and fluids, leading to hospitalization. Patient had hypotension 86/63, anemia, renal failure and Grade 3 neutropenia. Patient was treated symptomatically and given IV hydration and anti -hypertensive bisoprolol was discontinued. Dehydration resolved and renal function improved. On Cycle 16 D 24 910 days after the last investigational drug product administration patient presented with atrial fibrillation with rate of 150/min and was noted to have EF of 15% and diffuse hypokinesis, and signs of right heart failure. Patient was treated in the ICU with hemodiafiltration, cardiac management and IV broad spectrum antibiotics, antifungals and blood products. However, despite intensive management patient died 2 weeks later. Death was reported to be cardiac failure due to atrial fibrillation; however, age, medical history are confounding factors. Underlying infection and progressive disease could have also contributed to the general health deterioration and subsequently to recurrent atrial fibrillation and death.

Patient (b) (6) was a 62 year old who had received 4 prior lines of therapy. Patient developed abdominal pain on Cycle 4 day 28 and was diagnosed as cholecystitis and chronic liver disease confirmed by CT a week later. Subsequently patient also had candida albicans abdominal sepsis. by abdominal ultrasound. Approximately, On that day, laboratory tests showed alanine aminotransferase (ALT) at 45 IU/L (Grade 1, baseline value: 20 IU/L [Grade 0]), aspartate aminotransferase (AST) at 181 IU/L (Grade 3, baseline value: 32 IU/L [Grade 1]), alkaline phosphatase (ALP) at 644 IU/L (Grade 3, baseline value: 78 IU/L [Grade 0]), bilirubin at 45.1 µmol/L (Grade 2, baseline value: 8 µmol/L [Grade 0]). The highest reported values of AST and ALT values were reported at 9815 IU/L (Grade 4) and 395 IU/L (Grade 3); ALP was 470 IU/L (Grade 2) and bilirubin was 72.2 µmol/L (Grade 3) 35days after all study drugs were discontinued. On the same day, a urine fungal culture showed *Candida albicans.* An information request was sent during the review to request information on viral or imaging tests; however no further information was available. Based on the submitted narrative the likely cause of death appears to be sepsis secondary to candid albicans in the setting of immunosuppression secondary to disease and treatment with secondary liver enzyme elevation.

Serious Adverse Events

The Applicant's Position:

Pool 1 (core IPd combination studies)

Serious TEAEs in Pool 1 are presented in Table 25. The serious TEAEs reported in ≥3% of patients in 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 EFC14335 Pd, they were pneumonia, disease progression, and acute kidney injury (in 15.4% to 4.0% of patients). Comparing the IPd and Pd arms in study EFC14335, the incidence of the most frequent (≥3% of patients) serious TEAEs and Grade ≥3 serious TEAEs was similar and did not differ by ≥5%.

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Table 25 - 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)
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)

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	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
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

a Data Pool 1: EFC14335 and TCD14079 Part A

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

MedDRA 21.0

CTCAE 4.03

PGM=PRODOPS/SAR650984/OVERALL/POOL_MM_SUB_1/REPORT/PGM/ae_socpt_serf2_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_serf2_p1_s_t_i rtf (01APR2019 12:31)

Pool 2 (supportive single-agent isatuximab studies)

Overall, in Pool 2, serious TEAEs (all grades) were reported in 108 (35.4%) patients and they were Grade ≥3 in 101 patients. The most frequent serious TEAEs (incidence ≥2% of patients) included pneumonia, sepsis, disease progression, and acute kidney injury.

The FDA's Assessment:

The FDA agrees with the numerical rates of the SAEs as assessed by SOC and the individual preferred terms reported in the Applicant's table above. However, the FDA noted that pneumonia and upper respiratory tract infections was reported and captured under multiple PTs. FDA also did not separate assessment of SAEs by grade (Grade ≥3) and considered all SAEs of any grade relevant for assessment of safety. The recalculated rates of SAEs using grouped PT terms are shown in Table 26.

The SOCs with SAEs reported at ≥5% incidence in the IPd arm compared to the Pd arm were infections and infestation (Isa-Pd 39.5% vs Pd 30.9%), Blood and lymphatic system disorders (IPd 11.8%, Pd 6.7%) and Injury, poisoning and procedural complications (IPd 7.2%, Pd 1.3%). The Applicant noted that there were no differences in the rates of pneumonia or upper respiratory tract infections based on the individual PT terms. Based on the FDA's assessment, SAEs of pneumonia, upper respiratory tract infections and febrile neutropenia were higher in the IPd arm (≥5%) compared to the Pd arm in Study 14335. The revised rates of SAEs using the grouped terms should be presented in the USPI.

Table 26 Serious Adverse Events (SAEs)# - Study EFC14335

	IPd N=152		Pd N=149	
AEDECOD	n	%	n	%

Pneumonia*	39	25.7	29	19.4
Upper Respiratory Tract Infection*	10	6.6	6	4.0
Febrile neutropenia	10	6.6	3	2.0
Disease progression	7	4.6	7	4.7
Urinary tract infection	6	3.9	2	1.3
Infusion related reaction	6	3.9	1	0.7
Acute kidney injury	5	3.3	6	4.0
Neutropenia	5	3.3	2	1.3
Pathological fracture	5	3.3	3	2.0
Dyspnea	4	2.6	2	1.3
Sepsis	4	2.6	2	1.3
Arthralgia	4	2.6	2	1.3
Syncope	4	2.6	1	0.7

#Occurring >2% rate in the IPd arm; *Includes Grouped PT terms
Source: FDA Analysis

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Pool 1 (core IPd combination studies)
In study EFC14335 (Pool 1), the incidence of TEAEs leading to definitive treatment discontinuation of all study treatments in IPd and Pd was 7.2% and 12.8%, respectively. Of these TEAEs, those reported in ≥2 patients included death (2 patients) in IPd arm, and thrombocytopenia (7), pneumonia (3), neutropenia (2), and septic shock (2) in the Pd arm. In the IPd arm, the only TEAE leading to premature discontinuation of isatuximab was a Grade ≥3 infusion related reaction, which was reported in 4 (2.6%) patients. The protocol required discontinuation following Grade 3 infusion reactions without re-challenge.

In EFC14335, the all grade TEAEs leading to any dose modification 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%).

Pool 2 (supportive single-agent isatuximab studies)
Overall, TEAEs leading to treatment discontinuation in Pool 2 were reported in 17 of 305 patients (5.6%) and all were Grade ≥3 except in 1 patient. The number (%) of patients with Grade ≥3 TEAEs by dose group (<10 mg/kg, 10 mg/kg, 20 mg/kg, and

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20 mg/kg+dexamethasone), respectively, was 1 (2.1%), 6 (5.4%), 7 (6.0%), and 3 (10.0%). Overall, 8 of 305 patients (2.6%) experienced an infusion reaction Grade ≥3 leading to treatment discontinuation. The only other AE that occurred in >1 patient was acute kidney injury (2 patients [0.7%]).

The FDA's Assessment:

FDA agrees with the Applicant's assessment of treatment discontinuation on Study 14335 but notes that only information by individual AE terms is included in the Applicant's assessment. FDA used grouped terms to calculate rates of pneumonia, upper respiratory tract infections, dyspnea and cough which resulted in different rates from the Applicant's assessment for these AEs. Treatment discontinuation for all drugs in the combination (definitive treatment discontinuation) was generally low (<10%) on Study 14335 and lower in the IPd arm compared to the Pd arm. In the IPd arm, adverse events leading to definitive treatment discontinuation occurred most frequently in the SOC of infections and infestations (2.6%) and general disorders and administration site conditions (2.6%). In the IPd arm on Study 14335, the most frequent adverse event leading to definitive treatment discontinuation reported in the infections and infestations SOC was pneumonia (3 patients).

Premature treatment discontinuation defined as discontinuation of at least 1 study drug where at least one other study drug was continued was generally low across the arms. As reported by the Applicant, 4 patients had a TEAE leading to premature discontinuation of isatuximab due to occurrence of Grade 3 or 4 infusion related reaction consistent with the protocol recommendation. Premature discontinuation of pomalidomide due to TEAE was reported in 8 patients (5.3%) in the IPd arm. No patients discontinued pomalidomide alone in the Pd arm due to TEAEs. Two patients each in the IPd arm and Pd arm prematurely discontinued dexamethasone due to TEAEs.

FDA agrees with the Applicant's assessment of the most common TEAEs leading to any dose modification of isatuximab in ≥10% of patients in Study EFC14335 with the exception of the rates of pneumonia and upper respiratory tract infections. Using the grouped terms for pneumonia FDA noted that 23% and 22% of patients discontinued isatuximab due to AEs of pneumonia and upper respiratory tract infections respectively.

The rates of dose modifications for each drug in the respective arms are shown in the below in Table 27. Dose modifications (dose delays, omissions or reductions and interruptions) were assessed separately for each drug within the combination by arm on Study EFC14335. Dose modifications for isatuximab in the IPd arm assessed patients who had dose interruptions, dose omissions or dose delays (delay of the next cycle) of isatuximab due to TEAEs. Dose reductions for isatuximab were not permitted as per protocol. Dose modifications for pomalidomide and dexamethasone were assessed as dose delays, reductions or omissions due to TEAEs.
Any interruption of infusion of isatuximab was reported in 34.9% of patients and in 50 patients the interruption occurred during the first cycle of infusion. TEAEs as a reason for interruption of isatuximab infusion was reported in 30.9% of patients. The most frequent TEAE resulting in

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interruption of isatuximab was infusion related reaction (infusion related reaction 28.9%. The most frequent TEAE leading to dose delay was neutropenia (27.0%); and most frequent TEAE leading to dose reduction of isatuximab was upper respiratory tract infections (grouped terms: 14.5%).

Table 27 TEAE Leading to Dose Modifications[#] -Study EFC14335

	IPd Arm N=152 N (%)			Pd Arm N=149 N (%)	
	Isa	Pom	Dex	Pom	Dex
Dose Interruption	47 (30.9)	-	-	-	-
Dose Reduction	76 (50.0)	107 (70.4)	97 (63.8)	60 (40.3)	65 (43.6)
Dose Delays	89 (58.6)	91 (59.9)	40 (26.3)	57 (38.3)	11 (7.4)

Patients with at least 1 dose modification
Source: FDA analysis

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

In study EFC14335 (Pool 1), the incidence of TEAEs leading to definitive treatment discontinuation of all study treatments in IPd and Pd was 7.2% and 12.8%, respectively. Of these TEAEs, those reported in ≥2 patients included death (2 patients) in IPd arm, and thrombocytopenia (7), pneumonia (3), neutropenia (2), and septic shock (2) in the Pd arm. In the IPd arm, the only TEAE leading to premature discontinuation of isatuximab was a Grade ≥3 infusion related reaction, which was reported in 4 (2.6%) patients. The protocol required discontinuation following Grade 3 infusion reactions without re-challenge.

In EFC14335, the all grade TEAEs leading to any dose modification 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%).

Overall, TEAEs leading to treatment discontinuation in Pool 2 were reported in 17 of 305 patients (5.6%) and all were Grade ≥3 except in 1 patient. The number (%) of patients with Grade ≥3 TEAEs by dose group (<10 mg/kg, 10 mg/kg, 20 mg/kg, and 20 mg/kg+dexamethasone), respectively, was 1 (2.1%), 6 (5.4%), 7 (6.0%), and 3 (10.0%). Overall, 8 of 305 patients (2.6%) experienced an infusion reaction Grade ≥3 leading to treatment discontinuation. The only other AE that occurred in >1 patient was acute kidney injury (2 patients [0.7%]).

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The FDA's Assessment:

The above text is a repetition of the text described in the Section on Dropouts and/or Discontinuations Due to Adverse Effects.

Significant Adverse Events

The Applicant's Position:

As described in 8.2.1, significant AEs included IRs (including cytokine release syndrome [CRS]), second primary malignancies (SPMs), respiratory AEs (lower respiratory AEs and respiratory infections), neutropenia and neutropenic complications, infection, thrombocytopenia and hemorrhages, tumor lysis syndrome (TLS), hemolytic disorders and blood cell (red blood cells and platelet) transfusions, autoimmune disorders, anti-drug antibodies (ADAs), and long term adverse events. Each are summarized below.

Infusion reactions

Pool 1 (core IPd combination studies)
In study EFC14335, the incidence of patients with IR was 38.2%, and most IRs were Grade 1 or 2 (35.5%). The incidence Grade 3 and Grade 4 IRs was 1.3% for each. There were no Grade 5 IRs. Corrective treatment for IRs was administered to 49 of the 58 patients with an IR.
IRs led to isatuximab interruption in 28.9% of patients and to discontinuation of isatuximab in 2.6% (4) of patients. All four of these patients in study EFC14335 discontinued study treatment because of Grade 3-4 IRs, as required by the study protocol. All IRs leading to treatment discontinuation in study EFC14335 occurred during the first infusion.

In the pooled all IPd doses, among the 77 patients with at least 1 IR, 68 (88.3%) had only a single IR episode. The remaining 9 patients (11.7%) had 2 episodes. Of the 77 patients with at least 1 IR, 76 (98.7%) had an IR at their first infusion; the first IR had its onset at a subsequent infusion in only 1 patient, leading to treatment discontinuation. In all of the 86 infusions with IR episodes, IRs occurred on the same day as the infusion. While no post-infusion steroid prophylaxis was required by protocol, no delayed IRs were reported. All the IR symptoms were reversible: 84 (97.7%) of the 86 IR episodes recovered on the same day, while one episode recovered on the next calendar day and another episode within 9 days. In the pooled all IPd doses, the most frequent symptoms of IRs (reported in ≥5% of patients) were dyspnea (13.2% for all grades, 1% for Grade ≥3), cough (6.1%) , chills (5.6%), and nausea (5.1%).

Pool 4 (all patients exposed to isatuximab)
Overall, among all 576 isatuximab treated patients, 266 (46.2%) had at least one IR. Most IRs were Grade 1 (35 [6.1%]) or Grade 2 (211 [36.6%], with fewer Grade 3 (15 [2.6%] or Grade 4 (5 [0.9%]) events, and no fatalities. Most patients (237 of 266) who had an IR experienced only one IR episode and onset was most frequently during the first infusion (258 of 266 patients).

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Only 8 of 266 patients had their first IR during a subsequent infusion. There were no IRs with onset later than 2 calendar days from the start of the isatuximab administration. All the IRs recovered and most recovered within 1 day (284 of 369 [77.0%]).

Overall, IRs led to dose interruptions of isatuximab in 33.9% of patients. The median time from the infusion start to the first interruption was 56.0 minutes, with the majority of the infusions (218 out of 261 infusions interrupted) experiencing an interruption during the first 90 minutes from the start of the infusion. IRs led to treatment discontinuation of isatuximab in 3.3% of the patients (required by protocol if Grade 3 or higher). In all isatuximab-treated patients, no Grade ≥3 cytokine release syndrome or drug hypersensitivity were reported.

The FDAs Assessment:

FDA agrees with the Applicant's assessment of infusion related reactions on Study EFC14335. Infusion related reactions was the most frequent TEAE leading to isatuximab dose interruption. All 58 patients (38.2%) had infusion related reactions during first infusion; 2/58 patients (b) (6) had additional infusion related reaction during the second infusion and additional 2/58 patients (b) (6) had an infusion related reaction at the fourth infusion.

All patients reported infusion related reactions on the day of the infusion. However, it is important to note that for Study 14335 definition and analysis of infusion related reactions were based on Investigator reporting and TEAEs occurring within 24 hours after isatuximab administration that may be associated with infusion. It is possible that symptoms of infusion related reactions that occurred after 24 hours were not captured as an infusion related reaction. Symptoms related to IRs were collected on a different eCRF page and also reported. No precise diagnostic terms describing an IR were predefined. Symptoms of IRs were reported in 38.2% of patients and most frequently were dyspnea (15.1%), cough (6.6%), nausea (5.9%), and chills (5.3%). Grade 3 symptoms occurred in 7 (4.6%) patients (hypertension in 3 patients and dyspnea, bronchospasm, hypoxia, acute pulmonary edema, hypotension, tachycardia, syncope, and hyperglycemia each in 1 patient); Grade 4 symptoms occurred in 1 patient (dyspnea and wheezing). It should be noted that the severity grading for IRs, was defined by specific NCI-CTCAE criteria, and was not directly linked to the severity grading of the individual underlying symptoms.

Narrative

Patient (b) (6) 62 year old with past medical history of chronic obstructive pulmonary disease and hypothyroidism received premedication with intravenous (IV) chlorphenamine maleate 10 mg, IV paracetamol 1000 mg, and IV ranitidine prior to Cycle 1 D1 of Isa-Pd. Patient developed Grade 2 infusion related reaction with Grade 2 dyspnea. Isatuximab was interrupted and infusion related reaction was managed with supportive care. Infusion related reaction resolved on the same day. On Cycle 1 D8 the patient received premedication as prophylaxis

included IV chlorphenamine maleate, IV paracetamol 1000 mg, and IV ranitidine. Forty five minutes after the infusion started patient developed Grade 3 'dyspnea' dyspnea, Grade 3 hypotension, and Grade 3 tachycardia. The blood pressure was 80/50 mmHg and heart rate was 130 beats/minute. Treatment included IV chlorphenamine maleate, IV cortisone 250 mg and 300 mg, oral salbutamol and IV salbutamol . Later on, the blood pressure was 110/60mmHg and oxygen saturation rate returned to be normal. Isatuximab was permanently discontinued because of the infusion related reaction.

Second primary malignancies

In study EFC14335, 1 patient in the Pd arm and 6 patients in the IPd arm were diagnosed with second primary malignancies (SPMs) after start of study treatment. These SPMs consisted of skin cancer (squamous cell carcinoma [SCC]) in 1 patient in the Pd arm, while in the IPd arm there were 4 patients with SCC, 1 with solid non-skin cancer (breast angiosarcoma), and 1 with a hematologic malignancy (myelodysplastic syndrome [MDS]). None of the patients discontinued treatment because of the SPMs, with the exception of the patient who developed MDS with transformation to acute myeloid leukemia in the IPd arm (previously treated with high-dose melphalan).

In Pool 4 (all isatuximab-treated patients), SPMs were diagnosed in 17 (3.0%) patients. The median interval from the first dose of study treatment to the diagnosis of SPM onset was 7.16 months (range 0.5 to 26.5) in all the isatuximab-treated patients. Among all the patients treated with isatuximab, the most frequent SPMs consisted of skin cancer (in 1.6% of the patients: SCC 0.9%; BCC 0.7%), non-skin solid malignancies (1.2%), and hematologic malignancies (0.3%).

The background incidence of SPMs in patients with relapsed/refractory multiple myeloma has been reported to be as high as 6%, with prior lenalidomide and alkylating agent exposure being an identified risk factor (Palumbo et al 2014, Areethamsirikul et al 2015, Landgren et al 2014). The incidence of SPMs has been reported as 3.2% from a study on 345 RRMM patients treated with a median of 5 cycles of pomalidomide in combination with dexamethasone; these SPMs included 7 non-melanoma skin cancers (5 basal cell carcinomas, and 2 SCC), and 1 each of cholangiocarcinoma, malignant melanoma, MDS, and breast ductal carcinoma in situ (Ailawadhi et al 2018). Analogously, a post-authorization analysis of the Pd combination in a real world setting has revealed an incidence of SPMs of 3.6%, consisting of 1.7% solid non-skin malignancies, 1.4% non-melanoma skin malignancies, and 0.5% hematologic malignancies (Abildgaard et al 2018). In a clinical study with another anti-CD38 (daratumumab) agent in combination with bortezomib and dexamethasone (DVd) in MM, the incidence of SPMs was reported as 4.1% compared with the control arm (0.4%) (Spencer et al 2018).

The FDA's Comments:

The FDA agrees with the Applicant's reporting of the results of the SPM rates in the two arms in the EFC14335. FDA acknowledges the Applicant's review of the SPMs with Pd in real world and other clinical studies. However, the FDA considers SPMs as an important safety risk with the IPd combination based on reported higher rates in the IPd arm(3.9%) compared to the Pd arm (0.7%) in this large randomized controlled study. SPMs in the IPd arm included MDS with transformation to leukemia during the course of the study as well as rare type of breast cancer (breast angiosarcoma). An additional patients with SPM of metastasis to mandibular lymph nodes was reported in the IPd arm with additional follow up (120-day safety follow up). The Isatuximab USPI should include a Warnings and Precautions on the risk of SPMs with recommendations for monitoring for SPMs.

Respiratory AEs (lower respiratory AEs and respiratory infections)

Pool 1 (core IPd combination studies)

In study EFC14335 (Pool 1), the incidence of all grade lower respiratory TEAEs was 36.8% in the IPd arm compared to 25.5% in the Pd arm (7.9% and 3.4% for Grade ≥3). The TEAEs contributing the most (>2% difference) to this imbalance were dyspnea and productive cough. The incidence of all grade and Grade ≥3 respiratory infections was 74.3% and 36.2% in the IPd arm, compared to 53.0% and 24.2% in the Pd arm. The TEAEs contributing the most (>2% difference) to this imbalance were upper respiratory tract infection, pneumonia, bronchitis, and nasopharyngitis. For Grade ≥3 TEAEs, the TEAE contributing the most (>2% difference) to this imbalance were upper respiratory tract infection and bronchitis. However, the incidence of serious pneumonia was similar in the IPd and Pd arms, both for all grade (15.1% versus 15.4%, respectively) and for Grade ≥3 (14.5% versus 14.8%). When the incidence of pneumonia is adjusted by the duration of treatment, the rates by patient-years are similar between the two treatment arms (0.33 versus 0.36, respectively in IPd versus Pd). The IPd and Pd arms were similar in the incidence of patients with definitive treatment discontinuation caused by respiratory infections.

In the isatuximab clinical trial program, patients with a prior history of obstructive lung disease or altered baseline pulmonary function were eligible for recruitment. Of the 16 patients with a history of COPD/asthma in the IPd arm, 9 (56.3%) developed an infusion reaction: 8 patients with a single episode of Grade 2 infusion reaction, and one patient who developed a second episode of Grade 3 IR and prematurely discontinued isatuximab. Among these patients, no additional post-infusion inhaler or bronchodilator therapy (beyond the patients' chronic therapy) was required to be given during the first IPd cycle and no patients definitively discontinued treatment because of IRs.

Pool 2 (supportive single-agent isatuximab studies)

In Pool 2, lower respiratory TEAEs occurred in 29.2% (3.3% were Grade ≥3). The most frequently reported events of all grades were cough (15.4%) and dyspnea (8.5%); no PTs of Grade ≥3 were reported in ≥2% of patients. Respiratory infection TEAEs occurred in 37.4% of patients (9.8% were Grade ≥3). The most frequently reported events of all grades were upper respiratory tract infection (18.0%) and pneumonia (6.9%); the only event of Grade ≥3 occurring in ≥2% of patients was pneumonia (6.2%).

The FDAs Assessment:

The FDA agrees with the numerical numbers for the overall rates of lower respiratory AEs. Lower respiratory AEs were reported at a 10% higher incidence in the IPd arm compared to the Pd arm. The FDA also agrees with the Applicant's assessment of infusion related reactions and outcomes in patients with COPD/asthma. However, because of the small number of patients with COPD/asthma enrolled on the study any conclusions on the rates of infusion related reactions isatuximab should be interpreted with caution.

The FDA does not agree with Applicant's assessment of individual adverse event terms to report differences in rates of lower respiratory AEs and pneumonia and upper respiratory tract infections. Using FDA grouped terms, lower respiratory AEs of dyspnea (17.1%, 12.1%) and cough (13.8%, 8.7%) were reported at higher rates (≥5%) in the IPd arm compared to the Pd arm. Any Grade and Grade 3 or 4 pneumonia were also reported at higher rates (≥5%) in the IPd arm compared to the Pd arm. Any grade and Grade 3-4 pneumonia was reported in 30.9% and 25.0% in the IPd arm and 22.8% and 18.8% in the Pd arm. With the exception of fatal AEs of pneumonia, pneumonia resolved in all but 1 patient in the IPd arm and in 3 patients in the Pd arm. Fatal events of pneumonia (Grade 5) have been described in the section on deaths. Any grade and grade 3 upper respiratory tract infections were reported in 56.0% and 9.0% of patients in the IPd arm and 42% and 3.4 % in the Pd arm. Events of upper respiratory tract infection resolved in almost all patients except in 3 patients on the IPd arm and 1 patient in the Pd arm. There were no fatal upper respiratory tract infections on the IPd arm, and one death reported due to upper respiratory tract infection in the Pd arm. Rates of upper respiratory tract infections reported with IPd are similar to the rates reported with Daratumumab, pomalidomide and dexamethasone combination in patients with MM (Any grade: 50.0%, Grade 3 or 4: 5.0%).

