

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761163Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Clinical Microbiology/Virology

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	Biologics License Application (BLA)
Application Number(s)	761163
Priority or Standard	Priority
Submit Date(s)	December 28, 2019
Received Date(s)	December 30, 2019
PDUFA Goal Date	August 30, 2020
Division/Office	Division of Hematologic Malignancies II/Office of Oncologic Diseases
Review Completion Date	07/30/2020
Established Name	tafasitamab-cxix
(Proposed) Trade Name	Monjuvi
Pharmacologic Class	CD-19 directed cytolytic antibody
Code name	MOR208
Applicant	MorphoSys US Inc.
Formulation(s)	Injection
Dosing Regimen	The recommended dose of tafasitamab is 12 mg/kg as an intravenous infusion given according to the following schedule: • Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle • Cycle 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle • Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle
Applicant Proposed Indication(s)/Population(s)	In combination with lenalidomide (b) (4) (b) (4) for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for (b) (4) ASCT
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	In combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT)

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jennifer Lee, PharmD, RAC-US
Pharmacology/Toxicology Reviewer	Ramadevi Gudi, PhD
Pharmacology/Toxicology Team Leader	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewers	Vicky Hsu, PhD (DCPI) Ruoqing Li, PhD (DPM) Kate Drozda, PhD (DTPM)
Office of Clinical Pharmacology Team Leaders	Ruby Leong, PharmD, BCPS (DCPI) Lian Ma, PhD (DPM) Rosane Charlab Orbach, PhD (DTPM)
Clinical Reviewer	Alexandria Schwarsin, MD
Clinical Team Leader (Acting)	Bindu Kanapuru, MD
Safety Analyst (if applicable)	N/A
Statistical Reviewer	Kunthel By, PhD
Statistical Team Leader	Yu-te Wu, PhD
Associate Director for Labeling	Stacy S. Shord, PharmD
Cross-Disciplinary Team Leader	Bindu Kanapuru, MD
Deputy Division Director (DHOT)	Haleh Saber, PhD
Division Director (OCP)	Brian Booth, PhD
Division Director (OB)	Thomas Gwise, PhD
Division Director (Acting) (OOD/DHM2)	Nicole Gormley, MD
Deputy Director (Acting) and Associate Director for Immunotherapeutics (OOD) (designated signatory authority)	Marc Theoret, MD

DCPI: Division of Cancer Pharmacology I
 DPM=Division of Pharmacometrics
 DTPM: Division of Translational and Precision Medicine
 DHOT=Division of Hematology, Oncology, Toxicology
 OCP=Office of Clinical Pharmacology
 OB=Office of Biostatistics
 DHM2=Division of Hematologic Malignancies II
 OOD=Office of Oncologic Diseases

Additional Reviewers of Application

OPQ /OBP	Bazarragchaa Damdinsuren, MD, PhD, Application Technical Lead Christopher Downey, PhD, Review Chief Massod Rahimi, PhD, Primary Reviewer (DS/DP) Li Lu, PhD, Immunogenicity Scott Dallas, RPh, Labeling Assessor James Barlow, RPh, Labeling Assessor Vicky Borders-Hemphill, PharmD, Labeling Assessor
OPQ/OPMA	Thuy Thanh Nguyen, PhD, Facilities Team Leader/Branch Chief Candace Gomez-Broughton, PhD, Microbiology Team Leader Maxwell Van Tassell, PhD, Drug Substance Microbiology Reviewer Jeanne Fringer, PhD, Drug Product Microbiology Reviewer Wayne Seifert, Facility Reviewer
OPQ/OPRO	Anita Brown, Regulatory Business Process Manager
OPDP	Nisha Patel, PharmD, RAC, Regulatory Review Officer
PLT	Ruth Mayrosh, PharmD, Patient Labeling Reviewer Barbara Fuller, RN, MSN, CWOCN, Team Leader, Patient Labeling
OSI	Anthony Orenca, MD, FACP, Medical Officer Min Lu, MD, MPH, Team Leader Kassa Ayalew, MD, MPH, Branch Chief
OSE	Neil Vora, PharmD, MBA, PMP, Safety Regulatory Project Manager
OSE/DEPI	Richard Scott Swain, PhD, MPH, Reviewer Simone Pinheiro, ScD, MSc, Division Director Michael D. Blum, MD, MPH, Office Deputy Director (OPE)
OSE/DMEPA	Nicole Iverson, PharmD, BCPS, Safety Evaluator Carlos M. Mena-Grillasca, BS Pharm, Primary Reviewer Hina Mehta, PharmD, Team Leader Danielle Harris, PharmD, Deputy Director
OSE/DRM	Till Olickal, PhD, PharmD, Reviewer Naomi Boston, PharmD, Team Leader Cynthia LaCivita, PharmD, Division Director
Other	Interdisciplinary Review Team for Cardiac Safety Studies

OPQ=Office of Pharmaceutical Quality
 DS=Drug Substance
 DP=Drug Product
 OPMA=Office of Pharmaceutical Manufacturing Assessment
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 OPE= Office of Pharmacovigilance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRM=Division of Risk Management

Glossary

ADCC	Antibody dependent cellular cytotoxicity
ADME	absorption, distribution, metabolism, excretion
ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
ADCP	Antibody-dependent cell-mediated phagocytosis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALB	Albumin
ALC	Absolute Lymphocyte Count
ALL	Acute lymphoblastic leukemia
ASCT	Autologous stem-cell transplantation
BA	bioavailability
BEN	Bendamustine
BLA	biologics license application
CAR-T	Chimeric antigen receptor T cells
CDC	Complement-Dependent Cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence Interval
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
DCO	Data cut-off date
DCR	disease control rate
DE	dose escalation
DER	Dose-Response Exposure
DFS	Disease Free Survival
DHAP	Cisplatin, cytarabine, dexamethasone
DLBCL	diffuse large cell B cell lymphoma
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event free survival
ePS	Estimated Propensity Score
FAS	Full Analysis Set
FDA	Food and Drug Administration

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FL	follicular lymphoma
GCB	Germinal Center B-cell
GCP	good clinical practice
HDC	High-dose chemotherapy
ICH	International Conference on Harmonization
IND	Investigational New Drug
IV	intravenous
IRC	Independent Radiology Committee
ISS	integrated summary of safety
ITT	intent to treat
LEN	Lenalidomide
mAbs	monoclonal antibodies
MAS25	Matched Analysis Set 25
MC	multicenter
MCL	mantle cell lymphoma
MD	Multiple dose
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MZL	marginal zone lymphoma
Nab	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NHL	Non-Hodgkin's lymphoma
NK	Natural Killer
NME	new molecular entity
NTE	Not transplant eligible
Obs	Observational
OL	Open Label
OPQ	Office of Pharmaceutical Quality
ORR	overall/objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
QoL	quality of life
P	prospective
PD	pharmacodynamics
PFS	progression free survival
PH	Phase

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PI	prescribing information
PK	pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
Pola	Polatuzumab vedotin
PR	Partial response
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
R/R	relapsed or refractory
R	Retrospective
RA	Randomized
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RTX	Rituximab
RWE	Real world evidence
SA	Single Arm
SD	Stable disease
SAE	serious adverse event
SAP	statistical analysis plan
SLL	small lymphocytic lymphoma
SOC	standard of care
SMD	standardized mean difference
StD	standard deviation
Tafa	Tafasitamab
TBD	to be determined
TEAE	treatment emergent adverse event
TMDD	Target mediated drug disposition
TTNT	time to next treatment
TTP	time to progression
USPI	United States Prescribing Information
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Tafasitamab is an Fc-modified antibody that binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including diffuse large B-cell lymphoma. Upon binding to CD19, tafasitamab mediates B-cell lysis through apoptosis and immune effector mechanisms, including ADCC and ADCP.