Neutropenia and neutropenic complications

In study EFC14335 (Pool 1), the incidence of Grade 3-4 neutropenia was higher in the IPd arm than the Pd arm (84.8% versus 70.1%); Grade 4 neutropenia was twice as frequent in the IPd arm (60.5% versus 31.3%). The onset and duration of Grade 3-4 neutropenia was similar in the IPd and Pd arms, respectively: the median time to onset was 21 versus 22 days after the first administration of study treatment, and the median duration was 11 and 9 days. Neutropenia was handled by investigators through use of colony-stimulating factors (69.1% on IPd and 53.0% on Pd) and through dose reductions of pomalidomide (29.6% on IPd and 14.8% on Pd due to neutropenia). When neutropenic infections were analyzed only among those patients who had received G-CSF, the rate of neutropenic infection was similar between treatment arms (31.4% and 32.9% in the IPd and Pd arms, respectively).

Febrile neutropenia occurred as a TEAE at a higher incidence in the IPd arm compared with the Pd arm (11.8% versus 2.0%) and the incidence of neutropenic infections was also higher in the IPd arm (25.0% versus 19.5%). The incidence of Grade ≥3 neutropenic infections in the IPd arm was higher than in the Pd arm (13.2% and 9.4% in the IPd and Pd arms, respectively). In most cases, the patients were able to continue receiving the study treatments after dose modifications (dose delays or omissions/reductions). Neutropenic complications resulted in few patients who permanently discontinued treatment (1.3% and 3.4% in the IPd and Pd arms, respectively). Fatal infections with associated neutropenia were observed in 1 patient in the IPd arm (0.7%) (influenzal pneumonia with concurrent Grade 4 neutropenia) and 3 patients in the Pd arm (2.0%) (pneumonia with concurrent Grade 3 neutropenia; sepsis with concurrent Grade 4 neutropenia; septic shock with concurrent Grade 3 neutropenia). One of the deaths (pneumonia in the Pd arm) was assessed as related to study treatment.

In Pool 2, treatment emergent neutropenia based on laboratory assessment was reported in 48.3% of patients and was Grade 3/4 in 15.4%. Three patients (1.0%) had Grade 3 neutropenic complications consisting of febrile neutropenia. Among the 46 patients with Grade 3/4 neutropenia, the median time of first onset of Grade 3 or 4 was 22.0 days.

The FDAs Assessment:

FDA agrees with the Applicant's assessment of neutropenia reported as a laboratory abnormality. It is important to note that only clinically significant neutropenia events were asked to be reported as an adverse event in the AE dataset. This resulted in an underreporting of neutropenia as an AE. For instance, Grade 3 or 4 neutropenia as a laboratory abnormality in 84.8% of patients in the IPd arm, however clinicians reported Grade 3 or 4 neutropenia as an AE in only 46.7% of patients. FDA also agrees with the Applicant's assessment of the incidence of febrile neutropenia and neutropenic infections on the study. Rates of any grade and grade 3 or 4 neutropenia, incidence of febrile neutropenia and neutropenic infections were higher (≥5%) in the IPd arm compared to the Pd arm. The rates of neutropenia with IPd are similar to the rates of neutropenia reported with the DPd combination in patients with MM (Any grade: 95.0%, Grade 3 or 4: 82.0%). The FDA did not independently verify the time to onset of laboratory Grade 3 or 4 neutropenia or duration but reviewed the Applicant's assessment and notes that the time to onset of Grade or 4 neutropenia and duration of neutropenia were similar in the two arms.

The Applicant states that neutropenia was managed by growth factor use and dose reductions of pomalidomide and dexamethasone but fails to mention that neutropenia was also managed by isatuximab dose delays. As noted in the section on dose modifications above, neutropenia was the most common AE leading to isatuximab dose delay. The protocol recommended delay D1 of Cycle until recovery ≥1.0 x 10^9/L. FDA also considered the incidence of any grade infections and grade 3 or 4 infections regardless of neutropenia in the assessment of overall risk benefit profile of the IPd regimen as discussed, the subsection on infections. FDA agrees with the Applicant's assessment of infections (SOC) in Study EFC14335. As noted in the subsection above, pneumonia and upper respiratory tract infections were higher on the IPd arm compared

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to the Pd arm. However, in nearly all instances these events resolved, and fatal AEs related to infections were low. Neutropenia will be included in the Warnings and Precautions section of the USPI with recommendations for dose delay and use of growth factors as per standard guidelines.

Infections

In study EFC14335 (Pool 1), incidence of TEAEs of all grades and Grade ≥3, respectively, in the Infections and infestations disorders SOC was 80.9% and 42.8% in IPd arm, and 64.4% and 30.2% in Pd arm. The TEAEs contributing the most to these imbalances were upper respiratory tract infection, pneumonia, bronchitis, and nasopharyngitis. No more patients definitively discontinued study treatment or died due to infections TEAEs in the IPd arm compared to Pd.

In Pool 2, TEAEs in the infections and infestations SOC were reported in 48.5% of patients (Grade ≥3 in 16.7%). Grade ≥3 infections by PT reported in ≥2% of patients were pneumonia (6.2%) and sepsis (3.3%). Treatment related TEAEs in the infections and infestations SOC were reported in 6.6% of patients and 3% were Grade ≥3; no treatment related TEAEs Grade ≥3 were reported in ≥2% of patients. The incidence of infections occurring as TEAEs or AEs in the post-treatment period does not appear to be dose-dependent.

In study EFC14335, concomitant anti-viral medications were used with a similar incidence in both arms: 79.6% in IPd versus 75.2% in Pd. Herpes zoster infections occurred in 5 (3.3%) and 1 patients (0.7%), respectively, in the IPd and Pd arms (with no Grade ≥3 TEAEs). In all isatuximab-treated patients (Pool 4), herpes zoster was reported in 8 patients (1.4%), and herpes zoster disseminated in 1 (0.2%).

The FDA's Assessment:
FDA's assessment of infections on Study EFC14335 has been incorporated in the subsections of neutropenia and respiratory AEs. Infections are common in patients with multiple myeloma due to the underlying immunosuppression from the disease as well as previous therapy. Antibacterial and antiviral prophylaxis as per institutional and standard society guidelines as appropriate may be needed to prevent and manage symptoms in patients with MM receiving isatuximab, pomalidomide and dexamethasone combination. The incidence of Infections on Study EFC14335 will be described in the USPI in the adverse reactions section 6.1.

Thrombocytopenia and hemorrhages

In study EFC14335 (Pool 1), 30.9% patients in the IPd arm and 24.5% in the Pd arm had at least one Grade 3-4 thrombocytopenia; the median time to onset of Grade 3-4 thrombocytopenia were 11.5 and 15 days after the first administration of study treatment in IPd and Pd arms, respectively. The incidence of Grade 4 thrombocytopenia was similar between IPd (16.4%) and Pd (15.0%) arms.

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The incidence of hemorrhage (all grades) was similar in the IPd arm (8.6%) compared to Pd arm (11.4%). No hemorrhage following Grade 4 thrombocytopenia was reported in study EFC14335. In Pool 2, treatment emergent thrombocytopenia based on laboratory assessment was reported in 64.2% of patients. Grade 3 and Grade 4 thrombocytopenia were reported in 10.0% and 5.4% of patients, respectively. The median time to the first onset of Grade 3-4 laboratory thrombocytopenia was 17 days.

Hemorrhages (any grade) were reported in 11.8% of patients. Two patients had at least one hemorrhage (any grade) within 8 days after Grade 4 thrombocytopenia. These hemorrhages consisted of Grade 1-2 epistaxis, mouth hemorrhage, and ecchymosis.

The FDA's Comments:
The FDA agrees with the Applicant's assessment of thrombocytopenia (laboratory abnormality) and bleeding in the EFC14335 trial. There was a trend towards higher rates of Grade 3 or 4 thrombocytopenia, but the rates of Grade 4 thrombocytopenia and hemorrhage (all grades) was similar between the IPd Arms and Pd arms. Grade 4 or 5 hemorrhages were reported in 3 patients; 2 patients in the Pd arm were reported to have intracranial hemorrhage and 1 patient in the IPd arm had Grade 4 hemothorax that occurred following thromboembolic episode. The FDA did not independently analyze the results from Pool 2 given the differences in patient population and dose levels. The FDA notes that the rates of bleeding as reported by the Applicant for patients in Pool 2 are similar to that reported in the IPd arm in Study EFC14335. Thrombocytopenia rates (laboratory) from EFC14335 study will be included in the USPI.

Tumor lysis syndrome
Tumor lysis syndrome (TLS) reported as a TEAE was uncommon in isatuximab-treated patients (Pool 4), with an incidence of 3 of 576 patients or 0.5%. In 2 of the 3 patients, there was no evidence of laboratory TLS or clinical TLS.

Coombs testing and hemolysis
In study EFC14335, the indirect anti-globulin test (IAT) was performed during the treatment period in 99 (65.1%) patients in the IPd arm. In 32 of the 99 patients (32.3%) the IAT remained negative during treatment. In 67 of the 99 (67.7%) patients a positive test was observed, 47 (47.5%) of which were negative at baseline and 20 (20.2%) of which were missing at baseline. Twenty of the 67 (29.9%) patients with at least one positive post-baseline IAT test, received a red blood cell (RBC) transfusion. No complications of hemolysis were reported post-RBC transfusion in the IPd arm.

One patient in the IPd arm of study EFC14335 experienced Grade 1 hemolysis, assessed as related to the use of sulperazone: sulperazone was discontinued and the patient continued on study treatment with no recurrence of the hemolysis. The patient had not received a blood transfusion before the hemolytic episode. No hemolytic disorders were reported for patients in Pool 2 or 3.

Autoimmune disorders
No autoimmune disorders were reported in any patients.

Anti-drug antibodies
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 hemorrhagic complications revealed no evidence of an impact of ADA to isatuximab on clinical safety.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of tumor lysis syndrome, Coomb's testing and hemolysis, and autoimmune disorders on Study EFC14335. Interference with red blood cell serological testing will be communicated to the healthcare providers in the USPI. The assessment of anti-drug antibodies will be reviewed by the FDA's pharmacology reviewers.

Additional safety analysis:

The FDA also assessed other safety events based on the knowledge of safety profile of monoclonal antibodies approved in MM. No new safety signal was identified on Study EFC14335. FDA noted a numerically higher rate of adverse events reported in the cardiac SOC in the IPd (22 patients, 14.5%) arm compared to the Pd arm (6 patients, 4.0%). However, majority of these events were Grade 1 or 2. Adverse events ≥Grade 3 in the Cardiac SOC were reported in 7 patients in the IPd arm and 3 patients in the Pd arm. Atrial fibrillation was the most common adverse event reported in both arms and reported at a higher rate in the IPd arm (all Grades: 7 patients; ≥Grade 3: 3 patients) compared to the Pd arm (all Grades: 3 patients; ≥Grade 3: 1 patient). FDA reviewed the available narratives and data for the patients in the IPd arm. In most cases, other confounding factors like advanced age, prior medical history of cardiac disease and risk factors for events were noted. Based on the small number of cardiac events, confounding factors and the mechanism of action the available data does not indicate a relationship between cardiac events and isatuximab.

Long term adverse events

Among all 576 patients treated with isatuximab, 99 were treated with isatuximab for >12 months. Among these 99 patients, almost all (99.0%) had TEAEs with onset during ≤12 months of isatuximab treatment, while fewer (64.6%) had TEAEs with onset after 12 months of

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isatuximab treatment. The most frequent (in ≥5%patients) TEAEs with onset after 12 months of isatuximab treatment were upper respiratory tract infection, insomnia, dyspnea, diarrhea, musculoskeletal chest pain, musculoskeletal pain, headache, nausea, vomiting, arthralgia, extremity pain, and pyrexia (in 11.1% to 5.1% of the patients, respectively). Each of these TEAEs was also among the most frequent (in ≥5%patients) TEAEs with onset during ≤12 months of isatuximab treatment. Therefore, no new types of TEAEs were reported to have occurred after 12 months of isatuximab treatment, compared to those that had occurred earlier.

Among the 99 patients treated with isatuximab for >12 months, most (69.7%) had Grade ≥3 TEAEs with onset during ≤12 months of isatuximab treatment, and fewer (25.3%) had Grade ≥3 TEAEs with onset after 12 months of isatuximab treatment. Among the patients treated with isatuximab for >12 months, the most frequent (in ≥5% patients) Grade ≥3 TEAEs, each reported in 2 or 3 patients, were upper respiratory tract infection, pneumonia, urinary tract infection, neutropenia, anemia, and traumatic fracture. Among these, upper respiratory tract infection and traumatic fracture were the only ones for which the incidence after >12 months of isatuximab treatment (2 patients each) was greater than the incidence during ≤12 months of isatuximab treatment (0 patients each).

Two of the 99 patients had Grade 5 TEAEs: one died of disease progression during follow up and another suffered a fatal procedural hemorrhage at Cycle 21. None of these Grade 5 TEAEs was considered related to the study treatment.

Among all 576 patients treated with isatuximab, 8 patients were exposed to isatuximab therapy for >24 months: all 8 had TEAEs during ≤24 months of isatuximab treatment, and 6 experienced TEAEs >24 months after the first study dose. Four patients were in group Other combo, 3 patients were in group Isa(+/- Dex), and 1 in group IPd. None of the TEAEs occurred in >1 patient, except for upper respiratory tract infection in 6 patients. Grade ≥3 TEAEs were reported in 1 patient in group Isa(+/- Dex) and consisted of myelodysplastic syndrome and anemia. The analysis of first onset of TEAEs by period at ≤24 or >24 months did not suggest any notable differences in the type and severity of TEAEs among the groups in Data Pool 4. In addition, the analysis of TEAEs occurring >24 months after the first dose of study treatment in patients exposed to isatuximab for >24 months did not suggest notable differences in the type and severity of AEs observed in patients treated for ≤24 months.

The FDA's Assessment:

FDA reviewed the Applicant's assessment of adverse events with long term administration of isatuximab, but this analysis included exposure to single agent isatuximab and isatuximab with other combination regimens and study EFC14355. Despite the large pool of 576 patients less than 20% of patients were exposed to isatuximab for >12 months. In the EFC14335 study only 38 patients had >12 months exposure.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

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Pool 1 (core IPd combination studies)

An overview of the treatment-emergent AEs (TEAEs) in Data Pool 1 is presented in Table 28. Comparing the IPd and Pd arms in study EFC14335, the incidence of TEAEs was higher in the IPd arm for Grade ≥3 TEAEs (86.8% versus 70.5%), and serious TEAEs (61.8% versus 53.7%). Differences in incidences between TEAEs in IPd and Pd have to be analyzed in the context of the longer exposure in the IPd arm. When serious TEAEs were adjusted for the longer exposure in the IPd arm of study EFC14335, the incidence rate in patient years was similar in the IPd and Pd arms (1.36 and 1.30, respectively).

The IPd and Pd arms were also similar in relation to the incidence of TEAEs with a fatal outcome during the treatment period (7.2% versus 8.7%), and TEAEs leading to definitive treatment discontinuation (7.2% versus 12.8%).

The incidence of TEAEs in the two pooled IPd groups was similar to that in the IPd group in study EFC14335.

Table 28 - Overview of Treatment-Emergent Adverse Events - Data Pool 1 - Safety population

	EFC14335		Pooled[a]	
N(%)	**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

a Data Pool 1: EFC14335 and TCD14079 Part A

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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)

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

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

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

PGM=PRODOPS/SAR650984/OVERALL/POOL_MM_SUB_1/REPORT/PGM/ae_overview_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_p1_s_t_i rtf (01APR2019 10:31)

The most frequent TEAEs (reported in ≥15% of patients) in EFC14335 IPd 10 mg/kg were neutropenia, infusion related reaction, upper respiratory tract infection, diarrhea, bronchitis, pneumonia, fatigue, back pain, constipation, nausea, dyspnea, and asthenia (in 46.7% to 15.1% of patients, respectively). In EFC14335 Pd, they were neutropenia, fatigue, diarrhea, asthenia, constipation, upper respiratory tract infection, and pneumonia (in 33.6% to 17.4% of patients). The grade ≥3 TEAEs reported in ≥5% of patients in EFC14335 IPd 10 mg/kg were neutropenia, pneumonia, thrombocytopenia, febrile neutropenia, and disease progression (in 46.1% to 5.3% of patients). In EFC14335 Pd, they were neutropenia, pneumonia, thrombocytopenia, and disease progression (in 32.2% to 5.4% of patients).

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, diarrhea, bronchitis, dyspnea, 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.

Comparing the 3 IPd groups, the incidence of the most frequent TEAEs Table 29) was similar and did not differ by ≥5%, except for fatigue (17.1% in group EFC14335 IPd 10 mg/kg versus 24.0% and 27.4% in the pooled IPd 10 mg/kg and All IPd doses groups, respectively).

Infusion reactions occurred in 2 patients in the Pd arm following definitive discontinuation of Pd treatment and after they had started receiving post-treatment therapy with daratumumab. In both patients, the infusion related reactions occurred within 30 days from the last dose of study IMP and were attributed to daratumumab.

In summary, in study EFC14335, the TEAEs reported in ≥15% of patients in the IPd arm and with ≥5% higher incidence in the IPd arm consisted of neutropenia, infusion related reaction, upper respiratory tract infection, diarrhea, bronchitis, dyspnea, and nausea. The only Grade ≥3 TEAEs with a reported incidence ≥5% greater in group IPd were neutropenia and febrile neutropenia.

Table 29 - Number (%) of patients with TEAEs with an incidence >= 5% (all grades) or >= 2% (grades >= 3) by PT - Data Pool 1 - Safety population

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	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)
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)

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	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**
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

a Data Pool 1: EFC14335 and TCD14079 Part A

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

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

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

Note: Table sorted by decreasing frequency of PTs (all grades) in the pooled IPd arm.

PGM=PRODOPS/SAR650984/OVERALL/POOL MM SUB 1/REPORT/PGM/ae pt f5 s t.sas OUT=REPORT/OUTPUT/ae_pt_f5_p1_s_t_i rtf (01APR2019 10:45)

Within the pivotal study EFC14335, adverse reactions (ARs) were defined as any TEAEs reported in ≥10% of the IPd patients with ≥5% higher incidence than in the Pd treatment arm, regardless of relationship (Table 30). With this definition, ARs consisted of infusion reaction (in 38.2% versus 0% of patients), pneumonia (30.9% versus 22.8%), upper respiratory tract infection (28.3% versus 17.4%), diarrhea (25.7% versus 19.5%), bronchitis (23.7% versus 8.7%), dyspnea (15.1% versus 10.1%), nausea (15.1% versus 9.4%), and febrile neutropenia (11.8% versus 2.0%) and vomiting (11.8% versus 3.4%). Grade 3 ARs that occurred in ≥5 patients were pneumonia (21.7% versus 16.1%), febrile neutropenia (10.5% versus 1.3%), dyspnea (3.9% versus 1.3%), and upper respiratory tract infection and bronchitis (3.3% versus 0.7% each) . Grade 4 ARs consisted of pneumonia (3.3% versus 2.7%), and infusion reaction (1.3% versus 0%) and febrile neutropenia (1.3% versus 0.7%).

Table 30 - Summary of most common TEAEs with an incidence >= 10% (all grades) and >= 5% higher in IPd group (Adverse Reactions) by SOC and PT in EFC14335 study - Safety population

	EFC14335							
	Pd (N=149)				IPd 10 mg/kg (N=152)			
Primary System Organ Class Preferred Term [n(%)]	**All grades**	**Grade ≥ 3**	**Grade 3**	**Grade 4**	**All grades**	**Grade ≥ 3**	**Grade 3**	**Grade 4**
Infusion reaction[a]	0	0	0	0	58 (38.2)	4 (2.6)	2 (1.3)	2 (1.3)
Infections and infestations								
Upper respiratory tract infection	26 (17.4)	1 (0.7)	1 (0.7)	0	43 (28.3)	5 (3.3)	5 (3.3)	0
Pneumonia[b]	34 (22.8)	29 (19.5)	24 (16.1)	4 (2.7)	47 (30.9)	40 (26.3)	33 (21.7)	5 (3.3)

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	EFC14335							
	Pd (N=149)				IPd 10 mg/kg (N=152)			
Primary System Organ Class Preferred Term [n(%)]	**All grades**	**Grade ≥ 3**	**Grade 3**	**Grade 4**	**All grades**	**Grade ≥ 3**	**Grade 3**	**Grade 4**
Bronchitis	13 (8.7)	1 (0.7)	1 (0.7)	0	36 (23.7)	5 (3.3)	5 (3.3)	0
Blood and lymphatic system disorders								
Febrile neutropenia	3 (2.0)	3 (2.0)	2 (1.3)	1 (0.7)	18 (11.8)	18 (11.8)	16 (10.5)	2 (1.3)
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	15 (10.1)	2 (1.3)	2 (1.3)	0	23 (15.1)	6 (3.9)	6 (3.9)	0
Gastrointestinal disorders								
Diarrhoea	29 (19.5)	1 (0.7)	1 (0.7)	0	39 (25.7)	3 (2.0)	3 (2.0)	0
Nausea	14 (9.4)	0	0	0	23 (15.1)	0	0	0
Vomiting	5 (3.4)	0	0	0	18 (11.8)	2 (1.3)	2 (1.3)	0

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

a Infusion reaction was a TEAE considered to be related to infusion by site investigators.

b Pneumonia includes TEAEs in the narrow SMQ Infective pneumonia.

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

MedDRA 21.0

Revised from the source: PGM=PRODOPS/SAR650984/OVERALL/POOL_MM_SUB_1/REPORT/PGM/ae_socpt_f2_s_t.sas OUT=REPORT/OUTPUT/ae_socpt_f2_p1_s_t_i rtf (08APR2019 9:24)

To identify potential ARs, hematology laboratory abnormalities were also examined (Table 31). Comparing IPd versus Pd in study EFC14335, the only differences >5% in the incidence of treatment emergent hematological laboratory abnormalities (all grade, Grade 3, and Grade 4) were reported for neutropenia Grade 3 (37 [24.3%] versus 57 [38.8%]) and Grade 4 (92 [60.5%] versus 46 [31.3%]), and lymphopenia Grade 3 (64 [42.1%] versus 52 [35.4%]). No such group differences were reported for anemia and thrombocytopenia.

Table 31 - Treatment-emergent hematology laboratory abnormalities in EFC14335 - Safety population

	Pd (N=147)			IPd 10 mg/kg (N=152)		
Laboratory parameter n(%)	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Anemia	145 (98.6)	41 (27.9)	0	151 (99.3)	48 (31.6)	0
Thrombocytopenia	118 (80.3)	14 (9.5)	22 (15.0)	127 (83.6)	22 (14.5)	25 (16.4)
Neutropenia	137 (93.2)	57 (38.8)	46 (31.3)	146 (96.1)	37 (24.3)	92 (60.5)
Lymphopenia	137 (93.2)	52 (35.4)	12 (8.2)	140 (92.1)	64 (42.1)	19 (12.5)

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

* The denominator used for the percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

CTCAE version: 4.03

PGM=PRODOPS/SAR650984/OVERALL/POOL MM SUB 1/REPORT/PGM/lab allgrade hema teae s t.sas OUT=REPORT/OUTPUT/lab_allgrade_hema_teae_ep1_s_t_x rtf (28MAR2019 9:05)

Pool 2 (supportive single-agent isatuximab studies)

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Overall, at least one Grade ≥3 TEAE occurred in 49.5% of patients (treatment related in 13.1% of patients), a serious TEAE in 35.4% of patients (treatment related in 6.2%), and a fatal TEAE in 4.9% (none were treatment related).

A TEAE leading to definitive treatment discontinuation was reported in 5.6% patients. At the 4 respective dose groups (<10 mg/kg, 10 mg/kg, 20 mg/kg, 20 mg/kg+dexamethasone) the percent of patients was 2.1% (1 patient), 5.4% (6), 6.0% (7), and 10.0% (3).

Overall, those TEAEs that occurred in ≥10% of patients included infusion related reaction, fatigue, nausea, anemia, diarrhea, upper respiratory tract infection, headache, back pain, cough, vomiting, decreased appetite, and pyrexia (in 153 [50.2%] to 31 [10.2%] patients, respectively). The incidence of the most frequent TEAEs does not appear to be dose-dependent.

Grade ≥3 TEAEs that occurred in ≥2% of patients included anemia, thrombocytopenia, pneumonia, neutropenia, disease progression, sepsis, infusion related reaction, acute kidney injury, platelet count decreased, back pain, and bone pain (in 43 [14.1%] to 6 [2%] patients, respectively).

Pool 4 (all patients exposed to isatuximab)

In all 576 isatuximab-treated patients, at least one Grade ≥3 TEAE occurred in 66.8% of patients (treatment related in 39.9% of patients), a serious TEAE in 45.8% of patients (treatment related in 17.7%), a fatal TEAE in 6.4% (1 [0.2%] treatment related), and TEAE leading to definitive treatment discontinuation or premature discontinuation of isatuximab in 7.1% and 0.7%, respectively.

The most frequent TEAEs (≥15% of patients) were infusion related reaction, fatigue, diarrhea, upper respiratory infection, neutropenia, nausea, back pain, headache, and cough (in 46.5% to 16.1% of patients). The most frequent Grade ≥3 TEAEs (≥5% of patients) were neutropenia, anemia, pneumonia, and thrombocytopenia (in 21.5% to 8.3% of patients).