The recommended dose of tafasitamab is 12 mg/kg as an intravenous infusion given according to the following schedule:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle
- Cycle 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle
- Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle

Tafasitamab is administered in combination with lenalidomide for a maximum of 12 cycles and then tafasitamab is continued as monotherapy until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of tafasitamab in combination with lenalidomide for:

“The treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).”

This recommendation is based on a favorable benefit risk profile from trial, MOR208C203, a multicenter single arm trial of tafasitamab at the proposed dose and schedule in combination with lenalidomide 25 mg administered for up to 12 cycles in patients with relapsed or refractory DLBCL.

Trial MOR208C203 (L-MIND) enrolled 81 patients with relapsed or refractory DLBCL based on local pathology. Patients had relapsed or refractory DLBCL after 1 to 3 prior systemic therapies, including a CD20-directed cytolytic antibody, and were not candidates for high dose chemotherapy (HDC) followed by ASCT. The primary efficacy population was a total of 71 patients who had confirmed DLBCL based on central pathology. The median age was 71 years (range 41 to 86); 55% were male, 95% were White and 3% were Asian. The median number of prior therapies was two; 49% had one prior line of treatment, and 51% had 2 to 4 prior lines. Efficacy was established based on the best overall response rate (ORR), defined as the

proportion of patients with a complete or partial response assessed by an Independent Review Committee (IRC) using the International Working Group Response Criteria (Cheson 2007) supported by the duration of response. The best overall response rate was 55% (95% CI 43%, 67%); 37% of patients had a complete response and 18% of patients had a partial response. The median duration of response was 21.7 months (range-0-24 months).

The most common adverse reactions ($\geq 20\%$) were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite. Important safety risks include infusion related reactions, myelosuppression and infections. Fatal adverse reactions occurred in 5% of patients. The rates of permanent treatment discontinuation of tafasitamab due to adverse reactions was 15%.

Trial MOR208C201 provided evidence to support the contribution of tafasitamab to the treatment effect in patients with relapsed or refractory DLBCL. The ORR in the 35 patients with relapsed or refractory DLBCL enrolled on MOR208C201 who received single agent tafasitamab was 26% (95% CI: 13%, 43%). The ORR results of the L-MIND study were also considered in the context of an estimated ORR of 32% (95% CI: 21%, 43%) for single agent lenalidomide in Study MOR208C206 (RE-MIND), a retrospective observational cohort study evaluating lenalidomide monotherapy using real world data, and literature reports regarding the activity of single agent lenalidomide. However, there were several limitations to the observational study which render formal statistical comparisons unfeasible.

The uncertainty of the magnitude of the treatment effect with the addition of tafasitamab is a concern due to the small sample size. However, the observed depth of response, overall response, and response duration are clinically meaningful. These efficacy data provide substantial evidence of effectiveness and are the basis for the recommended accelerated approval. The approved indication will reflect the subtypes of DLBCL enrolled on the L-MIND trial; DLBCL not otherwise specified including DLBCL arising from low grade lymphoma. A Post-marketing requirement to confirm the benefit of tafasitamab in patients with (b) (4) DLBCL in a randomized controlled trial will be issued. A post marketing commitment will be issued to evaluate the efficacy and safety of tafasitamab in underrepresented racial subgroups.

1.3.Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Tafasitamab is an Fc-modified antibody that binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including diffuse large B-cell lymphoma. Upon binding to CD19, tafasitamab mediates B-cell lysis through apoptosis and immune effector mechanisms, including ADCC and ADCP.

Efficacy: Efficacy of tafasitamab in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) is based on results from a single, multicenter, single arm trial, MOR208C203 (L-MIND) in 71 patients with relapsed or refractory DLBCL confirmed by central pathology review. The median number of prior therapies was two; 49% had one prior line of treatment, and 51% had 2 to 4 prior lines. The primary reasons patients were not candidates for autologous stem cell transplantation (ASCT) included age (47%), refractoriness to salvage chemotherapy (27%), comorbidities (13%) and refusal of high dose chemotherapy/ASCT (13%). Race was collected in 92% of these patients and of these, 95% were white and 3% were Asian.