In groups IPd and Isa(+/-Dex), respectively, the incidence of Grade ≥3 TEAEs was at least 5% greater in group IPd for neutropenia (50.8% versus 3.6%), pneumonia (16.8% versus 6.2%), thrombocytopenia (11.2% versus 5.9%), and febrile neutropenia (9.1% versus 1.0%), and at least 5% greater in group Isa(+/-Dex) for anemia (3.6% versus 14.1%).

In groups IPd and Other combo, respectively, the incidence of Grade ≥3 TEAEs was at least 5% greater in group IPd for neutropenia (50.8% versus 17.6%), pneumonia (16.8% versus 6.8%), urinary tract infection (5.1% versus 0%), and febrile neutropenia (9.1% versus 4.1%), and at least 5% greater in group Other combo for anemia (3.6% versus 13.5%) and decreased neutrophil count (0.5% versus 13.5%), infusion related reaction (2.5% versus 8.1%), and decreased platelet count (0% versus 5.4%).

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The overall safety profile of isatuximab, when used as single agent as well as in combination settings, is characterized by the analysis of all the TEAEs across the data pools. Overall, in Data Pool 1, with the exception of neutropenia (46.7% and 49.7%, respectively, in EFC14335 IPd and Pooled IPd) and fatigue (17.1% and 24.0%), the incidence of TEAEs in study EFC14335 and study TCD14079 Part A are generally consistent and thus demonstrate that the safety profile of IPd is well characterized across these 2 studies. Pneumonia (20.8%), bronchitis (20.3%), constipation (20.3%), and dyspnea (19.8%), were among the most frequent TEAEs only in Data Pool 1. When isatuximab is used in combination with IMiDs, neutropenia was among the most common TEAEs, with an incidence of 51.3% and 21.1% (respectively with isatuximab in combination with pomalidomide/dexamethasone, and lenalidomide/dexamethasone). Across all the data pools, infusion related reaction (46.5%), fatigue (30.0%), diarrhea (25.7%), upper respiratory tract infection (24.7%), neutropenia (22.2%), and nausea (20.1%) were among the most common TEAEs.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the overview of TEAEs for Study EFC14335 presented in Table 28 and common TEAEs reported on Study 14335 in Table 29 and Table 30 with two exceptions.

1. Using FDA grouped terms, any grade and grade 3 upper respiratory tract infections were reported in 56% and 9% of patients in the IPd arm and 42% and 3.4 % in the Pd arm. Any grade and Grade 3 dyspnea was reported in 17%, and 5% of patients in the IPd arm and 12% and 1.3% in the Pd arm. No Grade 4 TEAEs of upper respiratory tract infections or dyspnea were reported on Study 14335.
2. The FDA does not agree with the Applicant's assessment that differences in incidences between TEAEs in IPd and Pd have to be analyzed in the context of the longer exposure in the IPd arm and that SAEs in the two arms are similar when adjusted for exposure. Patients in the real world may be expected to have exposures similar to that in Study EFC14335 and may experience rates of SAEs reported on the IPd arm in Study 14335.

FDA agrees with the evaluation of rates of cytopenia based on laboratory abnormalities as these are generally underreported in the adverse event datasets. The laboratory abnormalities are discussed in the section on "Laboratory Findings" below. The FDA did not independently confirm the Applicant's numbers in the other pooled population but notes that adverse events of neutropenia, pneumonia, upper respiratory tract infections and infusion related reactions are reported at rates consistent with the Study 14335.

Laboratory Findings

The Applicant's Position:

Hematological abnormalities in study EFC14335 are discussed in the context of potential adverse reactions and data on neutropenia and thrombocytopenia in Pool 1 are presented above.

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Clinical chemistry parameters and most liver and renal function parameters were similar among the groups in Pool 1. The exception was Grade 3 creatinine increased, where the incidence in Pd was 8.8% versus ≤3.6% in the 3 IPd groups. The higher incidence in the Pd arm was attributed to better myeloma control in the IPd arm leading to less renal dysfunction.

In Pool 2, treatment emergent hematology abnormalities classified as Grade 3 or Grade 4, respectively, included lymphocytes decreased in 25.8% and 6% of patients, anemia in 19.8%, and 0%, neutrophil count decreased in 11.4% and 4%, and platelet count decreased in 10% and 5.4%. There was no apparent dose dependency in the laboratory hematology evaluations: The incidence of Grade 3 and Grade 4 abnormalities in the two higher doses compared the two lower doses does not suggest a dose dependency.

In the laboratory evaluations of liver and renal function, the number of patients with Grade 3 or Grade 4 abnormality was ≤4 (1.3%) each for ALT increased, AST increased, alkaline phosphatase increased, blood bilirubin increased, and creatinine increased. There was no apparent dose dependency.

Among the patients treated with isatuximab (Data Pool 4), none of the 6 reports within the Hy's Law e-DISH quadrant or on the borderline meets the definition of Hy's Law cases, because of alternative etiology including progressive disease and general health deterioration, documented medical history of cholelithiasis or renal failure, concurrent Grade 3 cholecystitis and chronic liver disease documented by a cholangiogram, concurrent Grade 4 pacemaker site infection with coronary artery disease accompanied by low (25%) ejection fraction and Grade 4 hyperuricemia, and concomitant cephalosporin or lenalidomide.

The FDA's Assessment:

The Applicant did not present laboratory abnormalities on Study 14335 in this section and only noted the changes based on the different pooled populations. The FDAs analysis of laboratory abnormalities on Study 14335 is shown below in Table 32 Laboratory Abnormalities on Study 14335. Any grade and grade 3 or 4 neutropenia, lymphopenia, thrombocytopenia and anemia were higher in the IPd arm compared to the Pd arm. The rates of Grade 3 or 4 TEAE laboratory abnormalities of liver function and electrolytes were not different between the two arm on Study 14335. The rates of creatinine increased was higher in the Pd arm compared to the IPd arm. However, the FDA does not agree with the Applicant's assessment that the higher incidence of creatinine increased in the Pd arm can be attributed to better myeloma control in the IPd arm leading to less renal dysfunction. There is limited data to support conclusion at this time. FDA also reviewed the data of patients with LFT's in the Hy's law range as reported by the Applicant above. The narratives of two patients meeting Hy's law (b) (6) (b) (6) on Study 14335 and who also had a fatal AE are described in Section 8.2.3 in Deaths. Alternative causes for hepatic enzyme elevation were identified in these 2 patients with fatal TEAEs and 1 additional patient ((b) (6) occurred in the setting of cardiac pacemaker infection and resolved within 5 days) on Study 14335 who had LFT's in the Hy's law

range. Patient [redacted] (b) (6) in Study 14335 had elevation of ALT elevation to 8 x ULN and AST and T-Bili elevation 4 X ULN and ALP increase 2 x ULN on Cycle 4 D15 with AE of abdominal pain, patient was treated with supportive care and the LFT's resolved within a week. Patient had also received filgrastim in the earlier cycles. Patient had no further elevation of LFT's despite receiving additional treatment and LFT's were normal at the end of treatment visit.

FDA did not independently confirm the laboratory abnormality assessment from the other pooled populations given the differences in patient population, lack of control arm and different combination regimens.

Table 32 Laboratory Abnormalities -Study 14335

	IPd N=152				Pd N=149			
	Any Grade		Grade 3 and 4		Any Grade		Grade 3 and 4	
Laboratory Parameter	N	%	N	%	N	%	N	%
Anemia	151	99.3	48.0	31.6	145	97.3	41.0	27.5
Neutrophil count decreased	146	96.1	129.0	84.9	137	91.9	103.0	69.1
Platelet count decreased	127	83.6	47.0	30.9	118	79.2	36.0	24.2
Lymphocyte count decreased	140	92.1	83.0	54.6	137	91.9	64.0	43.0
Creatinine increased	131	86.2	4.0	2.6	136	91.3	13.0	8.7
ALT increased	54	35.5	6.0	3.9	46	30.9	4.0	2.7
Alkaline phosphatase increased	61	40.1	2.0	1.3	27	18.1	1.0	0.7
AST increased	38	25.0	4.0	2.6	34	22.8	4.0	2.7
Blood bilirubin increased	24	15.8	3.0	2.0	18	12.1	1.0	0.7
Hypoglycemia	9	5.9	0.0	0.0	20	13.4	0.0	0.0
Hyperglycemia	59	38.8	7.0	4.6	46	30.9	6.0	4.0
Hyperkalemia	39	25.7	2.0	1.3	31	20.8	2.0	1.3
Hypophosphatemia	132	86.8	22.0	14.5	107	71.8	22.0	14.8

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Hypocalcemia	81	53.3	4.0	2.6	66	44.3	2.0	1.3

Source: FDA Analysis

Vital Signs

The Applicant's Position:

Comparing the vital sign parameters during the treatment period (including before, during, and after any infusion) for groups IPd and Pd in study EFC14335, potentially clinically significant abnormalities (pre-defined threshold and changes from baseline) were more common in IPd for heart rate decrease (10 [6.6%] versus 2 [1.4%] patients, respectively) and increase (10 [6.6%] versus 2 [1.4%]), systolic blood pressure decrease (34 [22.4%] versus 9 [6.1%]) and increase (28 [18.4%] versus 21 [14.3%]), diastolic blood pressure decrease (16 [10.5%] versus 4 [2.7%]), and body weight decrease (54 [35.8%] versus 28 [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 versus 24.0 weeks, respectively), and more frequent monitoring during isatuximab infusion in IPd arm. In addition, the excess of PCSA for some tests didn't translate into an increase in the incidence of TEAEs in the vascular disorders and investigation SOCs. Vital signs in the 2 pooled IPd groups were similar those in the IPd group of study EFC14335.

The FDA's Assessment:

The Applicant assessed clinically significant changes in HR, BP and weight on Study 14335; HR changes: increased as >=120 beats /min and increase from baseline >=20 beats/min and decrease as <=50 beats/min and decrease from baseline<=20 beats/min; Systolic pressure decrease: <=95 mmHg and <=20 mmHg from baseline, systolic pressure increase: >=160 mm Hg and >=20 mm Hg increase from baseline; weight decrease:>=5% decrease from baseline, weight increase:>=5% increase from baseline. The FDA agrees with the numerical values of vital signs as reported above. The median HR in the IPd arm (73; range 40-160 beats/min) and the Pd arm (75, range 37-130 beats/min) were similar More patients in the IPd arm experienced decreases in systolic and diastolic pressure measurements and weight decrease. The FDA agrees with the Applicant's assessment that number of patients with TEAEs of hypertension were not different in the IPd arm (7 patients) compared to the PD arm (8 patients). TEAE of hypotension was reported in 6 patients in the IPD arm and 3 patients in the Pd arm. FDA did not independently confirm the vital sign changes on the other studies evaluating IPd or in the pooled population.

Electrocardiograms (ECGs)

The Applicant's Position:

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, and an ECG was abnormal at baseline and normal during treatment was reported in 31.7% (13 of 41) and 22.2% (6 of 27). In the 2 pooled IPd groups, pooled IPd

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10 mg/kg and pooled All IPd doses, the incidence of normal and abnormal ECGs during treatment was similar to that described above for group EFC14335 IPd 10 mg/kg, and the respective values differed by <3.2%.

The FDA's Assessment:

The FDA noted that the ECG monitoring and reporting on Study 14335 was limited precluding any definitive conclusions. FDA clinical pharmacology team assessment on the ECG data for this Application is presented in Section 6.3.2. and noted "Isatuximab is a monoclonal antibody; prolongation of the QT interval is unlikely. No changes were noted in any cardiac parameters evaluated in the safety pharmacology study in cynomolgus monkey. Thorough ECG monitoring was performed in Phase I Study TED10893 (0.3 mg/kg – 20 mg/kg) and did not show clinically relevant changes from baseline for any of the ECG parameters evaluated including QTcF. In Study TED10893, one patient experienced sinus tachycardia which was associated with an infusion-related reaction." FDA did not independently confirm the Applicant's ECG findings from pooled populations.

QT

The Applicant's Position:

An analysis of ECG monitoring data collected in 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.

The FDA's Assessment:
See FDAs assessment above under ECGs.

Immunogenicity

The Applicant's Position:

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.

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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 hemorrhagic complications revealed no evidence of an impact of ADA to isatuximab on clinical safety.

The FDA's Assessment:
The FDA's assessment of immunogenicity is discussed in detail in the Clinical pharmacology section

Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Fixed volume infusion

The isatuximab dilutent volume was based on body weight for all isatuximab studies except Phase 1b study TCD14079 Part B. As the infusion flow rate was based on mg/hours, the patient size impacted the total duration of each infusion. In study EFC14335, the following direction was provided:

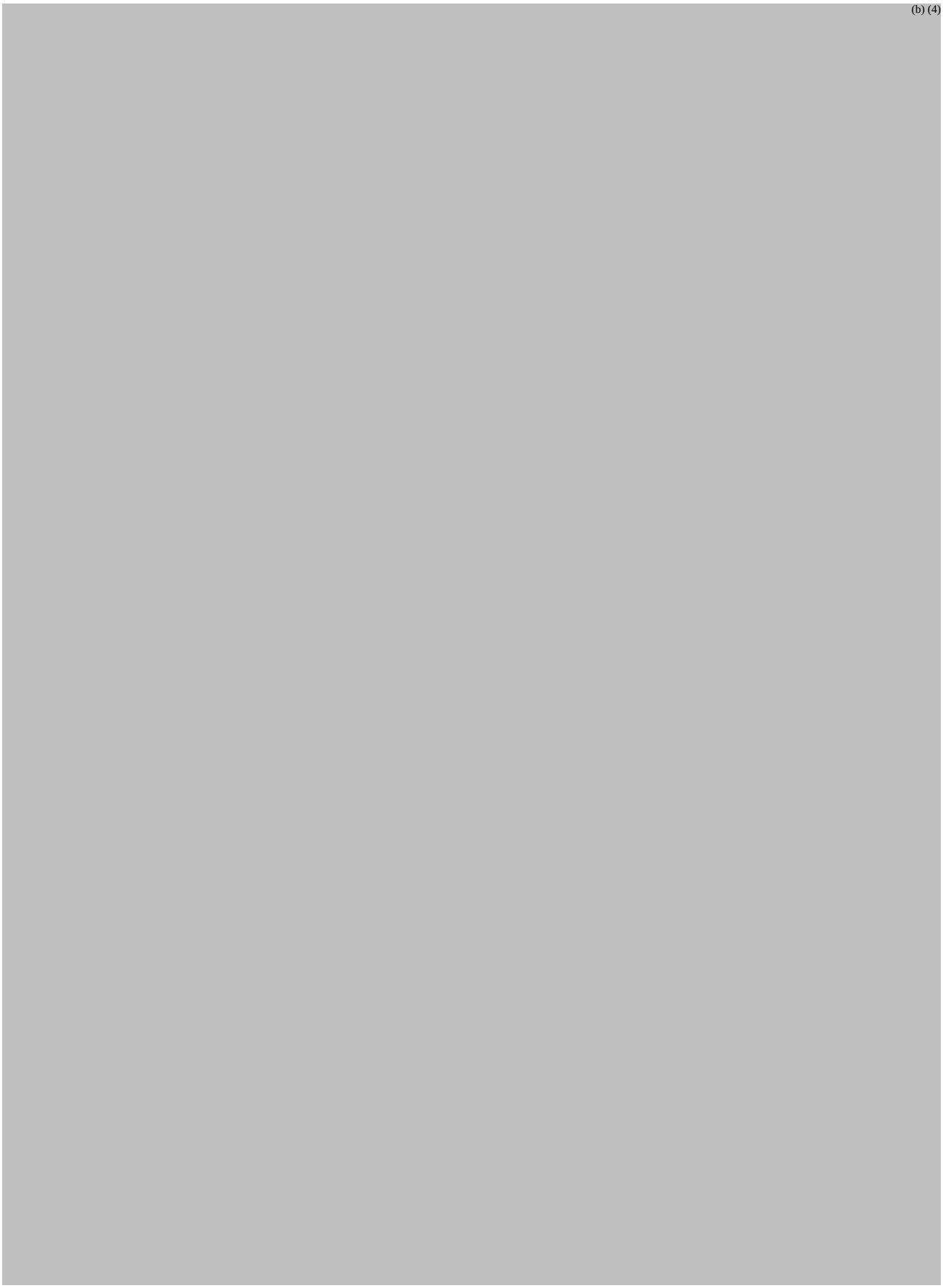
- First infusion: Infusion initiation at 175 mg/hour. In the absence of IRs, after 1 hour of infusion, rate is increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
- Subsequent infusions: Initiate infusion at 175 mg/hour. In the absence of IRs after 1 hour of infusion, rate is increased by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

In TCD14079 Part B, the feasibility of isatuximab administered with a fixed volume infusion method (Table 33) was evaluated in patients with RRMM. The occurrence of Grade ≥3 IRs was the primary endpoint.

Table 33 - Isatuximab administration method using a fixed infusion volume

	Dilution volume	Initial rate	Absence of IR	Rate increment	Maximum rate
First infusion	250 mL	25 mL/hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/hour
Second infusion	250 mL	50 mL/hour	For 30 minutes	50 mL/hour for 30 minutes; then, increase by 100 mL/hour every 30 minutes	200 mL/hour
Subsequent infusions	250 mL	200 mL/hour	---	---	200 mL/hour

Interim analysis of fixed volume infusion method


(b) (4)

(b) (4)



Recommendation for fixed-volume infusion method

(b) (4)



The FDA's Assessment:

The adequacy of the data to support the fixed volume infusion is detected in detail in the clinical pharmacology section above. The Applicant submitted additional data (total 47 patients) from the Part B portion of the study TCD 14079 during the review cycle. The clinical pharmacology reviewer noted that incidence of IRs with the fixed volume infusion was similar to the weight based infusion generally. However, there was trend towards higher rate and intensity of IRs in a subgroup of patients >100 Kg. The number of patients in this weight subgroup in the TCD14079 was small to make a definitive conclusion. The FDA clinical pharmacology team concluded that the fixed base volume infusion could be approved, however additional information on safety with respect to rate and severity of infusion reactions in

patients >100 Kg will be requested as a PMR.

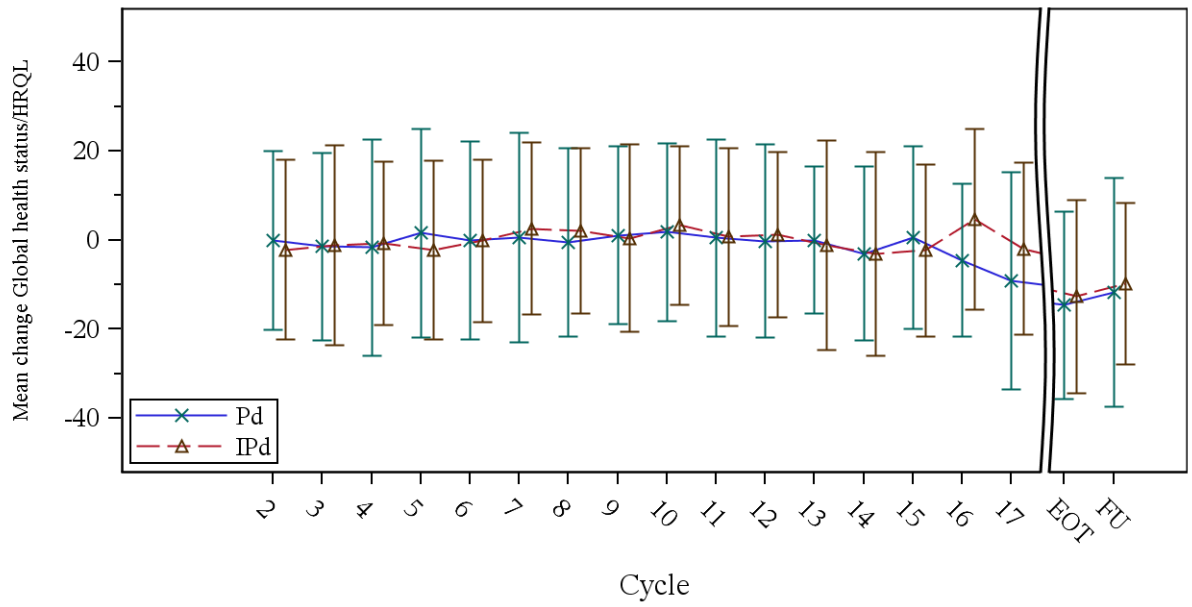
8.2.4. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

The Applicant defined clinically important changes from baseline as increases or decreases of 10 points for C30 and MY 20 summary scores, subscales and symptom items, 0.074 points for EQ-5D-5L health state utility values (HSUV) and 7 points for EQ 5D 5L VAS in patient reported outcomes. Statistical significance for within or between group differences was not assessed for any of the three ePRO measures.

Health related quality of life was maintained during the treatment period for both treatment arms based on lack of clinically important mean changes from baseline in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) (Figure 24).

Figure 24 - Mean change from baseline and standard deviation for global health status score over time - Safety population evaluable for Global health status



# patients																		
Pd	124	109	99	81	69	66	58	55	52	48	41	31	22	15	11	10	74	39
IPd	131	123	118	105	102	93	89	82	73	72	60	49	35	25	18	13	56	23

A higher score represents a better level of quality of life.
EOT: End of treatment, FU: Follow-up
End of treatment: 30 days after last study treatment administration, Follow-up: 60 days after last study treatment administration
Note: Cycles with less than 20 patients overall are not presented.
Safety population evaluable for quality of life assessment: patients from the safety population who have completed the baseline and at least 1 post baseline assessment.
PGM=PRODOPS/SAR650984/EFC14335/CIR/REPORT/PGM/eff_qlq_c30_line_s_f.sas
OUT=REPORT/OUTPUT/eff_qlq_c30_line_glb_chg_s_f_x rtf (19FEB2019 21:09)

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The FDA's Assessment:

The FDA did not independently confirm the analysis of PRO and the results of EORTC QLQ-C30 global health status (GHS)/quality of life (QoL). PRO analysis were not included in the statistical testing. Global health status may not completely represent the patient experience while on treatment and it is difficult to interpret maintenance of QOL in the context of the safety profile of isatuximab, pomalidomide and dexamethasone combination.

8.2.5. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Overall, there were no clinically meaningful differences in the analysis of the elderly patients ≥75 years category, nor in other demographic subgroup analyses (gender, race, ECOG, renal status, hepatic status). The RRMM population in EFC14335 is largely represented by elderly patients, and no meaningful differences in the safety profile of IPd versus Pd could be identified among the age groups. Details for each subgroup are presented below.

The IPd regimen can be administered safely to patients ≥75 years without impact on the incidence of adverse events leading to treatment discontinuation or fatal outcomes compared to the Pd regimen. In the analyses of patients entering with renal function impairment and mild hepatic impairment, the incidence of TEAEs leading to treatment discontinuation and of Grade 5 TEAEs were similar for the IPd and Pd regimens.

Age (<65, 65-74, and ≥75 years)

Overall, 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 to74 years, and 21.1% versus 16.8% aged 75-84 years. In study EFC14335, however, only 3 patients ≥85 years of age were enrolled in group Pd versus 0 in group IPd, while in Data Pool 4, 2 patients were ≥85 years of age in isatuximab single agent studies. Thus, the available data are too limited for an analysis of safety in patients aged ≥85.

In the IPd arm of study EFC14335, the overall incidence of all grade TEAEs was similar across the 3 age categories <65 years (98.1%), 65 to 74 years (100%), and ≥75 years (100%). A trend toward more Grade ≥3 TEAEs was observed in patients aged ≥75 years in the IPd arm (93.8%) compared to patients <65 years (85.2%) and in the pooled IPd groups , with a similar trend observed also in the Pd arm (75.0% and 64.7% , respectively).

In study EFC14335, a trend was observed towards more definitive treatment discontinuations because of TEAEs in patients aged ≥75 ears in the IPd arm (15.6%) compared to patients <65 years (7.4%). The same trend was observed also in the All IPd doses (15.4% and 5.6%), and in the Pd arm (14.3% and 10.3%, respectively).

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A trend towards higher incidence of serious TEAEs was observed in patients aged ≥75 years in the IPd arm (68.8%) compared to patients <65 years (57.4%), with a similar trend observed also in the All IPd doses (66.7% and 55.6%)and in the Pd arm (57.1% and 47.1%) respectively. The incidence of TEAEs with fatal outcome was lower in patients aged ≥75 years in the IPd arm (6.3%) compared to patients <65 years (11.1%), while the opposite trend was observed in Pd (14.3% versus 5.9%). The incidence rates in All IPd were similar between age groups (10.3% versus 9.7%).

In the IPd arm study EFC14335, the SOCs with TEAEs having an incidence ≥10% greater in patients aged ≥75 years versus patients aged <65 years consisted of Blood (68.8% versus 53.7%; with the same trend also observed in All IPd doses with 66.7% and 56.9%), Psychiatric (28.1% versus 14.8%, with similar incidences of 28.2% and 26.4% in the All IPd doses group, and an opposite trend in Pd patients with 10.7% versus 19.1%), Vascular (21.9% versus 11.1%, with a similar trend in All IPd doses with 20.5% and 16.7), Skin (40.6% versus 22.2%, with similar incidences of 35.9% and 31.9% in All IPd doses, and an opposite trend in Pd patients with 7.1% versus 32.4%), Renal (18.8% versus 7.4%, with a similar trend of 15.4% versus 11.1% in All IPd doses), Investigations (15.6% versus 5.6%, with a similar trend of 12.8% and 9.7% in All IPd doses, and 10.7% and 7.4% in Pd).

Among the IPd patients in study EFC14335, the incidence of Grade ≥3 TEAEs in the Vascular SOC, Psychiatric SOC, and Investigations SOC, in the age groups ≥75 years and <65 years was limited to 1 patient each.

Among the IPd patients in study EFC14335, the incidence of Grade ≥3 TEAEs in the Skin SOC in the ≥75 years was 0.

Among the IPd patients in study EFC14335, the incidence of TEAEs in the Infections in SOC was 81.3% in the ≥75 age group versus 74.1% in <65 years age group, however, the incidence in the 65-74 age group was the highest with 86.4%, indicating there was no increase in infections with age. The same trend was observed in All IPd.
Among the IPd patients in study EFC14335, the incidence of TEAEs in the Nervous system disorders in SOC was 40.6% in the ≥75 age group versus 38.9% in <65 years age group, however, the incidence in the 65-74 age group was the highest with 42.4%, indicating that there was no progressive increase in nervous system disorders with age. The opposite trend was observed in the All IPd arm (47.2% in the <65 years age group versus 41.0% in the ≥75 age group).

Among the IPd patients in study EFC14335, the incidence of TEAEs in the Cardiac disorders SOC was 18.8% in the ≥75 age group, 15.2% in the 65 to 74 age group, and 11.1% in <65 years age group. The same trend was observed in All IPd. The most frequent contributor to Cardiac disorders SOC was atrial fibrillation, which had a similar pattern of incidence: age group ≥75 years, 2 [6.3%] patients; 65 to 74 years, 4 [6.1%]; <65 years 1 [1.9%]). The same trend was observed in group Pd for atrial fibrillation.

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Although the incidence of TEAEs in the Skin SOC was higher in patients aged ≥75 years, compared to the younger age groups in the IPd arm study EFC14335, this finding was not present in Data Pool 4, where the incidence of TEAEs in the Skin SOC was similar across all the age groups (ranging from 25.2% in patients aged <65 years to 25.6% in patients aged ≥75 years). Similarly, the severity of the TEAEs in the Skin SOC was not affected by the age, with an incidence of Grade ≥3 TEAEs of 0.7% in patients aged <65 years and 1.2% in patients aged ≥75 years.

In study EFC14335, the SOCs with an incidence of Grade ≥3 TEAEs ≥10% greater in IPd patients aged ≥75 years versus patients aged <65 years consisted of Blood (68.8% versus 53.7%, with the same trend also present in Pd, 53.6% versus 33.8%), Metabolism (15.6% versus 1.9%), Renal (12.5% versus 1.9%), and Injury (12.5% versus 1.9%). For the SOCs of Metabolism, Renal, and Injury, the higher incidence in the older age group is driven primarily by adverse events that occurred in only 2 patients.

In group IPd, the incidence of Grade ≥3 TEAEs in the Renal SOC in patients aged ≥75 years, 65 to 74 years, and patients aged <65 years was 12.5%, 6.1%, and 1.9%, respectively. In group Pd, the incidence of these TEAEs was similar to IPd in the two older age groups, 10.7% and 5.7%, however, there was a higher incidence in the <65 years age group in Pd compared to IPd (8.8% versus 1.9%).
In study EFC14335, no Grade ≥3 TEAEs with an incidence ≥10% greater IPd patients aged ≥75 years versus patients aged <65 years was observed.

In study EFC14335, Grade 3-4 laboratory neutropenia occurred with similar frequency in IPd patients aged ≥75 years (87.5%) versus <65 years (88.9%), with the same trend observed also in All IPd doses (87.2% and 86.1%, respectively).

In study EFC14335, Grade 3-4 laboratory thrombocytopenia was slightly more frequent in IPd patients aged ≥75 years (34.4%) versus <65 years (29.6%), with the same trend observed also in All IPd doses (33.3% and 30.6%, respectively). A similar trend was apparent in Pd, with 28.6% in elderly patients and 22.1% in younger patients.

Among the IPd patients in the ≥75 year age category from study EFC14335, no other notable increases in TEAEs at the SOC level were observed.

In study EFC14335, the incidence of IRs was lower in the ≥75 age category (28.1%) compared with the <65 age category (46.3%); a similar trend was also observed in All IPd doses (28.2% and 50.0%, respectively).

In study EFC14335, lower respiratory AEs occurred with a similar frequency in the ≥75 age category compared with <65 (40.6% and 38.9%), and the same trend was also observed in All IPd doses (38.5% and 44.4%).

Gender

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Overall, 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%; the same trend was also observed in All IPd doses (5.1% and 10.2%, 66.1% and 53.2%, and 8.5% and 3.8, respectively).

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%).

In study EFC14335, the SOCs with an incidence of Grade ≥3 TEAEs with a ≥10% difference in IPd males versus females consisted of Infections (47.7% versus 35.9%, with the same trend of 42.4% and 31.6% for All IPd doses, but not in Pd, 27.9% versus 32.1%, respectively), and Blood (51.1 versus 65.6%, with the same trend of 54.2% and 69.6%also in All IPd doses, and 33.8% and 45.7% in the Pd arm). Among these SOCs, 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 44.9% and 59.5% also in All IPd doses, and 26.5% and 37.0% in the Pd arm.

Race

In the IPd arm of study EFC14335, the number of non-white patients was 24 and in Pd was 19, and the number of white patients in IPd was 116 and in Pd was 122. 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 number of patients with ECOG scores of 2 or 3 in the IPd arm was 16 and in the Pd arm was 14, and the number of patients with a ECOG score of 0 or 1 in IPd was 136 and in Pd was 135. No patients with ECOG score of 3 were reported at the baseline. 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 the same in IPd and All IPd doses (100%). Overall, 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). Overall, no safety signal is apparent for patients with ECOG score of 2.

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

Overall, in the IPd arm of study EFC14335, the incidence of Grade ≥3 TEAEs was similar across renal status: 86% [74] of patients with ≥60 mL/min/1.73 m^2 and 90.7% [49] 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 m^2 was higher than in

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patients with >60 mL/min/1.73 m^2, 9.3% versus 3.5%, 77.8% versus 51.2%, and 11.1% versus 5.8%; a similar trend was also observed in All IPd doses, with 11.3% and 4.4%, 76.1% and 51.3%, and 9.9% and 5.3%, respectively [5.1.10.1.1]. In group Pd, similar trends in renal status (≥60 [94 patients], <60 [47 patients]) were observed for Grade 5 TEAEs (12.8% versus 6.4%), serious TEAEs (59.6% versus 51.1%), TEAEs leading to definitive treatment discontinuations (14.9% versus 11.7%).

In the IPd arm of study EFC14335, the SOCs with an incidence of Grade ≥3 TEAEs ≥10% greater in patients with <60 mL/min/1.73 m^2 versus patients with ≥60 mL/min/1.73 m^2 consisted of Infections (55.6% versus 38.4%) , with a similar trend in All IPd doses (49.3% and 33.6%), and in the Pd arm of study EFC14335 (38.3% versus 28.7%), and Musculoskeletal (16.7% versus 3.5%), with a similar trend in All IPd doses (16.9% and 7.1%) and in the Pd arm of study EFC14335 (6.4% versus 3.2%). Among these same SOCs, 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 All IPd (23.9% versus 14.2%) and in the Pd arm (23.4% versus 12.8%).

Grade 3-4 laboratory neutropenia was similar in EFC14335 IPd patients with renal status <60 mL/min/1.73 m^2 versus renal status ≥60 mL/min/1.73 m^2 (85.2% versus 84.9%), with the same trend in All IPd doses (85.9% versus 84.1%).

Grade 3-4 laboratory thrombocytopenia was more frequent in the EFC14335 IPd arm patients with renal status <60 mL/min/1.73 m^2 versus renal status ≥60 mL/min/1.73 m^2 (38.9% versus 25.6%), with the same trend in All IPd doses (39.4% versus 26.5%) and in the EFC14335 Pd arm patient (34.0% versus 19.1%).

No notable difference across renal status were observed in the other significant adverse events. In group IPd of study EFC14335, the incidence of all grade TEAEs in the infection SOC and in the cardiac disorders SOC was higher in patients with renal impairment (90.7% versus 77.9%) and (22.2% versus 11.6%); the same trend was observed in All IPd doses.

Hepatic status

In this analysis a comparison is made between patients with normal hepatic function (130 patients in IPd and 126 in Pd) and patients with impaired hepatic status (22 patients in IPd and 22 in Pd), but it should be noted that patients in this latter group contained only patients with mild hepatic impairment, except for 1 patient in Pd with moderate hepatic impairment.

Overall, 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 (3 [13.6%] patients versus 8 [6.2%]) but the incidence of TEAEs leading treatment discontinuation and of serious TEAEs was similar (2 [9.1%] versus 9 [6.9%], and 14 [63.6%] versus 80 [61.5%], respectively. Similar

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trends were noted for these TEAEs, respectively, in All IPd doses (3 [12.0%] versus 13 [7.6%], 2 [8.0%] versus 11 [6.4%], and 15 [60.0%] versus 105 [61.0%]), and in EFC14335 Pd for Grade 5 TEAEs (3 [13.6%] versus 10 [7.9%]) and for serious TEAEs (11 [50.0%] versus 68 [54%]), but 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%]).

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%), the same trend was also observed in All IPd doses (24.0% and 9.3%) , and in Pd (18.2% and 11.1%).

In study EFC14335, the incidence of Grade 3-4 laboratory neutropenia was similar in IPd patients with mild hepatic impairment (86.4%) versus normal status (84.6%), with the same trend in All IPd doses (84.0% and 84.3%), while in Pd the incidence was higher in patients with hepatic impairment (86.4% and 65.9%). Grade 3-4 laboratory thrombocytopenia was more frequent in IPd patients with mild hepatic impairment (50.0%) versus normal status (27.7%) with the same trend in All IPd doses (48.0% and 29.1%) and Pd (40.9% and 20.6%), and no notable difference across the hepatic status was observed for other significant adverse events.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of safety analysis by age in the <65, 65-75 and >=75 years age groups on Study EFC14335. There was a higher rate of SAEs and treatment discontinuations in the <=75 years age group compared to the <65 years age group.

However, FDA does not agree with the Applicant's statement " The IPd regimen can be administered safely to patients ≥75 years without impact on the incidence of adverse events leading to treatment discontinuation or fatal outcomes compared to the Pd regimen." This statement is incorrect and misleading. The number of patients in the >=75 years age group is very small limiting definitive conclusion regarding the safety of isatuximab, pomalidomide and dexamethasone in this age subgroup of patients.

FDA agrees with the Applicant's assessment of safety by gender and renal impairment on Study EFC14335. FDA did not conduct separate safety analyses by race, ECOG subgroups and hepatic impairment as the number of patients in individual subgroups within each of these categories in Study 14335 were very small precluding definitive conclusions regarding safety in these subgroups. Study 14335 enrolled only 1 patient with moderate or severe hepatic impairment. FDA also did not independently confirm safety in the demographic subgroups for all IPd doses.

From the FDA clinical pharmacology review "FDA agrees with the applicant's position that no therapeutic individualization is needed based on Ig type multiple myeloma (i.e., IgG vs non-IgG), demographic factors (age, sex), in patients with hepatic, or in patients with renal impairment based on population PK analyses. An effect of age, sex, renal and hepatic impairment is not

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expected as isatuximab is a monoclonal antibody and its disposition is not expected to be impacted by renal or hepatic impairment. Body weight was identified as a significant covariate in the population PK analysis, with an increase in CL with increasing body weight, which supports the weight-based dosing approach."

8.2.6. Specific Safety Studies/Clinical Trials

The Applicant's Position:
No specific studies are planned.

The FDA's Assessment:
[The FDA agrees with the Applicant's assessment.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No genotoxicity studies have been performed to evaluate genotoxicity as this drug is a mAb with no potential to interact with cellular DNA; nor have carcinogenicity studies been conducted, as this drug is a therapeutic mAb being developed for oncology indications. There is no evidence or scientific rationale indicating a potential risk for tumorigenicity.

The FDA's Assessment:
The FDA concurs that no genotoxicity or carcinogenicity studies have been conducted. However, in the pivotal trial EFC14335, a higher rate of SPMs were reported in the isatuximab, pomalidomide, dexamethasone arm compared to the pomalidomide dexamethasone arm. Patients treated with IPd combination regimen should be monitored for the development of SPMs as per IMWG guidelines.

Human Reproduction and Pregnancy

The Applicant's Position:
Pregnant or lactating females were excluded from the clinical development program. No pregnancies have been reported in any data pool.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment above. The USPI will include the following information: "Isatuximab can cause fetal harm when administered to a pregnant woman". The assessment of isatuximab-irfc-associated risks on pregnancy is based on the mechanism of action and data from target antigen CD38 knockout animal models. There are no available data on isatuximab use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction toxicity studies have not been conducted with isatuximab-irfc.

The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child."

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
No studies have been completed in the pediatric population.

The FDA's Assessment:
The FDA agrees that no studies have been conducted in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
An overdose (accidental or intentional) of study treatment was defined as a ≥30% increase from the dose planned to be administered in the specified duration or if the dose was administered in less than half the recommended duration of administration. Reports of overdose were considered to be AESIs and were to be reported to the sponsor within 24 hours. A dexamethasone overdose was reported as an AESI in 1 patient in group Pd in study EFC14335. No patients with isatuximab overdose have been reported in any Data Pool.

Drug abuse and withdrawal and rebound have not been reported.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Patients were treated at doses up to 20 mg/kg intravenously in clinical studies.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

At the time of this filing, isatuximab is not approved for marketing in any country.

The FDA's Assessment:
The Agency agrees with the Applicant's assessment.

8.2.9. Integrated Assessment of Safety

The Applicant's Position:

Reference ID: 4568595

The safety profile of isatuximab in combination with pomalidomide and dexamethasone has been carefully evaluated compared to pomalidomide and dexamethasone in patients with RRMM in study EFC14335, supported by a Phase 1b study with the same combination (TCD14079 Part A). Although some TEAEs were more frequent in the IPd arm, the overall safety profile is generally favorable. No dose dependency in the isatuximab safety profile was seen through the analyses of the single agent studies in Pool 2.

The duration of exposure in study EFC14335 was almost twice as long in the IPd arm compared with the Pd arm (median of 41 weeks versus 24 weeks).

In study EFC14335, TEAEs leading to definitive treatment discontinuation were not higher in IPd compared to Pd, 7.2% and 12.8% of the patients, respectively; The most frequent SOCs leading to treatment discontinuations were Infections and infestations (2.6% versus 5.4% in the IPd and Pd arms, respectively), and Blood and lymphatic system disorders (0.7% versus 4.7%).

During the treatment period, a similar number of deaths were reported in the IPd arm and Pd arms (7.2% and 8.7%, respectively), with 3 and 6 patients, respectively, having died because of AEs.

The overall incidence of serious TEAE was 61.8% and 53.7% in the IPd and Pd arms, respectively. The most common serious TEAEs in the IPd arm were pneumonia (15.1% and 15.4% of the patients in the IPd and Pd arms, respectively), and febrile neutropenia (6.6% and 2.0%). When serious TEAEs were adjusted for the longer duration of exposure in the IPd arm, however, their overall incidence rates in patient-years were similar (1.36 and 1.30 in the IPd and Pd arms, respectively).

In study EFC14335, the median duration of the isatuximab infusions was 3.3 hours during the first infusion, and 2.8 hours for the subsequent infusions, consistent with the experience across the patients treated with IPd (3.4 hours, and 2.8 hours, respectively). An alternative fixed infusion volume method was evaluated in the study TCD14079 Part B to simplify the method of administration of isatuximab and abbreviate its infusion time; based on the results from the interim analysis with 34 patients, this method allowed a considerably shorter median duration of 75 min (1.25 hours) from 3rd infusion onwards, without affecting the risk of IRs (incidence of IRs was 47.1% with no Grade ≥3 IRs reported, with no IR beyond first infusion). The fixed-volume method also reduces the steps required for the preparation of isatuximab prior to its administration, thereby reducing the possibility of human errors and inappropriate dosing of isatuximab to patients.

Infusion reactions were reported in 38.2% of the patients in the IPd arm of study EFC14335. Most of the patients had Grade 1 (3.9%) or Grade 2 (31.6%) IRs; Grade 3 and Grade 4 IRs were reported each in 1.3% of the patients, and no fatal IRs occurred. The majority of the patients with IRs had a single episode. All the patients with IRs had their first onset during the first infusion, and on the same day of the infusion. All the IRs resolved without sequelae, most frequently on the same day. No delayed IRs occurred, and no post-infusion prophylactic

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medications against the risk of IRs were administered, in accordance with the study protocol. No IRs occurred after the 4th infusion.

In most cases, the IRs were managed with infusion interruption and/or medications. Isatuximab treatment discontinuation occurred in only 4 patients (2.6%) who could continue their treatment with Pd, as per protocol.

Besides infusion reactions, the most frequent all grade treatment-emergent AEs in study EFC14335 reported with a higher frequency in the IPd arm were neutropenia (46.7% and 33.6% in the IPd and Pd arms, respectively), upper respiratory tract infection (28.3% and 17.4%), diarrhea (25.7% and 19.5%), and bronchitis (23.7% and 8.7%).

In study EFC14335, within the SOC of Infections and infestations, with the exception of urinary tract infection (4.6% and 1.3% in the IPd and Pd arms, respectively), the most frequently reported Grade ≥3 infections occurred with a similar incidence in the IPd and Pd arms: pneumonia (16.4% and 15.4% in the IPd and Pd arms, respectively), bronchitis (3.3% and 0.7%), and lower respiratory tract infection (3.3% and 2.7%). There was no difference in the incidence of infections leading to definitive treatment discontinuation or leading to fatal outcome between the treatment arms (2.6% in IPd versus 4.0% in Pd). When adjusted for the longer duration of exposure in the IPd arm, the incidence of treatment-emergent serious infections was similar (0.72 versus 0.67 incidence rate per patient year in the IPd and Pd arms, respectively).

The incidence and severity of lower respiratory TEAEs in the IPd arm (36.8%; Grade ≥3: 7.9%) was higher compared with the Pd arm (25.5%; Grade ≥3: 3.4%). The most frequently reported lower respiratory TEAEs, however, occurred with similar incidences in the 2 treatment arms and included dyspnea (15.1% and 10.1% in the IPd and Pd arms, respectively), and cough (9.2% and 7.4%). No patient in the IPd arm definitively discontinued treatment because of a lower respiratory TEAE. In the IPd arm, 1 patient prematurely discontinued pomalidomide because of pneumonitis.

In study EFC14335, SPMs were reported in one (0.7%) patient in the Pd arm and in 6 (3.9%) patients in the IPd arm, and consisted of cutaneous squamous cell carcinoma (cSCC) in the patient in Pd arm; in the IPd arm, cSCC occurred in 4 patients, breast post-radiation angiosarcoma in 1, and MDS in another patient. None of the patients discontinued their study treatment because of an SPM, with the exception of the patient who developed MDS with transformation to AML. All the patients with SPMs had been previously exposed to lenalidomide and alkylating agents.

Across all the isatuximab studies in Pool 4, the overall incidence of SPMs was 3.0%, with a median from the first dose of study treatment to the diagnosis of 7.16 months (range 0.5 to 26.5). The background incidence of SPMs in patients with relapsed/refractory multiple myeloma has been reported to be as high as 6%, and recent reports from clinical trials studying daratumumab in combination with bortezomib/dexamethasone and Pd in MM, the incidence of

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SPMs was reported as 3.2 to 4.1% (Landgren et al 2014, Palumbo et al 2014, Areethamsirikul et al 2015, Ailawadhi et al 2018, Abildgaard et al 2018, Spencer et al 2018). Therefore, the overall incidence of SPMs observed in patients treated with isatuximab is consistent with the background incidence of SPMs in patients treated for MM, where the risk of SPMs is compounded by older age, immunosuppression due to the underlying disease, and the effect of prior exposure to alkylating agents (eg, melphalan) and to lenalidomide.

In the IPd arm, TEAEs in the SOC Nervous system disorders (40.8% versus 28.9%; Grade ≥3: 7.9% versus 5.4%), and in the SOC Cardiac disorders (14.5% versus 4.0%; Grade ≥3: 4.6% versus 2.0%) were more frequent than in the Pd arm. Treatment discontinuations or fatal outcomes, however, were not reported more frequently in the IPd arm because of cardiac or nervous TEAEs.

Although laboratory Grade 3-4 neutropenia was more frequent in the IPd arm (84.9% versus 69.1%), the onset and duration of these abnormalities were generally similar between treatment arms and they were reversible: in the IPd and Pd arms, the median time to the first episode of Grade 3-4 neutropenia was 22 and 21 days respectively, and the median duration of the first episode of Grade 3-4 neutropenia was 9 and 11 days, respectively. Neutropenia was handled through colony-stimulating factor use and pomalidomide dose reductions. When neutropenic infections were analyzed among those patients treated with colony stimulating factors, the rate of neutropenic infection was similar (31.4% and 32.9% in the IPd and Pd arms, respectively.

Incidence of Grade 4 thrombocytopenia and Grade 3-4 anemia were similar in both arms. The addition of isatuximab to Pd did not increase the incidence of thromboembolic AEs above what was observed for the Pd arm.
In summary, the safety profile of IPd is characterized by infusion reactions, and an increase of neutropenia and infections compared to Pd which did not interfere with the treatment duration or the overall quality of life as assessed by the Global Health Score of EORTC QLQ-C30.

The FDA's Assessment:

FDA reviewed the applicant's position above. FDA's independent analysis of safety has been presented above in section 8.2.3. A brief summary is presented below.

FDA's integrated assessment of safety of the isatuximab, pomalidomide, dexamethasone combination focused primarily on the analysis of safety data from the pivotal Study EFC14335. Safety analyses from Study EFC14335 was based on a clinical database lock (DBL) of 22-November -2018. In study EFC14335, the safety population consisted of 301 patients with RRMM who received either IPd (152 patients) or Pd (149 patients). The duration of exposure in the pivotal study EFC14335 was almost twice as long in the IPd arm compared with the Pd arm (median 41 weeks versus 24 weeks, respectively).

Grade 3-4 TEAEs were reported more frequently in the IPd arm compared to the Pd arm (84.9% versus 69.1%) and serious TEAEs were also reported more frequently in the IPd arm compared to the Pd arm (61.8% and 53.7%). Based on the FDAs assessment using grouped terms, SAEs of pneumonia, upper respiratory tract infections and febrile neutropenia were higher in the IPd arm (≥5%) compared to the Pd arm in Study 14335.

Neutropenia, infusion related reactions and upper respiratory tract infections were the most frequent adverse events leading to isatuximab dose delay, dose interruption and dose omission of isatuximab respectively.

The most frequent (≥20% in the IPd arm) all grade treatment-emergent AEs in study EFC14335 reported with a higher frequency in the IPd arm were neutropenia (46.7% and 33.6% in the IPd and Pd arms, upper respiratory tract infection (56.0% and 42.0%), infusion related reactions (38.0% and none on the Pd arm), pneumonia (30.9% and 22.8%), and diarrhea (25.7% and 19.5%). Infusion related reactions, neutropenia and second primary malignancies are important safety risks noted with the isatuximab, pomalidomide and dexamethasone combination on Study 14335. The FDA considers SPMs as an important safety risk with the IPd combination based on reported higher rates in the IPd arm (3.9%) compared to the Pd arm (0.7%) in this large randomized controlled study. The USPI will include Infusion related reactions, neutropenia and second primary malignancies in the Warnings and Precautions section. Dose modifications and supportive care were effective in managing the adverse events and majority of these events resolved. The incidence of Grade 5 (fatal) TEAEs (7.9% and 9.4% in the IPd and Pd arms, respectively) and the any TEAEs leading to definitive treatment discontinuation of all study treatments (7.2% and 12.8% in the IPd and Pd arms) in study 14335 were generally low and similar between the two arms.

Routine risk minimization activities (i.e., risk communications through prescribing information, labeling, or packaging) are considered sufficient to manage the key risks associated with the use of isatuximab, pomalidomide, dexamethasone in patients with multiple myeloma who have received two prior therapies including a proteasome inhibitor and lenalidomide.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

EFC14335 is a well-controlled and well-conducted randomized clinical trial. There was one planned interim analysis for overall survival and the level of significance was adjusted to account for this analysis. Since there were only 45% of the planned 220 death events for the OS analyses, it would be beneficial if the patients were followed for a longer duration and updates on the OS were provided at the later point in the future. The Applicant was asked to provide an updated OS report as a PMC. This report will be generated in approximately 2021.

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Study TCD14079 was designed an early phase dose finding trial with an expansion cohort of patients treated at the recommended dose level. With 31 patients treated at the 10mg/kg dose level, the study results provided sufficient evidence of the appropriate dose selection. Due to the single-arm nature of the trial, no comparative statistical inference could be conducted.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the favorable risk-benefit profile of isatuximab with pomalidomide and dexamethasone, the clinical and statistical reviewers recommend approval of: isatuximab in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and proteasome inhibitor.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
Not Applicable.

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10 Pediatrics

The Applicant's Position:

Under the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c), the requirement of pediatric studies does not apply to any drug for an indication for which orphan designation has been granted.

The FDA's Assessment:

Isatuximab has an orphan drug designation for treatment of multiple myeloma based on Request #14-4319 and granted on May 22, 2014. Due to orphan drug designation of isatuximab for this indication, it is exempt from PREA requirements. This information was submitted in Section 1.9.1 of the BLA Application.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant's Position:

The FDA's Assessment:

It is important to note that isatuximab-pomalidomide and dexamethasone has been referred to as IPd in the text above and as Isa-Pd in the sections below..

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1 INDICATION AND USAGE	(b) (4) [redacted]	Added "adults" to specify age of indicated population per the Indications and Usage Guidance.
2 DOSAGE AND ADMINISTRATION	2.1 Recommended dose and schedule The recommended dose of SARCLISA is 10 mg/kg body weight administered as an	Revised heading to "Recommended Dosage", as the

	intravenous infusion in combination with pomalidomide and dexamethasone, according to the schedule in Table 1. Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. (b) (4) (b) (4) If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.	term dosage describes the dose and schedule. Added statement regarding administration of premedication's and cross-referenced to 2.2. Added recommendation regarding need for infusion location to have emergency equipment available. Added that dosing was based upon actual body weight.
	2.2 (b) (4) (b) (4) • Dexamethasone 40 mg PO or IV (or 20 mg PO or IV for patients ≥75 years of age). • Acetaminophen 650 mg to 1000 mg PO (or equivalent). • H2 antagonists (b) (4) • Diphenhydramine 25 mg to 50 mg IV or PO (or equivalent (b) (4) The intravenous route is preferred for at least the first 4 infusions.	Revised heading to "Recommended Premedication's". Revised text to active voice. Removed (b) (4)

	The above recommended dose of dexamethasone (PO or IV) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the backbone treatment, before SARCLISA and pomalidomide administration. (b) (4) (b) (4)	(b) (4)
	2.3 Dose Modifications No dose reduction of SARCLISA is recommended. (b) (4)	Added reference to USPI for other drugs used in combination for dose-modifications of those drugs. Details of dose modifications moved to Warnings and Precautions section.

	(b) (4)		
	2.4 Preparation	(b) (4) (b) (4)	Edited to use active voice. Added required text regarding parenteral product inspection.

	(b) (4)	
Infusion rates	2.5 Administation (b) (4) <u>Infusion rates</u> (b) (4)	Revised to use active voice.

<table>
<tr><td></td><td>(b) (4)</td><td></td></tr>
<tr><td>Table 2: Infusion rates (b) (4) SARCLISA administration
<table>
<tr><th></th><th>Dilution Volume</th><th>Initial Rate</th><th>Absence of IR</th><th>Rate Increment</th><th>Maximum Rate</th></tr>
<tr><td>First infusion</td><td>250 mL</td><td>25 mL/hour</td><td>For 60 minutes</td><td>25 mL/hour every 30 minutes</td><td>150 mL/hour</td></tr>
<tr><td>Second infusion</td><td>250 mL</td><td>50 mL/hour</td><td>For 30 minutes</td><td>50 mL/hour for 30 minutes then increase by 100 mL/hour every 30 minutes</td><td>200 mL/hour</td></tr>
<tr><td>Subsequent infusions</td><td>250 mL</td><td>200 mL/hour</td><td>–</td><td>–</td><td>200 mL/hour</td></tr>
</table></td><td></td></tr>
<tr><td>3 DOSAGE FORMS AND STRENGTHS</td><td>Injection: (b) (4)</td><td>Added individual bullets for reach presentation.</td></tr>
<tr><td>4 CONTRAINDICATIONS</td><td>SARCLISA is contraindicated in patients with hypersensitivity to isatuximab or to any of its excipients.</td><td>No change.</td></tr>
<tr><td>5 WARNINGS AND PRECAUTIONS</td><td>--</td><td>Added new warning for “Second Primary Malignancies”. Added new warning for “Embryo-Fetal Toxicity”.</td></tr>
<tr><td></td><td>5.1 (b) (4) (b) (4)</td><td>Revised heading to “Infusion-Related Reactions” per our current approach. Removed</td></tr>
</table>

	(b) (4)	exculpatory language (i.e., mostly mild or moderate). Rounded rates per Adverse Reactions guidance. Management of infusion related reactions updated to reflect management on Study EFC14335.
	(b) (4) Interference with serological testing (b) (4) SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-MM, the indirect antiglobulin test was positive during SARCLISA (b) (4) treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. (b) (4)	Relocated to lower number (5.4) and revised heading to "Laboratory Test Interference" per PLR Guidance.

	(b) (4) If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices [see Drug Interactions (7.1)].	
	(b) (4) Neutropenia: (b) (4) Monitor complete blood cell counts periodically during treatment. (b) (4) Monitor patients with neutropenia for signs of infection. (b) (4)	Moved to higher number (5.2). Revised to report all Grade neutropenia and grade 3-4. Added rate of febrile neutropenia due to its clinical significance.
	5.4 (b) (4) (b) (4) SARCLISA is an IgG kappa monoclonal antibody that can be incidentally 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. (b) (4)	Relocated to within 5.4 “Laboratory Test Interference”.

	(b) (4)	
6 ADVERSE REACTIONS	The following (b) (4) adverse reactions from SARCLISA are also described in other sections of the labeling: (b) (4)	Revised (b) (4) to "clinically significant" per Adverse Reactions Guidance. Added newly added warnings (see above for new W&P).
6.1 Clinical trials experience	Multiple Myeloma (b) (4)	Added subheading for indicated disease "Multiple Myeloma". Revised text to reflect our current approach. Removed (b) (4)

	(b) (4)	(b) (4)
	Description of Selected Adverse Reactions (b) (4)	No change.

	In ICARIA-MM, [redacted] defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (38[redacted]%) treated with SARCLISA. All patients who experienced [redacted] experienced them during the 1st infusion of SARCLISA, with 3 patients (2.0%) also having [redacted] at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 [redacted] were reported in 3.9%, Grade 2 in [redacted]%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher [redacted] included dyspnea, hypertension, and bronchospasm. The incidence of infusion interruptions because of [redacted] was [redacted]%. [redacted] Infections In ICARIA-MM, the incidence of Grade 3 or higher infections was [redacted]%. Pneumonia was the most commonly reported severe infection with Grade 3 reported in [redacted]% of patients in Isa-Pd	

	group compared to 16 (b) (4) % in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 5.4% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4.0% in Pd group.	
6.2 Immunogenicity	As with all therapeutic proteins, there is a potential for immunogenicity (b) (4) (b) (4)	Revised text to reflect our current approach, as described in the Biosimilar Labeling Guidance.
7 DRUG INTERACTIONS	7.1 (b) (4) (b) (4) SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests) , antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with SARCLISA [see Warnings and Precautions ((b) (4))].	Revised heading to "Laboratory Test Interference". Included proposed 7.1 and 7.2 under 7.1.
	(b) (4)	See above.

	(b) (4)	
8 USE IN SPECIFIC POPULATIONS	8.1 Pregnancy Risk Summary There are no available data on SARCLISA use in pregnant women. Animal reproduction toxicity studies have not been conducted (b) (4) (b) (4)	Revised to reflect recommended approach per PLLR Guidance. Added clinical considerations and Data sections.
	8.2 Lactation Risk Summary There are no available data on the presence of (b) (4) in human milk, milk production, or the effects on the breastfed infant. (b) (4)	Updated to current approach and per PLLR guidance.

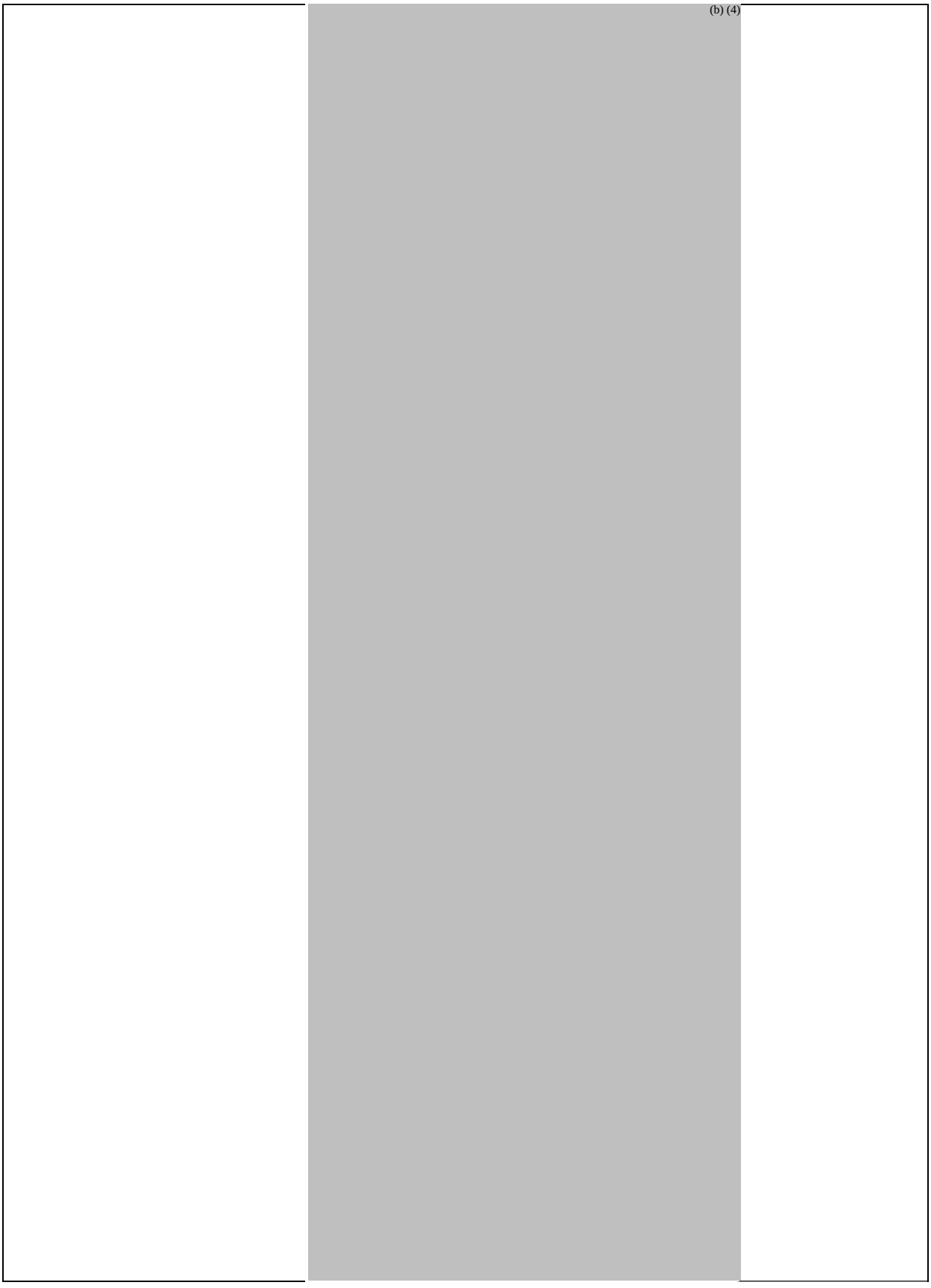
	(b) (4)	Added Pregnancy Testing.
	8.3 Females and Males of Reproductive Potential <u>Contraception</u> Females (b) (4)	Removed (b) (4)
	8.4 Pediatric Use (b) (4)	Revised to reflect required statement for products without a pediatric indication.
	8.5 Geriatric Use (b) (4)	Revised to reflect required text (describing number of patients per geriatric age category and discuss relevant differences between older and younger patients. Deleted (b) (4) per (b) (4)

		labeling Guidance.
	(b) (4)	Deleted (b) (4) per (b) (4) labeling Guidance.
10 OVERDOSAGE	(b) (4) In the event of overdose of SARCLISA, monitor the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.	Revised to remove (b) (4)
11 DESCRIPTION	(b) (4)	Added "chimeric" and "cytolytic" to description of antibody. Removed (b) (4)

	(b) (4)	
12 CLINICAL PHARMACOLOGY		
	12.1 Mechanism of action (b) (4)	Simplified text, focused disease reference to MM. Deleted information not relevant to the direct mechanism of action of isatuximab.

	(b) (4)	
	12.2 Pharmacodynamics (b) (4)	Revised for brevity. Added Cardiac Electrophysiology subsection.

	(b) (4)	
	12.3 Pharmacokinetics (b) (4)	Revised to provide introductory summary of PK and removed (b) (4)


(b) (4)

	Specific populations (b) (4)	Removed (b) (4)
13 NONCLINICAL TOXICOLOGY	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity and genotoxicity studies have not been conducted with (b) (4). (b) (4)	
14 CLINICAL STUDIES	14.1 Multiple Myeloma ICARIA-MM (b) (4) The efficacy and safety of SARCLISA in combination with pomalidomide and low-dose dexamethasone were evaluated in ICARIA-MM (b) (4), a multicenter, multinational, randomized, open-label, 2-arm, phase III study in patients with relapsed and refractory multiple myeloma. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor.	Removed (b) (4) (b) (4) and added NCT number to ease the identification of studies described in labeling by prescribers. Updated demographics and baseline

	A total of 307 patients were randomized in a 1:1 ratio to receive either SARCLISA in combination with pomalidomide and low-dose dexamethasone (Isa-Pd, 154 patients) or pomalidomide and low-dose dexamethasone (Pd, 153 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA 10 mg/kg was administered as an I.V. infusion weekly in the first cycle and every two weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (PO/IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 67 years (range 36-86), (b) (4)% of patients were ≥75 years; 10(b) (4)% of patients entered the study with a history of COPD or asthma . The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was (b) (4)% (b) (4) The International Staging System (ISS) Stage at (b) (4) was I in (b) (4)%, II in (b) (4)% and III in (b) (4)% of patients. Overall, (b) (4)% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14) and t(14;16) were present in 12(b) (4)%, 8(b) (4)% and (b) (4)% of patients, respectively. The median number of prior lines of therapy was 3 (range 2-11). All patients received a prior proteasome inhibitor , all patients received prior lenalidomide , and 56(b) (4)% of patients received prior stem cell transplantation ; The majority of patients ((b) (4)%) were refractory to lenalidomide,	characteristics using ITT population as a denominator. Removed (b) (4)

(b) (4) % to a proteasome inhibitor, and (b) (4) % to both an immunomodulator and a proteasome inhibitor (b) (4)

The median duration of treatment was 41.0 weeks for Isa-Pd group compared to 24.0 weeks for Pd group.

(b) (4)

Table 5
Figure 1

(b) (4)

	(b) (4)	Removed (b) (4)
16 HOW SUPPLIED/ STORAGE AND HANDLING	16.1 How Supplied SARCLISA (isatuximab) Injection is a colorless to slightly yellow solution, essentially free of visible particulates, available as follows: One 100 mg/5 mL single-dose vial in a carton: NDC xxxx-xxxx-xx	No change.

	One 500 mg/25 mL single-dose vial in a carton: NDC xxxx-xxxx-xx 16.2 Storage (b) (4) Do not Freeze. Do not shake. (b) (4) 16.3 Handling and Disposal (b) (4) All materials that have been utilized for dilution and administration should be disposed of according to standard procedures.	
17 PATIENT COUNSELING INFORMATION	(b) (4) (b) (4) Instruct patients to immediately report any occurrence of symptoms occurring within 24 hours of start of infusion to their healthcare provider [see Warnings and Precautions (5.1)]. (b) (4) Inform patients about the risk of neutropenia and infection during SARCLISA treatment and the importance of reporting immediately any fever or symptoms of infection to their healthcare provider [see Warnings and Precautions (5.3) (b) (4) <u>Interference with Laboratory Tests</u> Advise patients to inform healthcare providers and transfusion center personnel that they are treated with SARCLISA in case a red blood cell transfusion is planned [see Warnings and Precautions (5.2) and Drug Interactions (7.1)].	Added information on new Warnings.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

The applicant believes that the routine and additional risk mitigation measures including the USPI, (b) (4) will adequately mitigate the identified and potential risks of isatuximab, thereby ensuring the safe and appropriate use of the product.

The FDA's Assessment:
Not applicable

Reference ID: 4568595

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
Clinical PMR and PMCs:

PMR -Clinical

Conduct long term safety monitoring of patients enrolled in study (ICARIA) titled; "A Phase 3 Randomized, Open-label, Multicenter 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", to determine the incidence of acute myeloid leukemia, myelodysplastic syndrome and other second primary malignancies in patients receiving isatuximab in combination with pomalidomide and dexamethasone and it's potential to have a detrimental impact on overall survival. Include incidence rates, time to onset, predisposing factors, and outcomes with the final report.

PMR Schedule Milestones

Draft Protocol Submission:	06/2019 (completed)
Final Protocol Submission:	03/2020
Trial Completion:	06/2021
Final Report Submission:	12/2021

PMR – Clin Pharm

Submit the final interim report and datasets containing at least 40 patients enrolled on studies TCD13983 VRDI Part B, TCD15484, EMN 24, EFC15992, supplemented by data from other studies with similar pre-medications, if required, to assess the frequency and severity of infusion-related reactions, occurrence of intravenous infusion interruptions, infusion rate reductions, and discontinuation during the first two infusions of isatuximab administered via the fixed-volume infusion method in patients weighing ≥100 kg compared to patients weighing <100 kg.

PMR Schedule Milestones

Final Report Submission:	09/2022

PMC - Clinical

Submit the overall survival analysis and datasets with the final report for clinical trial (ICARIA) titled; "A Phase 3 Randomized, Open-label, Multicenter Study Comparing Isatuximab (SAR650984) in Combination With Pomalidomide and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Patients With

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Refractory or Relapsed and Refractory Multiple Myeloma" to provide additional long term efficacy data that may inform product labeling.

PMC Schedule Milestones

Draft Protocol Submission:	06/2019 (completed)
Final Protocol Submission:	03/2020
Trial Completion:	06/2021
Final Report Submission:	12/2021

PMC - Clinical

Develop a validated assay to detect interference of isatuximab to any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response (CR) in patients with multiple myeloma. Complete and submit the final report of the validation study, that may provide information to prescribers about the use of the assay to determine CR.

PMC Schedule Milestones

510(k) Submission:	10/2020
Final Report Submission:	02/2021

Rationale for PMR: The rate of second primary malignancies (SPM) in the pivotal trial was higher (3.9%) of patients in the IPd arm compared to (0.7%) to the Pd arm. Malignancies were primary skin cancers but also included 1 hematologic malignancy and breast cancer. Additional case of second primary malignancy prostate cancer was reported at the 120 day safety follow up in the IPd arm and none in the Pd arm. The risk for SPMs with isatuximab will be included in the label but the short follow up from the pivotal study is inadequate to characterize the risk of hematologic and solid tumor SPMs that may occur with longer exposure to isatuximab in combination with pomalidomide and dexamethasone. This PMR is to further characterize the incidence and rate of hematologic malignancies including AML, myelodysplastic syndrome and solid tumor secondary malignancies with longer follow up in isatuximab to adequately describe the serious risk of SPMs with isatuximab in the USPI . Additionally, the impact on overall survival will also be assessed.

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Division Director (DHOT)

APPEARS THIS WAY ON ORIGINAL

X_____

14 Division Director (OCP)

APPEARS THIS WAY ON ORIGINAL

X _____

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15 Division Director (OB)

APPEARS THIS WAY ON ORIGINAL

X _____

Reference ID: 4568595

16 Division Director (Clinical)

APPEARS THIS WAY ON ORIGINAL

X _____

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17 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

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18 Appendices

18.1. References

The Applicant's References:

Abildgaard N, Vekemans M-C, Gamberi B, Di Raimondo F, Ramirez Payer A, Kyriakou C et al. Safety in Patients with Multiple Myeloma Treated with Pomalidomide in a Real-World Setting According to Last Prior Treatment: A European Post-Authorization Safety Study. Blood. 2018 Dec 2;132(Suppl.1):3286.

Ailawadhi S, Mikhael JR, LaPlant BR, Laumann KM, Kumar S, Roy V, et al. Pomalidomide-dexamethasone in refractory multiple myeloma: long-term follow-up of a multi-cohort phase II clinical trial. Leukemia 2018 Mar;32(3):719-28.

Areethamsirikul N, Reece DE. The risk of secondary primary malignancies after therapy for multiple myeloma. Leuk Lymphoma. 2015;56(11):3012-21.

Arnall JR, Moore DC, Hill HL, Griffin S, Mueller MK, Lavery LA, et al. Enhancing the feasibility of outpatient daratumumab administration via a split-dosing strategy with initial doses. Leuk Lymphoma. 2019 Mar 8:1-4. [Epub ahead of print]

Chari A, Suvannasankha A, Fay JW, Arnulf B, Kaufman JL, Ifthikharuddin JJ, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 2017 Aug 24;130(8):974-81.

Dimopoulos MA, Terpos E, Chanan-Khan A, Leung N, Ludwig H, Jagannath S, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol. 2010 Nov 20;28(33):4976-84.

Dimopoulos MA, Palumbo A, Corradini P, Cavo M, Delforge M, Di Raimondo F, et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. Blood. 2016 Jul 28;128(4):497-503.

Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med. 2018 Nov 8;379(19):1811-22.

Jelinek T, Paiva B, Hajek R. Update on PD-1/PD-L1 Inhibitors in Multiple Myeloma. Front Immunol. 2018 Nov 16;9:2431.

Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia 2012 Jan;26(1):149-57.

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Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014 May;28(5):1122-8.

Landgren O, Mailankody S. Update on second primary malignancies in multiple myeloma: a focused review. Leukemia 2014 Jul;28(7):1423-6.

Leleu X, Attal M, Arnulf B, Moreau P, Traulle C, Marit G, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. Blood. 2013 Mar 14;121(11):1968-75.

Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015 Sep 24;373(13):1207-19.

Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016 Apr 9;387(10027):1551-60.

Maes H, Delforge M. Optimizing quality of life in multiple myeloma patients: current options, challenges and recommendations. Expert Rev Hematol. 2015 Jun;8(3):355-66.

Miguel JS, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-66.

Moreau P, San Miguel JS, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl 4):vi133-7.

Palumbo A, Bringhen S, Kumar SK, Lupparelli G, Usmani S, Waage A, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol. 2014 Mar;15(3):333-42.

Richardson PG, Siegel DS, Vij R, Hofmeister CC, Baz R, Jagannath S, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014 Mar 20;123(12):1826-32.

San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. Lancet Haematol. 2016 Nov;3(11):e506-15.

Sonneveld P, Verelst SG, Lewis P, Gray-Schopfer V, Hutchings A, Nixon A, Petrucci MT. Review of health-related quality of life data in multiple myeloma patients treated with novel agents.

Leukemia. 2013 Oct;27(10):1959-69.

Spencer A, Lentzsch S, Weisel K, Avet-Loiseau H, Mark TM, Spicka I, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica 2018; 103(12):2079-87.

Trakada G, Kastritis E, Gavriatopoulou M, Velentza L, Fotiou D, Ziogas DC, et al. Pulmonary function abnormalities are common in patients with multiple myeloma and are independently associated with worse outcome. Ann Hematol. 2019 Mar 5. [Epub ahead of print].

Usmani S, Ahmadi T, Ng Y, Lam A, Desai A, Potluri R, Mehra M. Analysis of Real-World Data on Overall Survival in Multiple Myeloma Patients With ≥3 Prior Lines of Therapy Including a Proteasome Inhibitor (PI) and an Immunomodulatory Drug (IMiD), or Double Refractory to a PI and an IMiD. Oncologist. 2016 Nov;21(11):1355-1361.

Varga C, Laubach JP, Anderson KC, Richardson PG. Investigational agents in immunotherapy: a new horizon for the treatment of multiple myeloma. Br J Haematol. 2018 May;181(4):433-46.

Yee AJ, Raje NS. Panobinostat and Multiple Myeloma in 2018. The Oncologist 2018;23(5):516-7.

Zonder JA, Mohrbacher AF, Singhal S, van Rhee F, Bensinger WI, Ding H, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. Blood 2012 Jul 19;120(3):552-9.

Zweegman S, Engelhardt M, Larocca A; EHA SWG on 'Aging and Hematology'. Elderly patients with multiple myeloma: towards a frailty approach? Curr Opin Oncol. 2017 Sep;29(5):315-21.

The FDA's References:

Darzalex USPI https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761036s024lbl.pdf
Empliciti USPI https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761035s010lbl.pdf

18.2. Financial Disclosure

The Applicant's Position:

As the sponsor of the submitted study, Sanofi certifies that it has not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Sanofi also certifies that each listed clinical investigator required to disclose to the applicant whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests.

Sanofi further certifies that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Sanofi obtained financial disclosure information for all but 2 investigators for the covered clinical study (Table 34). Sanofi was unable to obtain complete financial disclosure information for these 2 clinical investigators.
The monitoring ream made at least 2 attempts to collect the information from both subinvestigators.

Table 34 - Clinical investigators, including subinvestigators, at initiated centers with enrolled patients whose financial disclosure information is missing or incomplete

Country	Study No.	Center ID	Investigator Name (Prinicipal Investigator in bold)	Center Name and Address
AUSTRALIA	EFC14335	0360005	Tze Ven JONG	Peter MacCallum Cancer Centre 305 Grattan St Melbourne 3000 Victoria
AUSTRALIA	EFC14335	0360005	Kay HTUN	Peter MacCallum Cancer Centre 305 Grattan St Melbourne 3000 Victoria

Additionally, the Sponsor conducted a search within the Sponsor's financial systems to identify individuals who received financial compensation which make them eligible for reporting their financial interest. This search is independent of the initial financial disclosure information obtained from investigators at time of clinical study participation, and none of the below noted sub-investigators received SPOOS payments.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the financial disclosure information of the investigators for Study 14335.

Covered Clinical Study (Name and/or Number):* EFC14335

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

Reference ID: 4568595

		Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant and confirmed/edited by the FDA.

18.3. Nonclinical Pharmacology/Toxicology

Instruction to the Applicant: This is reserved for data that could not fit under PT section (Section 5), e.g. carci data. Limit Section 19.3 to 2 pages

The Applicant's Position:
None needed

The FDA's Assessment:
FDA agrees; no additional data needs to be presented.

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18.4. OCP Appendices (Technical documents supporting OCP recommendations)

18.4.1. Pharmacometrics Review

1. Applicant' Population PK analysis

1.1 Introduction

The primary objectives of this analysis were to:

1. Characterize the pharmacokinetics of isatuximab when administered as a single agent and in combination with dexamethasone and pomalidomide (Pd) and to obtain key exposure metrics.
2. Explore factors influencing isatuximab pharmacokinetics.

1.2 Model development

1.2.1 Data

Data from 476 patients with multiple myeloma (MM) (7697 plasma concentrations) treated in the single agent studies (TED10893 Phase 1, Phase 2 Stage 1, Phase 2 Stage 2 and TED14154 Part A) and in combination with pomalidomide/dexamethasone studies (Phase 1b TCD14079 Part A and Phase 3 EFC14335). Isatuximab was administered as either QW, Q2W or Q2W for 8 weeks then Q4W (Q2W/Q4W) or QW for 4 weeks, then Q2W (QW/Q2W) by IV infusion at doses ranging from 1 to 20 mg/kg. Brief descriptions of the studies included are presented in Table 35.

Summary statistics of the baseline demographic covariates in the analysis dataset is provided in Table 36.

Table 35. Summary of Studies with PK Sampling Included in Population PK Analysis

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type	Dose(s) [mg]
Study TED10893: A dose-escalation trial to evaluate the safety, tolerability, PK, and PD of isatuximab (Phase I); A dose finding portion (Phase 2 Stage 1) and dose expansion cohort (Phase 2 Stage 2).	Administered as IV infusion as single agent in ascending doses to evaluate PK, safety & tolerability. Phase 2 Stage 2 evaluated the dose of 20 mg/kg QW/Q2W.	Total of 258 patients with multiple myeloma: - Phase 1 (N=73); - Phase 2 Stage 1 (N=95); - Phase 2 Stage 2 (N=90).	Single agent (0.0001 to 20 mg/kg, QW or Q2W).

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TED14154 Part A: Phase 1, open-label, nonrandomized, dose-escalation study evaluating the safety, tolerability, PK, and PD of isatuximab (b) (4) with IV administration in RRMM patients.	Administered as IV infusion as single or combo to evaluate PK, safety & tolerability and find optimal dose.	26 patients with MM.	Single agent 10 and 20 mg/kg QW/Q2W.
TCD14079 Part A: Phase 1b, open label, dose escalation study of isatuximab in combination with pomalidomide and low-dose dexamethasone in patients with RRMM.	Administered as IV infusion for isatuximab dose finding in combination with Pd.	44 patients with RRMM; isatuximab administered in combination with Pd.	In combination with Pd at dose levels of 5, 10, and 20 mg/kg QW/Q2W.
Study ICARIA: prospective, multicenter, multinational, randomized, open-label, parallel group, 2-arm Phase 3 study evaluating the efficacy of IPd compared with Pd for the treatment of patients RRMM.	Administered as IV infusion; pivotal trial for efficacy and safety.	148 patients with RRMM; isatuximab administered in combination with Pd.	In combination with Pd at 10, mg/kg QW/Q2W.

Table 36. Summary of Baseline Demographic Covariates for Analysis

	n;%	n missing;%	Mean	SD	CV(%)	Min	Median	Max	P5	P95
Demography										
Age (yrs)	476	0	64.7	9.1	14.1	36.0	65.0	85.0	49.0	79.0
Age (yrs) - (n;%)										
65[	226;47.5%	0								
[65-75[	180;37.8%									
[75	70;14.7%									
Wght (kg)	476	0	77.4	17.6	22.7	34.3	75.6	152.5	51.3	109.5
Wght (kg) - (n;%)										
50[	14;2.9%	0								
[50-100[	418;87.8%									
[100	44;9.2%									
BSA (m^2)	476	0	1.87	0.23	12.5	1.15	1.86	2.73	1.49	2.25
BMI (kg/m^2)	476	0	27.5	5.4	19.5	17.0	26.6	47.6	20.4	38.0
BMI (kg/m^2) - (n;%)										
18.5[	7;1.5%	0								
[18.5-25[	164;34.5%									
[25-30[	184;38.7%									
[30	121;25.4%									
Obesity - (n;%)										
Non obese	355;74.6%	0								
Obese	121;25.4%									
Obesity class - (n;%)										
I	77;16.2%	0								
II	29;6.1%									
III	15;3.2%									
Gender - (n;%)										
Male	269;56.5%	0								
Female	207;43.5%									
Race - (n;%)										
Caucasian	377;79.2%									
Black	18;3.8%	23;4.83%								
Asian	25;5.3%									
Other	33;6.9%									
Ethnicity - (n;%)										
Not Hispanic	356;74.8%	101;21.2%								
Hispanic	19;4.0%									

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	n;%	n missing;%	Mean	SD	CV(%)	Min	Median	Max	P5	P95
Treatment										
Formulation - (n;%)										
(b) (4)	191;40.1%	0								
	285;59.9%									
Dose (mg/kg) - (n;%)										
1	3;0.6%									
3	28;5.9%	0								
5	11;2.3%									
10	286;60.1%									
20	148;31.1%									
Laboratory values										
GFR_MDRD (mL/min/1.73m²)	476	0	71.8	26.6	37.1	13.5	68.3	189.3	35.0	119.2
Renal impairment from MDRD - (n;%)										
Normal	109;22.9%	0								
Mild	192;40.3%									
Moderate	163;34.2%									
Severe	12;2.5%									
CLCR by C&G (mL/min)	476	0	79.8	34.1	42.7	21.6	73.3	231.3	35.9	142.6
Renal impairment from CLCR - (n;%)										
Normal	155;32.6%	0								
Mild	177;37.2%									
Moderate	141;29.6%									
Severe	3;0.6%									
ALB (g/L)	476	0	37.1	5.75	15.5	16.0	37.5	54.0	26.6	45.4
ALB_group - (n;%)										
35[	156;32.8%	0								
[35	320;67.2%									
ALB_N	476	0	0.695	0.114	16.4	0.291	0.700	1.02	0.491	0.873
ALK_N	476	0	0.567	0.302	53.2	0.0950	0.507	3.12	0.259	1.12
AST_N	476	0	0.678	0.445	65.7	0.188	0.559	3.50	0.299	1.53
ALT_N	476	0	0.470	0.455	96.7	0.0980	0.362	5.23	0.173	1.07
BILI_N	476	0	0.422	0.200	47.3	0.0670	0.382	1.63	0.182	0.809
BILI_group - (n;%)										
1[	469;98.5%									
[1-1.5[	6;1.3%	0								
[1.5-3[	1;0.2%									
[3	0;0%									
Hepatic impairment - (n;%)										
Normal	411;86.1%									
Mild	65;13.7%	0								
Moderate	1;0.2%									
Severe	0;0%									

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	n;%	n missing;%	Mean	SD	CV(%)	Min	Median	Max	P5	P95
Tumor burden										
BMPC (%)	476	0	33.7	28.0	83.0	0.100	27.5	100	1.00	90.0
BMPC (%) - (n;%)										
0	10;2.1%	0								
]0-5[	55;11.6%									
[5-20[	122;25.6%									
[20-50[	151;31.7%									
[50	138;29.0%									
Beta2µG (mg/L)	476	0	4.81	3.45	71.7	1.10	3.90	27.0	1.87	12.0
Beta2µG (mg/L) - (n;%)										
3.5[	204;42.9%	0								
[3.5-5.5[	151;31.7%									
[5.5	121;25.4%									
LDH_N	476	0	1.05	0.777	74.3	0.263	0.858	9.21	0.507	2.22
Disease										
MM Type - (n;%)										
Serum_M_Prot	365;76.7%	0								
Not_Serum_M_Prot	111;23.3%									
Ig Type - (n;%)										
IgG	262;55.0%	0								
Not_IgG	214;45.0%									
MPROT (g/L)	476	0	21.4	18.7	87.2	0.0484	18.0	95.0	0.0484	55.4
ISS - (n;%)										
1	173;36.3%	0								
2	182;38.2%									
3	121;25.4%									
ECOG - (n;%)										
0	152;31.9%	0								
1	277;58.2%									
2	47;9.9%									
Lymph (Giga/L)	476	0	1.15	0.629	54.7	0.100	1.00	5.50	0.400	2.38
Previous Lines_Grp - (n;%)										
1	2;0.4%	0								
2	67;14.1%									
3	111;23.3%									
]3	296;62.2%									

(Source: Table 4, PopPK report (poh0503).

Base model

The final base model was a described by a 2-compartment model with parallel linear and Michaelis-Menten eliminations from the central compartment (approximation of target mediated - drug disposition model) with a combined error model and inter-individual variability on all parameters. Time-varying change was modeled as a sigmoidal function (CL_lin =CL_inf * exp [CLm * (1 – tγ / (KCL γ + t γ))]) with CLm being the maximum change from baseline

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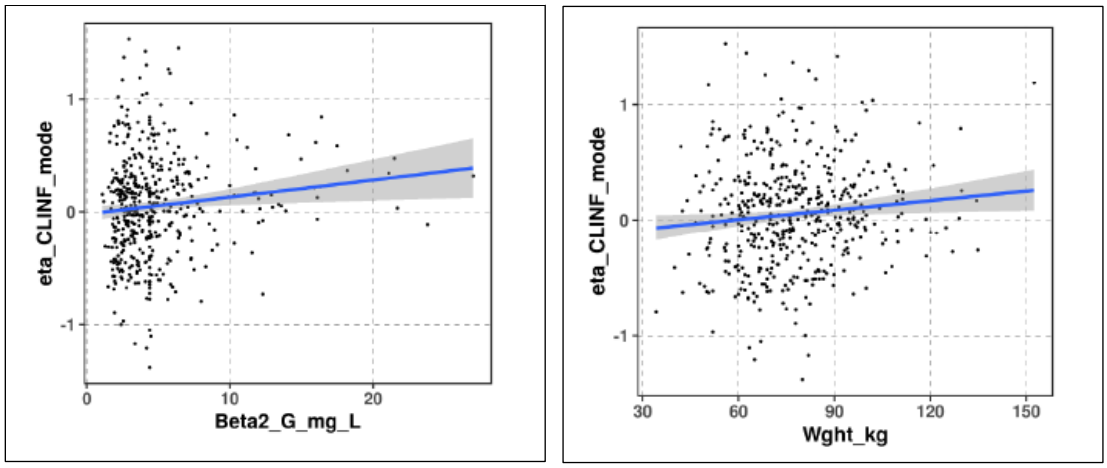
clearance to steady-state clearance (CL_inf), KCL being the time estimated to achieve 50% change in linear clearance and Gamma (γ) being the sigmoidal coefficient.
Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation, successful model convergence, and diagnostic plots.

Covariate analysis

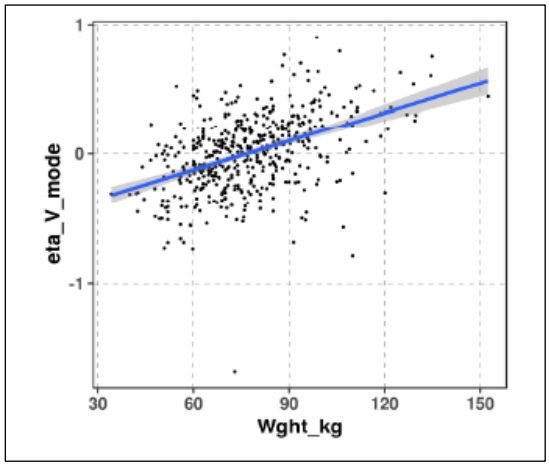
A full covariates model was developed by incorporating the effect of all pre-specified covariate parameter relationships. The final PopPK model was developed by retaining covariates that improved a goodness-of-fit statistic (MOFV). Clinical judgment, physiologic relevance, prior knowledge and mechanistic plausibility were used to determine which covariates should be tested with the various PK parameters. Covariate parameters, including age, sex, race, body surface area, body mass index, albumin, serum alkaline phosphatase, alanine amino transferase, aspartate amino transferase, bilirubin, beta-2 microglobulin, bone marrow plasma cells, serum M-protein, main Ig Type, Multiple Myeloma Type, ECOG, ISS, renal and hepatic impairment on pertinent PK parameters were evaluated.

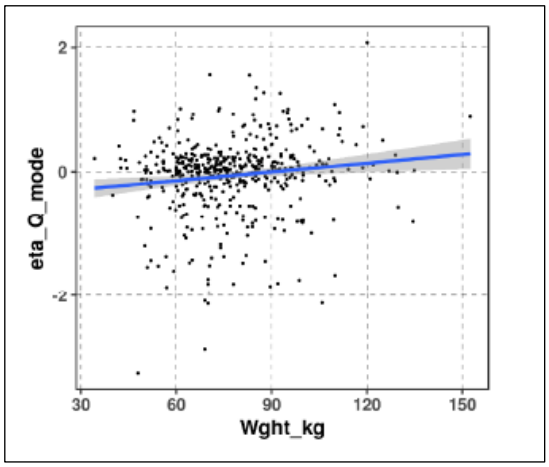
The reviewer's analysis of covariates effect on PK was similar to that of the applicant. The effects of body weight on CL/F, V1/F, Q, and V2/F, the effects of Ig MM type and β2-microglobulin on CL/F are most clinically relevant and are explored in Figure 25. The model estimated covariate effects on PK parameters are illustrated in Figure 27.

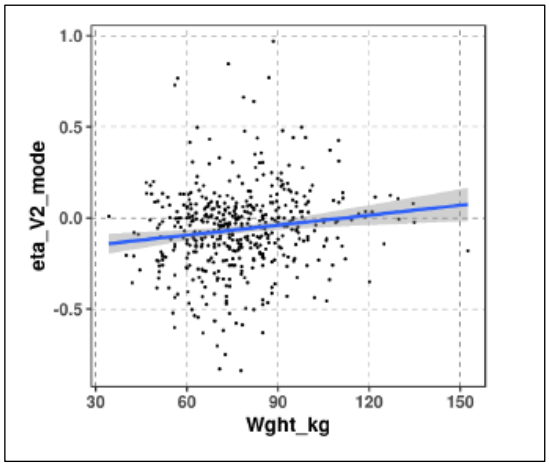
Figure 25 Parameter-Covariate Plots

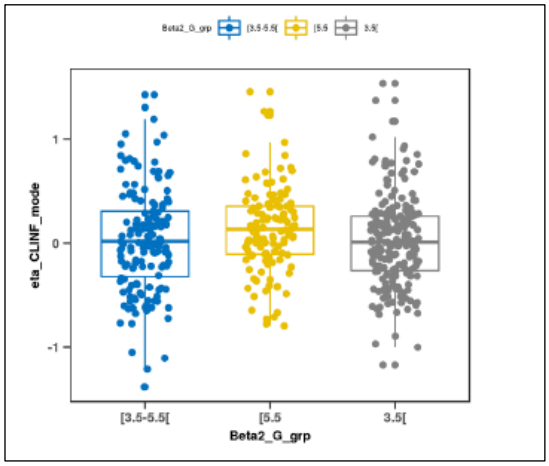


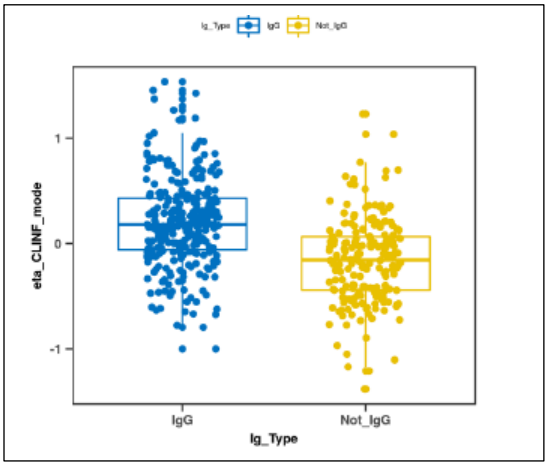
Reference ID: 4568595











Source: Reviewer's analysis

Reference ID: 4568595

Table 37. Covariate Effects on PK Parameters

Covariate	Quantiles	CLinf (L/h)	% change	V1 (L)	% change	V2 (L)	% change	Q (L/h)	% change	KCL (h)	% change[b]
Median patient[a]		0.0955		5.13		3.62		0.0432		1055	
Weight (kg)	5%: 51.3 kg		-21%		-17%		-24%		-17%		
	95%: 109.5 kg		+26%		+19%		+31%		+19%		
β2 microglobulin	5%: 1.87 mg/L		-22%								
	95%: 12 mg/L		+47%								
Myeloma type	Non-IgG		-53%								-61%
Gender	Female				-12%						
Race	Asian				-24%						
Isatuximab material	P2F2				-13%						

CLinf: clearance at steady state; Ig: immunoglobulin; KCL: time to decrease 50% of the linear CL; V_1: volume of the central compartment; V_2: volume of the peripheral compartment; Q: inter-compartmental clearance

a Typical patient: weight: 75.6 kg, β2 microglobulin: 3.9 mg/L, Ig type= IgG, race=non-Asian, drug material= (b) (4), gender=male

b % change represents the change for the 5th or 95th percentile relative to the median (typical) patient

Source: Table 8, Summary of clinical pharmacology studies.

Reference ID: 4568595

1.3 Results

The parameter estimates for the final covariate model are listed in Table 38. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 26. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in Figure 27.

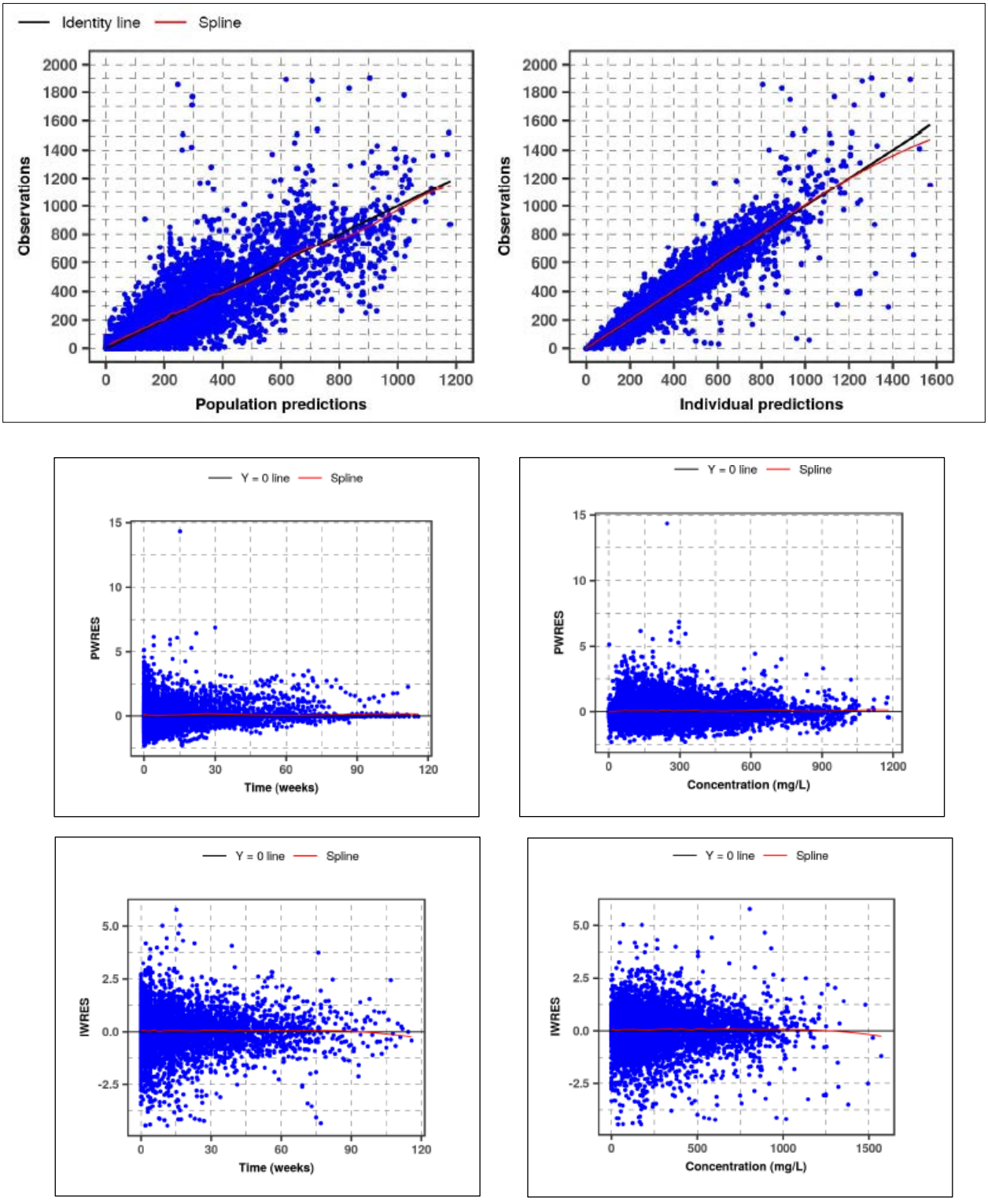
Table 38. Parameter Estimates for the Final Model

Parameter	Estimate	RSE (%)	Wald p-value
CL_inf (L/h)	0.00955	3.80	
β1 ~ B2M	0.343	15.2	4.45E-11
β2 ~ IgType=Not_IgG	-0.751	7.63	<2.2e-16
β3 ~ Wght	0.621	19.6	3.38E-07
CLm	0.664	9.20	
KCL (h)	1055	12.0	
β4 ~ IgType=Not_IgG	-0.93	21.3	2.54E-06
Gamma	3.91	12.0	
V (L)	5.13	2.43	
β5 ~ Formulation=P2F2	-0.137	19.8	4.68E-07
β6 ~ Race=Asian	-0.275	22.3	7.63E-06
β7 ~ Sex=Female	-0.126	23.2	1.69E-05
β8 ~ Wght	0.472	13.9	7.23E-13
Q (L/h)	0.0432	6.89	
β9 ~ Wght	0.477	57.5	0.0820
V2 (L)	3.62	3.28	
β10 ~ Wght	0.719	18.7	8.27E-08
Vm (mg/L.h)	0.136	4.50	
Km (mg/L)	0.300	11.1	
ω(CL_inf) (%)	47.5	4.51	
ω (CLm) (%)	97.2	4.51	
ω(KCL) (%)	115	7.60	
ω(Gamma) (%)	118	6.89	
ω(V1) (%)	25.7	4.03	
ω(Q) (%)	85.8	6.65	
ω(V2) (%)	45.6	5.79	
ω(Vm) (%)	61.5	5.34	
ω(Km) (%)	88.9	10.05	
σ_{add} (mg/L)	0.00196	19.1	
σ_{prop} (%)	22.5	0.979	

Source: Table 1, PopPK report (poh0503).

Reference ID: 4568595

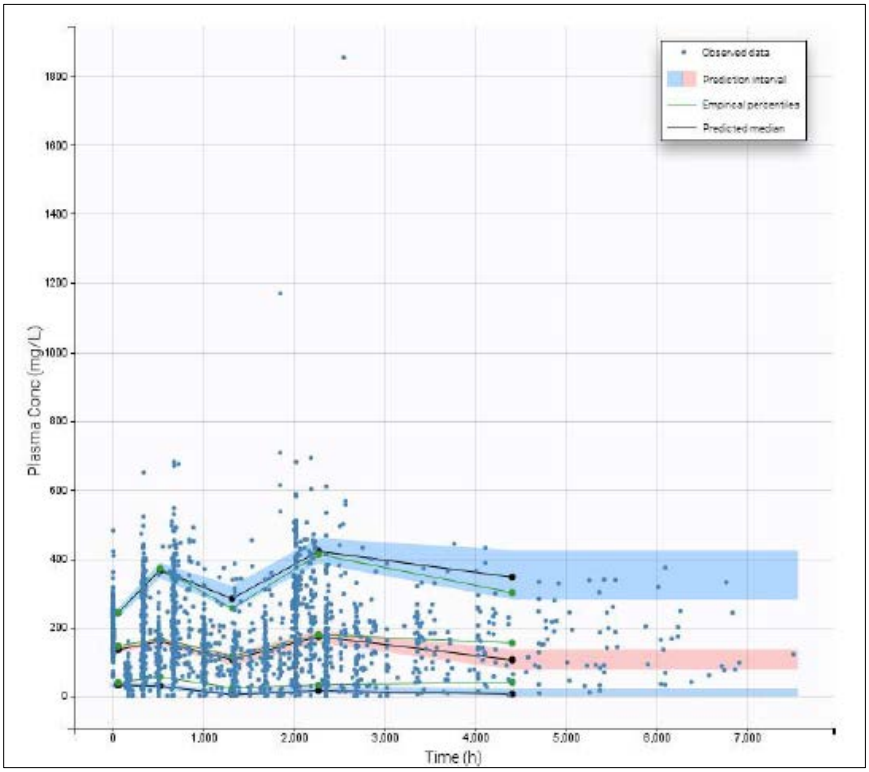
Figure 26 Goodness-of-Fit Plots for Final Covariate Model



Source: PopPK report (poh0503).

Reference ID: 4568595

Figure 27 VPC Plot for Final Covariate Model



The black lines represent the predicted median and the green lines represent the 10th, 50th and 90th percentiles of the observed concentrations. The shaded areas are the 90 % prediction intervals for the simulated datasets.

<u>Reviewer's comments:</u> The applicant's population PK analysis is acceptable for descriptive labeling purpose. The goodness-of-fit plots and the visual predictive check indicate that the population PK model is adequate in characterizing the PK profile of isatuximab in patients with RRMM. The inter-individual variability for CL_inf is moderate-high. The estimated PK parameters, such as CL_inf, V1, and V2 appear reasonable. Linear clearance was found to account for ~90% of the total clearance at 10 mg/kg QW for 4 weeks then Q2W, indicating saturation of target-mediated clearance at the recommended dosing regimen for isatuximab and Pd combination therapy. The applicant's analyses were verified by the reviewer, with no significant discordance identified. Of note, the estimated Eta shrinkage values were moderate for CL_inf and CLm (43%), and high ranging from 60% to 90% for V2, Vm, Km and Gamma. High shrinkage values associated with modeling aspects of the nonlinear and time-varying PK of isatuximab may negatively affect the confidence in the predicted values utilized in the exposure-response (E-R) analyses. The clinical relevance of covariate effects such as race and formulation on V1/F is questioned. The developed model was used to support the current submission as outlined in Table 39.

Table 39 Specific Comments on Applicant's Final Population PK model

Utility of the final model	Reviewer's Comments

Reference ID: 4568595

Support labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	"Isatuximab-irfc exposure (AUC) at steady state decreases with increasing body weight. The following factors have no clinically meaningful effect on the exposure of isatuximab-irfc: age (36 to 85 years, 70 patients were >75 years old), sex, race (Caucasian, Black, Asian), renal impairment, and mild hepatic impairment (total bilirubin 1 to 1.5 times upper limit of normal [ULN] or aspartate amino transferase [AST] > ULN)." "No dose adjustments are recommended in these specific patient populations."	*The statements are acceptable. The covariate analysis indicated that age, sex, race, renal function, and mild hepatic impairment cause no evident difference in PK.*
	Extrinsic factor	"The elimination of isatuximab-irfc was similar when given as a single agent or as combination therapy."	*The statement is acceptable. The covariate analysis revealed that coadministration with Pd causes no evident difference.*
Derive exposure metrics for Exposure-response analyses	Trough plasma concentration at Week 4 (CT4W), C_{max} on the first administration of Cycle 1 ($C_{maxD1C1}$).		*High eta shrinkage values of parameters associated with the nonlinear and time-varying PK may negatively impact the prediction of the exposure metrics used in the E-R analyses and thus limit the interpretation of E-R results.*

2. Exposure-Response Analysis

2.1 Exposure-efficacy relationship

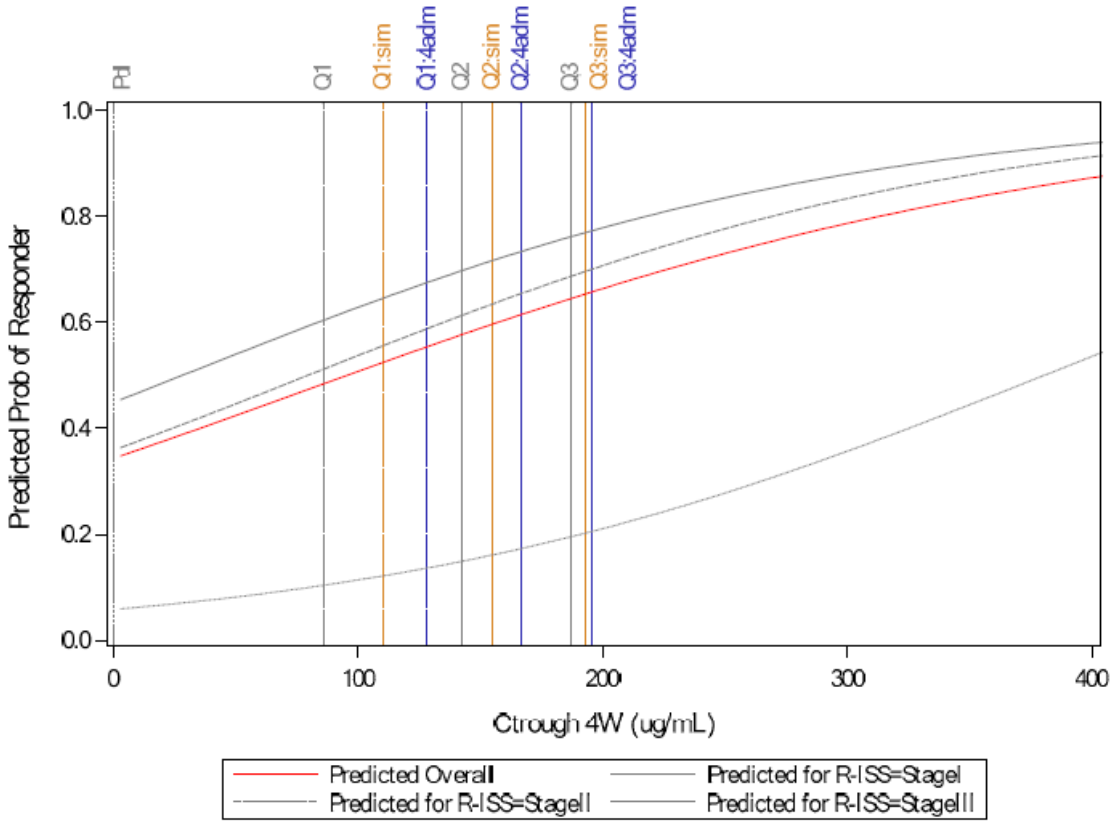
2.1.1 Applicant' analysis

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Exposure-response analyses were performed for efficacy (ORR and PFS) using study EFC14335 (148 patients in the Isa-Pd arm and 149 patients in the Pd arm).

The impact of isatuximab exposure on ORR was investigated using logistic regression model with CT4W, which is defined as the C_{trough} after the 4th weekly dose. The final model included time since diagnosis and Revised-ISS (R-ISS) score and an interaction between time since diagnosis and R-ISS. The probability of an ORR was found to increase with a linear increase of CT4W, with the predicted responders below and above the median CT4W being 52% and 72%, respectively. ORR increased as time since diagnosis increased and ORR decreased with higher R-ISS stage as shown in Figure 28.

Figure 28 Model-predicted probability of ORR by R-ISS stage for 10 mg/kg QW/Q2W



Q represents the predicted proportion of responders for each quartile of CT4W group for overall population. Qsim represents the predicted proportion of responders for each quartile of CT4W group assuming all patients received 4 weekly administrations. Q 4admin represents the predicted proportion of responders for each quartile of CT4W for patients who completed 4 weekly administrations.

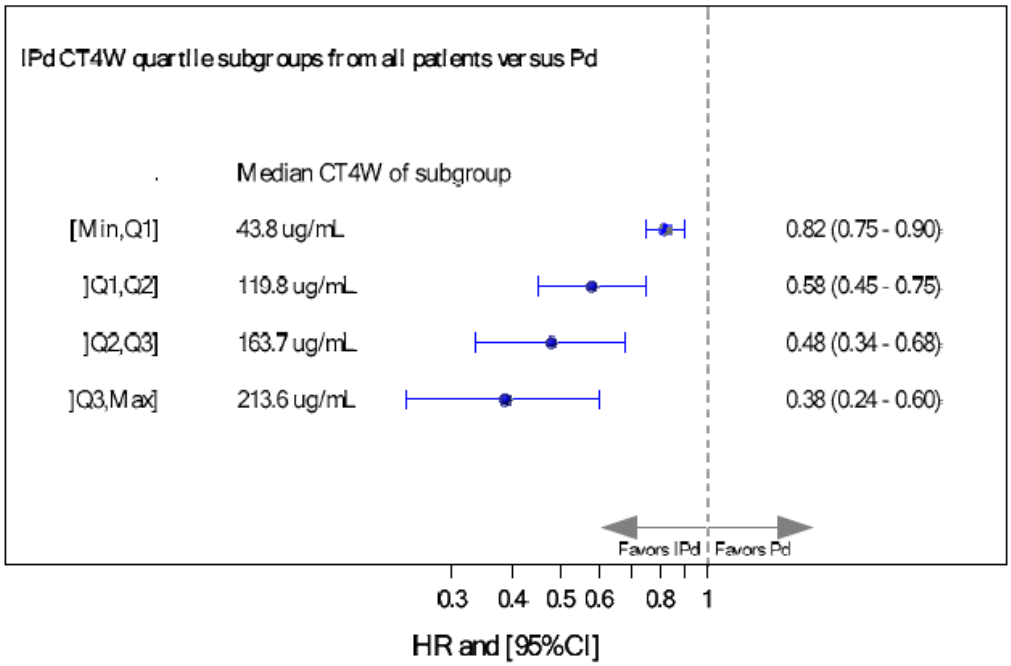
Source: Figure 12, Applicant's exposure-response analysis (poh0648).

While patients in all isatuximab exposure quartiles have positive treatment effect (HR<1), the treatment effect is more pronounced in the 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. This may be due to confounded observations by the different myeloma baseline characteristics and high incidence of pomalidomide and isatuximab dose modifications in this quartile.

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The impact of isatuximab exposure on PFS was investigated using Kaplan-Meier analysis where CT4W was found to be linearly associated with improved PFS. The final model included the covariates plasmacytomas, albumin and R-ISS at baseline. The PFS hazard ratio (HR) associated with CT4W quartiles are summarized in Figure 29.

Figure 29 Forest plot of HR associated with CT4W of PFS at the median, 5th and 95th percentiles by CT4W quartiles when comparing Pd arm



Source: Figure 14, Applicant's exposure-response analysis (poh0648).

2.1.2 Reviewer's Comments

The reviewer's analysis was in general consistent with the applicant's results. However, the reviewer did not include the time since diagnosis as a covariate or the interaction term between time since diagnosis and R-ISS in final model of ORR. While a lower probability of ORR is expected with a higher R-ISS stage, a lower probability of ORR associated with a shorter time since diagnosis is not clinically plausible. Importantly, the reviewer notes that high eta shrinkage value associated with the PopPK modeling aspects of the nonlinear and time-varying PK of isatuximab may negatively impact the confidence levels in in generation of exposure metrics used in the E-R analyses, and thus limit the interpretation of the results.

2.2 Exposure-safety relationship

2.2.1 Applicant's analysis

Exposure-response analyses were performed for safety (IRRs, thrombocytopenia, anemia, neutropenia, lymphopenia, infections, and respiratory events) using data pooled from studies TCD14079 Part A and EFC14335.

There was no apparent relationship between an increase of isatuximab $C_{max,c1d1}$ and IRRs,

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nor between an increase in $C_{max,c1d1}$ or $C_{post\text{-}infusion,max}$ and an increase in the incidence of the examined AEs of interest including, thrombocytopenia, neutropenia, lymphopenia, respiratory events, and nervous system disorders. Nevertheless, 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.

2.2.2 Reviewer's Comments

The reviewer did not identify an exposure-safety relationship for safety AEs. However, as summarized in Table 40, a trend towards higher incidence of respiratory infections and infestations of all grades is seen in the Isa-Pd arm compared to the Pd arm. A higher incidence of Grade 3 febrile neutropenia and Grade 4 neutropenia is seen in the Isa-Pd arm compared to the Pd arm.

Table 40 Comparison of Adverse Events of Interest between the Pd and Isa-Pd Arms in Study ICARIA

Primary System Organ Class [n(%)]	**Isa-Pd (N=152)**			**Pd (N=149)**		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Infusion reaction	58 (38.2)	2 (1.3)	2 (1.3)	0	0	0
Infections and infestations						
Upper respiratory tract infection	43 (28.3)	5 (3.3)	0	26 (17.4)	1 (0.7)	0
Pneumonia	47 (30.9)	33 (21.7)	5 (3.3)	34 (22.8)	24 (16.1)	4 (2.7)
Bronchitis	36 (23.7)	5 (3.3)	0	13 (8.7)	1 (0.7)	0
Blood and lymphatic system disorders						
Febrile neutropenia	18 (11.8)	16 (10.5)	2 (1.3)	3 (2.0)	2 (1.3)	1 (0.7)
Anemia	151 (99.3)	48 (31.6)	0	145 (98.6)	41 (27.9)	0
Thrombocytopenia	127 (83.6)	22 (14.5)	25 (16.4)	118 (80.3)	14 (9.5)	22 (15.0)
Neutropenia	146 (96.1)	37 (24.3)	92 (60.5)	137 (93.2)	57 (38.8)	46 (31.3)
Lymphopenia	140 (92.1)	64 (42.1)	19 (12.5)	137 (93.2)	52 (35.4)	12 (8.2)

Source: Reviewer's analysis.

18.5. BioAnalytical Method Performance Summary

The tables below provide the bioanalytical performance summary for both isatuximab (Table 41) and pomalidomide (Table 42) with cross validation for isatuximab (Table 43).

Reference ID: 4568595

Table 41. Summary method performance of a bioanalytical method to measure isatuximab (or SAR65084) in human K3-EDTA plasma.

Bioanalytical method validation report name, amendments, and hyperlinks	- GMPK method validation DOH0716 titled: Method and validation of an ELISA for the quantitation of SAR650984 in human ethylenediaminetetraacetic acid (EDTA) plasma , CTD module 5.3.1.4 - Bioanalytical validation study report SPH0304 titled: Long term stability study at -20°C and -80°C of SAR650984 in human EDTA plasma by ELISA method, CTD module 5.3.1.4		
Method description	It is a quantitative sandwich enzyme immunoassay using a rabbit affinity purified anti-isatuximab antibody coated on the microplate for the capture and a biotinylated CD38-Fc for the detection.		
Materials used for calibration curve & concentration	human K3-EDTA plasma		
Validated assay range	0.500 to 20.0 ng/mL (DOH0716) The quantitation range was extended up to 8.00 mg/mL: ULOQ at 20.0 ng/mL multiplied by the highest dilution factor tested, i.e. 400 000 (SPH0304)		
Material used for QCs & concentration	K3-EDTA human plasma		
Minimum required dilutions (MRDs)	No MRD		
Source & lot of reagents (LBA)	- Coating: Affinity purified anti-SAR650984 antibody, ref L08112/A33086 from (b) (4) - lot L050.08112.1 - Detection: biotinylated CD38-Fc (sanofi-aventis), lot VAB.UEH1.207		
Regression model & weighting	Unweight parabolic regression		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ Standard Calibrators at levels of 0.500 (LLOQ), 1.00, 2.50, 5.00, 7.50, 10.0, 15.0 and 20.0 (ULOQ) ng/mL	8	[Table 4] of report DOH0716 (module
	Cumulative accuracy (%bias) from LLOQ to ULOQ Standard Calibrators at levels of 0.500 (LLOQ), 1.00, 2.50, 5.00, 7.50, 10.0, 15.0 and 20.0 (ULOQ) ng/mL	-2.8% to +5.8%	[Table 4] of report DOH0716 (module
	Cumulative precision (%CV) from LLOQ to ULOQ Standard Calibrators at levels of 0.500 (LLOQ), 1.00, 2.50, 5.00, 7.50, 10.0, 15.0 and 20.0 (ULOQ) ng/mL	≤ 3.4%	[Table 4] of report DOH0716 (module
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs n=18 data per level LLOQ: 0.500 ng/mL Low QC: 1.20 ng/mL Mid QC: 5.00 ng/mL ULOQ: 20.0 ng/mL Super HighQC: 250 000 ng/mL	-5.7% to 14%	[Table 5] of report DOH0716 (module 5.3.1.4)

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	Inter-batch %CV QCs: n=18 data per level LLOQ: 0.500 ng/mL Low QC: 1.20 ng/mL Mid QC: 5.00 ng/mL ULOQ: 20.0 ng/mL Super HighQC: 250 000 ng/mL	≤ 6.2%	[Table 5] of report DOH0716 (module 5.3.1.4)
	Total Error (TE) QCs: n=18 data per level LLOQ: 0.500 ng/mL Low QC: 1.20 ng/mL Mid QC: 5.00 ng/mL ULOQ: 20.0 ng/mL Super HighQC: 250 000 ng/mL	≤ 20%	Not published in report DOH0716 (data on file)
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue 10 individual human K3-EDTA plasma lots tested at LLOQ and ULOQ levels. LLOQ level: 9 out 10 within 20% acceptance criteria. Range of bias: -22% to +8.4% ULOQ level: 10 out 10 within 20% acceptance criteria Range of bias: -13% to +3.0%		[Table 10] of report DOH0716 (module 5.3.1.4)
Interference & specificity	- Interference with rabbit polyclonal anti-isatuximab antibodies: 1 lot of pool human K3-EDTA plasma spiked at Low (1.20 ng/mL) and High (16.0 ng/mL) levels of isatuximab. The presence of rabbit polyclonal anti-isatuximab antibodies (ADA) at dilutions equal to or lower than 10 000 may interfere with isatuximab quantitation in human K3-EDTA plasma. Range of bias: -89% to -2.0% - Interference with anti-human IgG1 antibody: 1 lot of pool human K3-EDTA plasma spiked at Low (1.20 ng/mL) and High (16.0 ng/mL) levels of isatuximab. No interference of anti-human IgG1 antibody tested at dilutions from 2000 to 200 000 was observed on isatuximab quantitation in human K3-EDTA plasma. Range of bias: -11% to +1.3% - Interference with human CD31: 1 lot of pool human K3-EDTA plasma spiked at Low (1.20 ng/mL), High (16.0 ng/mL) and SuperHigh-a (0.250 mg/mL) levels of isatuximab. No interference of human CD31, tested at 0.500 µg/mL was observed on isatuximab quantitation in human K3-EDTA plasma. Range of bias: -7.4% to +6.1%. - Interference with drugs concomitantly administered with isatuximab in clinical trials: lenalidomide, carfilzomib, dexamethasone, cyclophosphamide, pomalidomide, bortezomib and cemiplimab (RGN2810): 1 lot of pool human K3-EDTA plasma spiked at Low (1.20 ng/mL), High (16.0 ng/mL), SuperHigh-b (0.500 ng/mL) and SuperHigh-c (2.00 mg/mL) levels of isatuximab and tested separately for each drug. No impact on the isatuximab quantitation in human K3-EDTA plasma was observed whatever		[Table 21] of report DOH0716 (module 5.3.1.4) [Table 22] of report DOH0716 (module 5.3.1.4) [Table 23] of report DOH0716 (module 5.3.1.4) [Table 13a], [Table 13b], [Table 13c], [Table 13d], [Table 13e] and [Table 13f], of report SPH0304 (module 5.3.1.4)

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	Range of relative bias with lenalidomide: -1.9% to +13% Range of relative bias with carfilzomib: -7.6% to +9.4% Range of relative bias with dexamethasone: -1.6% to 31% Range of relative bias with cyclophosphamide: 0.07% to 6.8% Range of relative bias with pomalidomide: -5.4% to +7.9% Range of relative bias with bortezomib: -7.9% to +2.8% Range of relative bias with cemiplimab: 0.41% to +22% - Interference with daratumumab (Darzalex®), an anti-CD38 mAb that may be administered previously to isatuximab in clinical trials. 1 lot of pool human K3-EDTA plasma spiked with isatuximab concentrations ranging from 1.00 to 1000 µg/mL. 1 lot of pool of incurred human K3-EDTA plasma specimens containing from about 50.0 to 500 µg/mL of isatuximab. The quantitation of SAR650984 in spiked or incurred plasma specimens was not impacted by the presence of daratumumab tested at a concentration of 500 µg/mL. Range of relative bias with pooled incurred samples: -13% to 16%. - Interference with target antigen CD38: 1 lot of pool K3-EDTA plasma spiked at Low (1.20 ng/mL) and High (16.0 ng/mL) levels of isatuximab. No impact of target antigen CD38 from 1.00 pg/mL up to 10.0 ng/mL was observed on the isatuximab quantitation in human K3-EDTA plasma. At higher concentrations of target antigen CD38 (tested from 100 ng/mL up to 10.0 µg/mL), the isatuximab quantitation in	[Table 14] of report SPH0304 (module 5.3.1.4) [Table 16a] and [Table 16b] of report SPH0304 (module 5.3.1.4)
Hemolysis effect	Hemolyzed effect was evaluated with pool of human K3-EDTA plasma with 3% hemolyzed blood spiked at Low (1.20 ng/mL), High (16.0 ng/mL) and SuperHigh-a (0.250 mg/mL) levels of isatuximab. At Low and High levels, range of bias: -3.1 to 1.1%. At SuperHigh-a level, bias: -14% with 2 out 6 results outside ±20% criteria	[Table 20] of report DOH716 (module 5.3.1.4)
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue Not assessed	Not applicable
Dilution linearity & hook effect	Highest concentration tested and number of dilution factors. Range of observed bias Dilution linearity was evaluated with pool of human K3-EDTA plasma spiked at SuperHigh-a (0.250 mg/mL), SuperHigh-b (0.500 mg/mL) and SuperHigh-c (2.00 mg/mL) levels of isatuximab. - SuperHigh-a level: dilution factors tested: 1, 15 000, 50 000 and 150 000 using human K3-EDTA plasma - analyzed over 3 different runs. Range of bias: 1.1% to 3.8%. No hook effect observed. - SuperHigh-b level: dilution factors tested: 30 000, 100 000 and 300 000 using human K3-EDTA plasma - analyzed over 3 different runs. Range of bias: -14% to -9.8%.	[Table 19] of report DOH00716 (module 5.3.1.4) [Table 12a] of report SPH0304 (module 5.3.1.4)

Reference ID: 4568595

	SuperHigh-c level: dilution factors tested: 125 000, 250 000 and 400 000 using human K3-EDTA plasma - analyzed over 4 different runs. Range of bias: -15% to -10%.	[Table 12b] of report SPH0304 (modul e
Bench-top/process stability	The stability of isatuximab in pool human K3-EDTA plasma spiked at Low (1.20 ng/mL), High (16.0 ng/mL) and SuperHigh-a (0.250 mg/mL) levels of isatuximab was established after storage at room temperature and at approximately 4°C for 2 and 24 hours. After 24 hours at room temperature, the %bias was between -9.5% and -0.21% and from -6.5% to 6.1 after 24 hours at +4°C	[Table 17] and [Table 18] of report DOH0716 (modul
Freeze-Thaw stability	The freeze/thaw stability was established with pool of human K3-EDTA plasma spiked at Low (1.20 ng/mL), High (16.0 ng/mL), SuperHigh-a (0.250 mg/mL), SuperHigh-b (0.500 mg/mL) and SuperHigh-c (2.00 mg/mL) levels of isatuximab. - At Low (1.20 ng/mL), High (16.0 ng/mL), SuperHigh-a (0.250 mg/mL) levels of isatuximab, after 3 additional freeze/thaw cycles at -80°C and -20°C, the bias ranged between -14% and +12%. At SuperHigh-b (0.500 mg/mL) levels of isatuximab, after 6 additional freeze/thaw cycles at -80°C, the bias ranged between 6.8% and 11%. At SuperHigh-c (2.00 mg/mL) levels of isatuximab, after 6 additional	[Table 12] and [Table 13] of report DOH0716 [Table 11a] of report SPH0304 [Table 11b] of report SPH0304
Long-term storage	The long term stability of isatuximab was conducted using the following samples: - Spiked human K3-EDTA plasma samples at Low (1.20 ng/mL), High (16.0 ng/mL) and SuperHigh (0.250 mg/mL, 0.500 mg/mL then 2.00 mg/mL) levels of isatuximab. They were then stored at -20°C and -80°C for up to 24 months for Low, High and SuperHigh-a levels and for up to 26 months for SuperHigh-c levels at 2.00 mg/mL. The superHigh-b level was tested for up to 7 months at -20°C and for up to 13 months at -80°C - Pools of incurred K3-EDTA plasma specimens prepared at Low (104 ng/mL), High (93774 ng/mL) and SuperHigh (1.00 mg/mL) concentration levels and collected from patients with selected CD38+ hematological malignancies and administered with isatuximab. They were then stored at -20°C or at -80°C for up to 33 months for Low and High levels and for up to 40 months for SuperHigh level. Human K3-EDTA plasma samples spiked with isatuximab up to 2.00 mg/mL could be stored for up to 24 months at about -20°C and -80°C in polypropylene tubes. Incurred human plasma specimens containing up to about 1.00 mg/mL of isatuximab could be stored for up to 15 months at	[Table 5], [Table 6], [Table 7], [Table 8], [Table 9] and [Table 10] of report SPH0304 (modul e 5.3.1.4)
Parallelism	The parallelism was assessed by analyzing 9 incurred Phase 1 TED10893 study specimens coming from 9 different patients, after 3	Section 9.3 of [phase report

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	serial dilutions with blank human K3-EDTA plasma to obtain resulting concentrations in the low, mid and high part of the calibration curve. The dilution factors tested covered those used during the study specimen analyses. The precision (%CV) of the back-calculated concentrations of specimens in a dilution series ranged between 0.72% and 12% over the dilution factors tested, i.e. from 20 up to 1 000 000 demonstrating no issue on parallelism.	TED10893-BA1] ([16.2.5.2.1] in clinical report TED10983-Phase 1, CTD module 5.3.3.2
Carry over	Not applicable	Not applicable
Method performance in study TED10893 Phase 1 There are 2 supportive Bioanalysis Phase Reports for TED10893 Phase 1: -TED10893 Phase 1-BA1: Determination of SAR650984 by ELISA method in human EDTA plasma samples from Phase 1 of the study TED10893: A Phase 1/2 Dose Escalation Safety, Pharmacokinetic and Efficacy Study of Multiple Intravenous Administrations of a Humanized Monoclonal Antibody (SAR650984) Against CD38 In Patients with Selected CD38+ Hematological Malignancies Report results of isatuximab in specimens collected from the start of the Phase 1 study (23-June-2010) up to 30- April-2015 -TED10893 Phase 1-BA4: Determination of SAR650984 by ELISA method in human EDTA plasma samples from Phase 1 of the study TED10893: A phase 1/2 dose escalation safety, pharmacokinetic and efficacy study of multiple intravenous administrations of a humanized monoclonal antibody (SAR650984) against CD38 in patients with selected CD38+ hematological malignancies Report results of isatuximab in specimens collected from 13-August-2014 up to 31-August-2016. These 2 reports are appended to the clinical study report TED10893 Phase 1, CTD module 5.3.3.2 Appendices location: 16-2-5-cdc-data [16.2.5.2.1] TED10893 Phase 1-BA1: [16.2.5.2.1.1] TED10893 Phase 1-BA4: [16.2.5.2.1.4]		
Assay passing rate	BA1 report: total of 123 different runs of analysis including 3 runs with samples for ISR assessment. 5 runs out of 123 rejected for QC acceptance criteria not met BA4 report: total of 18 runs of analysis and 3 runs out of 18 rejected for QC acceptance criteria not met. The data presented above include incurred sample reanalysis (ISR)	Section 9.4 of [phase report TED10893-BA1] (16.2.5.2.1.1) Section 8.2 of [phase report TED10893-BA4] (16.2.5.2.1.4)
Standard curve performance	BA1 report - Cumulative bias range: -2.00% to +2.00% - Cumulative precision: ≤ 4.64% CV BA4 report - Cumulative bias range: -3.40% to +2.00% - Cumulative precision: ≤ 6.42% CV	[Table 2] of phase report TED10893 BA1 and BA4 (16.2.5.2.1.1 and 16.2.5.2.1.4)
QC performance	BA1 report • Cumulative bias range: -6.60% to +0.83% • Cumulative precision: ≤ 18.84% CV • TE: ≤ 23.01% (LBA only) BA4 report	[Table 4] of phase report TED10893 BA1 and BA4

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	- Cumulative bias range: -11% to +2.50% - Cumulative precision: : ≤ 12.87% CV - TE: ≤ 22.52% (LBA only)	and 16.2.5.2.1.4)
Method reproducibility	Incurred sample reanalysis was performed in 129 (7.9% of) study samples and 84 % of samples met the pre-specified criteria	Section 9.2 of [phase report TED10893-BA4] (16.2.5.2.1.1)
Study sample analysis/ stability	All samples were analyzed within 15 months of storage at nominal -80°C, which correspond to the established long-term frozen matrix stability.	
Method performance in clinical study TED10893 Phase 2 Stage 1 Phase Report Bioanalysis - TED10893 - P2 - BA1: Qualitative detection of anti-SAR650984 antibodies in human EDTA plasma samples from Phase 2 Stage 1 of the study TED10893 using a polyethylene glycol extraction and an acidification step followed by an ECL immunoassay: SAR650984: A phase 1/2 dose escalation safety, pharmacokinetic and efficacy study of multiple intravenous administrations of a humanized monoclonal antibody (SAR650984) against CD38 in patients with selected CD38+ hematological malignancies This phase report is appended to the clinical study report TED01893 phase 2 stage 1, module 5.3.5.1 Appendix location : 16-2-5-cdc-data [16.2.5.2.1.2]		
Assay passing rate	Total of 92 different runs of analysis and 4 runs out of 92 rejected for QC acceptance criteria not met. The data do not include incurred sample reanalysis (ISR) as not performed.	Section 9.2 of [phase report TED10893-BA4] (16-2-5-cdc-data 16.2.5.2.1.2)
Standard curve performance	- Cumulative bias range: -1.80% to +2.00% - Cumulative precision: ≤ 5.20% CV	[Table 2] of phase report TED10893-P2-BA1 (16-2-5-cdc-data 16.2.5.2.1.2)
QC performance	• Cumulative bias range: -12.5% to +2.50% • Cumulative precision: ≤ 24.69% CV • TE: ≤ 30.52% (LBA only)	[Table 4] of phase report TED10893-P2-BA1 (16-2-5-cdc-data 16.2.5.2.1.2)
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	Not applicable
Study sample analysis/ stability	All samples were analyzed within 15 months of storage at nominal -80°C, which correspond to the established long-term frozen matrix stability.	
Method performance in clinical study TCD14079 Part A Abbreviated Phase Report Bioanalysis - TCD14079 - BA1 "A Phase 1b Study of SAR650984 (Anti-CD38 mAb) in Combination with Pomalidomide and Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma" - Quantification of SAR650984 by ELISA method in human K3-EDTA plasma study samples This abbreviated Phase Report is appended to clinical study report TCD14079, module 5.3.3.2 Appendix location : 16-2-5-cdc-data [16.2.5.2.1.1]		
Assay passing rate	Total of 80 different runs of analysis and 10 runs out of 80 rejected for QC acceptance criteria not met. The data do not include incurred sample reanalysis (ISR) as not performed.	Data on file- Not published in the Abbreviated Phase Report Bioanalysis -

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		TCD14079 - BA1 (16.2.5.2.1.1)
Standard curve performance	- Cumulative bias range: -3.1% to 2.4% - Cumulative precision: ≤ 5.2% CV	Data on file - Not published in the Abbreviated Phase Report Bioanalysis - TCD14079 - BA1 (16.2.5.2.1.1)
QC performance	- Cumulative bias range: -14% to +1.9% - Cumulative precision: ≤ 20% CV - TE: ≤ 26% (LBA only)	Published in the [Abbreviated Phase Report Bioanalysis - TCD14079 - BA1] (16.2.5.2.1.1)
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	Not applicable
Study sample analysis/ stability	All samples were analyzed within 15 months of storage at nominal -80°C, which correspond to the established long-term frozen matrix stability.	
Method performance in clinical study EFC14335 Phase Report Bioanalysis – EFC14335 - BA1 (b) (4) Study Number 8368717): Determination of SAR650984 in Human Plasma (EDTA) in support of Clinical Trial EFC14335 using Enzyme-Linked Immunosorbent Assay (ELISA). This phase Report is appended to clinical study report EFC14335, A Phase 3 randomized, open-label, multicenter 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 (EFC14335), CTD module 5.3.5.1 Appendix location: 16.2.5 cdc-data [16.2.5.2.1]		
Assay passing rate	Total of 146 runs of analysis with 124 runs accepted and 22 rejected. The data include incurred sample reanalysis (ISR)	Section "Run summary table" from pages 13 to 19 of [phase report EFC14335-BA1] (16-2-5-cdc-data 16.2.5.2.1)
Standard curve performance	• Cumulative bias range: -0.13% to +0.55% • Cumulative precision: ≤ 3.4% CV	[Table 1] of phase report BA1 (16-2-5-cdc-data 16.2.5.2.1)
QC performance	• Cumulative bias range: -10% to +3.5% • Cumulative precision: ≤ 12.5% CV • TE: ≤ 22% (LBA only)	[Table 2] of phase report EFC14335-BA1 (16-2-5-

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		cdc-data 16.2.5.2.1)
Method reproducibility	Incurred sample reanalysis was performed in 206 (7.9% of) study samples and 71.84 % of samples met the pre-specified criteria	[Table 6] of phase report EFC14335-BA1 (16-2-5-cdc-data (16.2.5.2.1)
Study sample analysis/ stability	All samples were analyzed within 15 months of storage at nominal -80°C, which correspond to the established long-term frozen matrix stability All samples were stored at -80°C nominal prior to analysis from the date of initial sample collection 10th January 2017, until the final day of sample processing on the 19th December 2018. The maximum sample storage duration between collection and analysis for samples was 708 days. The current stability interval established under study SPH0304 is 445 days (15 months). Seven samples from one patient were analyzed	

Source: Table 1, Response to Agency Request, July 10, 2019.

Table 42. Summary of method modification(s) and cross-validation results.

Bioanalytical method validation report name and hyperlink	Final Study Report - DOH1417 ((b) (4) 8345277) and the Addendum 1 titled: Method Transfer and Cross-Validation of a Method for the Determination of SAR650984 in Human Plasma (EDTA) between (b) (4) and Sanofi-Aventis using Enzyme-Linked Immunosorbent Assay (ELISA), CTD module 5.3.1.4		
Changes in method	The regression model & weighting were changed to weighted curve fit 4PL (1/Y2)		
New validated assay range if any	Not applicable		
Validation parameters	**Cross-validation performance**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ Standard calibrators at of 0.500 (LLOQ), 1.00, 2.50, 5.00, 7.50, 10.0, 15.0 and 20.0 (ULOQ) ng/mL	-1.0% to +2.6%	[Table 1] of Addendum 1 to final study report DOH1417 (CTD module 5.3.1.4)
	Cumulative precision (%CV) from LLOQ to ULOQ Standard calibrators at of 0.500 (LLOQ), 1.00, 2.50, 5.00, 7.50, 10.0, 15.0 and 20.0 (ULOQ) ng/mL	≤ 5.9%	[Table 1] of Addendum 1 to final study report DOH1417 (CTD module 5.3.1.4)

Reference ID: 4568595

QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 6 QCs QCs n=18 data per level LLOQ: 0.500 ng/mL LQC: 1.20 ng/mL MQC: 5.00 ng/mL HQC: 16.0 ng/mL ULOQ: 20.0 ng/mL	-1.2% to +10.6%	[Table 3] of Addendum 1 to final study report DOH1417 (CTD module 5.3.1.4)
	Inter-batch %CV QCs n=18 data per level LLOQ: 0.500 ng/mL	≤16.6%	[Table 3] of Addendum 1 to final study report DOH1417
	LQC: 1.20 ng/mL MQC: 5.00 ng/mL HQC: 16.0 ng/mL ULOQ: 20.0 ng/mL		(CTD module 5.3.1.4)
	Percent total error (TE) QCs n=18 data per level LLOQ: 0.500 ng/mL LQC: 1.20 ng/mL MQC: 5.00 ng/mL HQC: 16.0 ng/mL ULOQ: 20.0 ng/mL	≤ 17.8%	[Table 3] of Addendum 1 to final study report DOH1417 (CTD module 5.3.1.4)

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Cross-validation	Numbers of spiked or incurred samples analyzed and results: - Spiked cross validation samples: n= 6 samples analyzed blinded (b) (4) at the following levels: one blank sample, two spiked samples at a concentration between the low and medium QC levels, two spiked samples at a concentration between the medium and high QC levels and one spiked sample above the ULOQ. 6 out of 6 (100%) of the results generated within each laboratory were within 30% of each other: Relative difference ranged between -6.8% and +4.3%. - Incurred study samples: n= 39 pooled incurred samples analyzed blinded (b) (4) A total of 32 out of 39 (82.1%) of the results generated within each laboratory were within 30% of each other.		[Table 10] and [Table 11] of Addendum 1 to final study report DOH1417 (CTD module 5.3.1.4)
List other parameters	Dilution Assessment was performed with spiked samples at Super High levels of isatuximab: - Super High QC-1 at 250 000 ng/mL, diluted in replicate (n=3) 15000-fold, 50000-fold and 150000-fold with pooled blank human EDTA plasma, prior to assay - Super High QC-2 at 2 000 000 ng/mL, diluted in replicate (n=3) 125000-fold, 250000-fold and		[Table 5a], [Table 5b], [Table 6a] and [Table 6b] of Addendum 1 to final study report DOH1417 (CTD module
	400000-fold with pooled blank human EDTA plasma, prior to assay. For each dilution series the mean of the back- calculated concentrations was within 20% of the expected value		

Source: Table 1, Response to Agency Request, July 10, 2019.

Table 43. Summary method performance of a bioanalytical method to measure pomalidomide in human K3-EDTA plasma.

Bioanalytical method validation report name, amendments, and hyperlinks	Final Study Report - DOH1324 ((b) (4) 8310389) and the Addendum 1 titled: Validation of a Method for the Determination of Pomalidomide in Human Plasma by HPLC with MS/MS Detection" , CTD module 5.3.1.4
Method description	Pomalidomide was extracted from 100 µL human plasma sample aliquots along with its internal standard Thalidomide using supported liquid extraction. Detection was made on a mass spectrometer (Sciex API 5500) after undergoing high pressure liquid chromatography (Shimadzu, SIL-HTc, 10 Series).
Materials used for calibration curve & concentration	Human K3-EDTA plasma

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Validated assay range	0.200 to 200 ng/mL		
Material used for QCs & concentration	Human K3-EDTA plasma		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Quadratic regression with $1/x^2$ weighting		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ Single calibration curve at levels 0.200, 0.400, 1.5, 5.00, 20.0, 80.0, 170, and 200 ng/mL	8	[Table 6.9] of report DOH1324 (module 5.3.1.4)
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-6.3 to 3.0%	[Table 6.9] of report DOH1324 (module 5.3.1.4)
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 5.9%	[Table 6.9] of report DOH1324 (module 5.3.1.4)
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 18 QCs** QCs: LLOQ (0.200 ng/mL) LOQ (0.600 ng/mL) MQC (10.0 ng/mL) HQC (160 ng/mL)	-5.5 to -2.5%	[Table 6.11] of report DOH1324 (module 5.3.1.4)

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	Inter-batch %CV QCs LLOQ (0.200 ng/mL) LOQ (0.600 ng/mL) MQC (10.0 ng/mL) HQC (160 ng/mL)	≤ 9.3%	[Table 6.11] of report DOH1324 (module 5.3.1.4)
	Total Error (TE) QCs: Not applicable		Not applicable
Selectivity & matrix effect	No interference peaks were detected at the retention time of pomalidomide or its internal standard for six blank plasma lots. The mean accuracy value range for the six lots spiked at the LQC (n=3/lot) was 91.3 to 100.8%.		[Figure 8.1], [Figure 8.2], [Figure 8.3], [Figure 8.4], [Figure 8.5]; [Table 6.2]; [Table 6.3]; [Table 6.4]; [Table 6.5]; [Table 6.6]; [Table 6.7] of report DOH1324 (modul
Interference & specificity	Interference was initially tested with dexamethasone and inadvertently cyclophosphamide monohydrate instead of SAR650984 (isatuximab). The test was repeated in Run 33 by spiking 500 ng/mL dexamethasone and 500 ng/mL SAR650984 (isatuximab) into LQC and HQC (n=3/level) and blank matrix. However, the blank matrix spiked with 500 ng/mL of SAR650984 (isatuximab) and 500 ng/mL of dexamethasone in Run 33 contained an interference peak at the		[Figure 8.6], [Figure 8.7], [Figure 8.8]; [Table 6.3], [Table 6.4], [Table 6.5], [Table 6.6] of
	retention times of interest, likely due to carry over. The test was repeated in Run 34 where no interference peaks were observed. The mean accuracy for Run 34 was 102.5% at the LQC level and was 101.3% at the HQC level with %CV ≤1.6% at both levels.		report DOH1324 (module 5.3.1.4)
Hemolysis effect	Six replicates at LQC (bias -5.0 to 5.5%) and HQC (bias -0.6 to 3.1%) prepared in 2% lysed whole blood.		[Table 6.25] of report DOH1324 (modul e

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Lipemic effect	Six replicates at LQC (bias -5.5 to -0.2%) and HQC (bias -2.5 to 1.3%) prepared in pooled plasma with a lipid content ≥300 mg/dL triglyceride level.	[Table 6.26] of report DOH1324 (modul e
Dilution linearity & hook effect	One dilution factor (10-fold) tested at 1000 ng/mL (DQC). Bias -4.2 to 1.0%.	[Table 6.11] of report DOH1324 (modul e
Bench-top/process stability	Bench-top stability – confirmed for 30 hours on wet ice. Processed-samples stability – confirmed for 288 hours at nominal 4°C	[Table 6.21] and [Table 6.18] of report
Freeze-Thaw stability	Confirmed for five freeze/thaw cycles at nominal -20°C and -70°C	[Table 6.20] of report DOH1324 module 5.3.1.4
Long-term storage	Confirmed for 848 days at nominal -70°C.	[Table 6.5] of report DOH1324 Addendum No. 1 (module 5.3.1.4)
Parallelism	Not applicable	
Carry over	No significant carry over was observed for accepted runs.	[Figure 8.9] of report DOH1324 (modul e

Method performance within clinical study TCD14079- Part A: Determination of Pomalidomide in Human Plasma Samples from TCD14079 by HPLC with MS/MS Detection in study TCD14079 (A Phase 1b Study of SAR650984 (Isatuximab) in Combination with Pomalidomide and Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma (CTD module 5.3.3.2) This phase Report is appended to clinical study report TCD104079 part A, module 5.3.3.2 Appendix location :16-2-5-cdc-data [16.2.5.2.1.3]		
Assay passing rate	18 accepted batches (3 rejected) of 21 total batches analyzed = 85.7% passing rate. This incurred sample reanalysis (ISR)	[Table 9.1] in Phase report 16-2-5-cdc-data (16.2.5.2.1.3)

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Standard curve performance	- Cumulative bias range: -1.33 to 2.75 % - Cumulative precision: ≤ 5.28% CV	[Table 9.3] from Phase report 16-2-5- cdc-data (16.2.5.2.1.3) in module
QC performance	- Cumulative bias range: -0.67 to 1.00% - Cumulative precision: :≤ 7.92% CV - TE: ≤ x% (LBA only) : Not applicable	[Table 9.5] from Phase report 16-2-5- cdc-data (16.2.5.2.1.3)
Method reproducibility	Incurred sample reanalysis was performed in 54 (10.3%) of study samples and 93% of samples met the pre-specified criteria	[Table 9.7] from phase report 16-2-5- cdc-data (16.2.5.2.1.3)
Study sample analysis/ stability	All samples were analyzed within 339 days of storage at nominal -70°C, within established long-term frozen matrix stability of 848 days at nominal -70°C.	

Source: Table 1, Response to Agency Request, July 10, 2019.

1.2. Additional Safety Analyses Conducted by FDA

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Shwu-Luan Lee, PhD	OOD/DHOT	Sections: 5	Select one: ☑ Authored ☑ Approved
	Signature: Shwu-luan Lee -S	Digitally signed by Shwu-luan Lee -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Shwu-luan Lee -S, 0.9.2342.19200300.100.1.1 1300192057 Date 2020.02.25 16 57 46 -05'00'		
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Select one: ☑ Authored ☑ Approved
	Signature: Brenda Gehrke -S	Digitally signed by Brenda Gehrke -S cn Brenda Gehrke -S, 0.9.2342.19200300.100.1.1 0012062023 DN c US, o U.S. Government, ou HHS, ou FDA, ou People, Date 2020.02.25 16 34 18 -05'00'		
Nonclinical Team Deputy Division Director	Haleh Saber, PhD	OOD/DHOT	Sections: 5	Select one: ☑ Authored ☑ Approved
	Signature: Haleh Saber -S	Digitally signed by Haleh Saber -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Haleh Saber -S, 0.9.2342.19200300.100.1.1 1300212858 Date 2020.02.2609 54 37-05'00'		
Clinical Pharmacology & Pharmacometrics Reviewer	Amal Ayyoub, B.Pharm, PhD	OCP/DCPI I	Sections: 6	Select one: ☑ Authored ☑ Approved
	Signature: Amal Ayyoub -S	Digitally signed by Amal Ayyoub -S DN c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amal Ayyoub -S, 0.9.2342.19200300.100.1.1=2002027436 Date 2020.02.26 18 27 25-05'00'		
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DCPI	Sections: 6	Select one: ☑ Authored ☑ Approved
	Signature: Lian Ma -S	Digitally signed by Lian Ma -S DN c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2020.02.27 11 15 49 -05'00'		
Clinical Pharmacology Team Leader	Olanrewaju Okusanya, PharmD, MS	OCP/DCPI	Sections: 6	Select one: ☑ Authored ☑ Approved
	Signature: Olanrewaju Okusanya -S	Digitally signed by Olanrewaju Okusanya -S DN: c=US o=U.S. Government ou=HHS ou=FDA ou=People 0.9.2342.19200300.100.1.1=2001410838 cn=Olanrewaju Okusanya -S Date:2020.02.2711:52:59-05'00'		
Clinical Pharmacology Director	Brian Booth, PhD	OCP/DCPI	Sections:6	Select one: ☑ Authored ☑ Approved
	Signature: Brian P. Booth -S	Digitally signed by Brian P. Booth -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Brian P. Booth -S, 0.9.2342.19200300.100.1.1 1300137436		
		OOD/DHMII	Sections:	☑ ☑ Select one: Authored Approved

	Signature:

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Statistics Reviewer	Laura Fernandes, PhD	OB/DBIX	Sections: 8	Select one: ☑ Authored ☑ Approved
	Signature: Laura Fernandes -S Digitally signed by Laura Fernandes -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9 2342.19200300.100.1.1=2001528044, cn=Laura Fernandes -S Date: 2020.02.27 13:05:17 -05'00'			
Statistics Team Leader	Yu-te Wu, PhD	OB/DBIX	Sections:	Select one: ☑ Authored ☑ Approved
	Signature: Yute Wu -S Digitally signed by Yute Wu -S Date: 2020.02.27 13:38:13 -05'00'			
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections:	Select one: ☑ Authored ☑ Approved
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Associate Director for Labeling (ADL)	Virginia Kwitkowski, MS, RN, ACNP-BC	ODE1/DHP	Sections:	Select one: ☑ Authored ☑ Approved
	Signature: Virginia E. Kwitkowski -S Digitally signed by Virginia E. Kwitkowski -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 1300395223, cn Virginia E. Kwitkowski -S Date 2020.02.2517 49 39-05'00'			
Primary Clinical Reviewer/ Cross-Disciplinary Team Leader (CDTL)	Bindu Kanapuru, MD	OOD/DHMII	Sections:	Select one: ☑ **Authored** ☑ **Approved**
	Signature: Bindu Kanapuru -S Digitally signed by Bindu Kanapuru -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Bindu Kanapuru -S, 0.9.2342.19200300.100.1.1 0012593628 Date 2020.02.28 08 15 12 -05'00'			
Clinical Team Leader/ Division Director	Nicole Gormley, MD	OOD/DHMII	Sections:	Select one: ☑ Authored ☑ Approved
	Signature: Nicole J. Gormley -S			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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