Patients received tafasitamab 12 mg/kg in combination with lenalidomide 25 mg for 12 cycles given on days 1-21 of a 28 day cycle followed by tafasitamab monotherapy. Tafasitamab was administered according to the following schedule:

- Cycle 1: Days 1,4, 8, 15 and 22 of the 28-day cycle
- Cycle 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle
- Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle

Efficacy was established based on best overall response rate (ORR) assessed by an Independent Review Committee (IRC) using the International Working Group Response Criteria (Cheson 2007) and duration of response. The best overall response rate was 55% [95% CI (43%, 67%)] with a duration of response of 21.7 months (range 0, 24). The complete response (CR) rate was 37%.

The contribution of tafasitamab to the activity in the combination was informed by the efficacy data from MOR208C201, a single arm trial evaluating single-agent tafasitamab in patients with relapsed or refractory non-Hodgkin's Lymphoma. The ORR in the 35 patients with relapsed or refractory DLBCL enrolled on MOR208C201 who received single agent tafasitamab was 26.0%(95% CI: 13%, 43%). The efficacy data from the L-MIND trial was considered in the context of the estimated ORR of 32% noted with single

agent lenalidomide in the MOR208C206 Study (RE-MIND), a retrospective observational cohort study evaluating lenalidomide monotherapy using real world data, and literature reports regarding the activity of single agent lenalidomide. However, there were several limitations to the observational data and formal comparisons to the data from RE-MIND were not made.

Safety: Tafasitamab demonstrated an acceptable safety profile for the patient population. L-MIND served as the primary trial for the safety evaluation, this was supported by a pooled analysis of three trials evaluating tafasitamab as monotherapy. Important safety risks include infusion related reactions, myelosuppression and infections. Fatal adverse reactions occurred in 5% of patients. The rates of permanent treatment discontinuation of tafasitamab due to adverse reactions was 15%.

Benefit-Risk: The available data provides evidence of the benefit risk of tafasitamab in combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for ASCT. The intended population has very few, if any, treatment options, and toxicities with tafasitamab and lenalidomide combination tended to be manageable with supportive care and dose modifications. The risks and the benefit/risk profile are acceptable for the intended population. The final patient population will reflect the types of DLBCL lymphoma enrolled, including DLBCL not otherwise specified and DLBCL arising from low grade lymphoma.

The limitations of the data are 1) the uncertainty of the magnitude of effect due to the small sample size and lack of a comparator arm 2) the limitations of the retrospective observational data referenced, 3) and the data collected on time-to-event endpoints are not interpretable, therefore, it cannot be determined if PFS or OS are prolonged. A post-marketing requirement to confirm the benefit of tafasitamab in patients with (b) (4) DLBCL in a randomized controlled trial will be issued. A post-marketing commitment will be issued to evaluate the efficacy and safety of tafasitamab in underrepresented racial subgroups.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Relapsed or refractory diffuse large B cell lymphoma (DLBCL) is fatal if not cured. In relapsed or refractory DLBCL, standard salvage regimens produce ORRs of 20-30%, with <15% CR and an estimated median OS of 6 months.	Relapsed or refractory DLBCL remains an incurable disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• High dose therapy followed by autologous stem cell transplantation (ASCT) remains the standard of care for relapsed/refractory patients with DLBCL if eligible. However, many patients may be ineligible for transplant either due to age or comorbidity or refractory disease. • Widely used less intensive regimens include gemcitabine, bendamustine and lenalidomide, but there is no standard of care and response rates are not durable. • Axicabtagene ciloleucel and tisagenlecleucel have regular approval and selinexor and polotuzumab vedotin have accelerated approval for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. • There is no FDA-approved therapy for patients with DLBCL after failure of one prior therapy or for patients who are ineligible for autologous stem cell transplantation.	• Patients with relapsed or refractory DLBCL who are ineligible for autologous stem cell transplant have limited treatment options and is a population with unmet medical need.
Benefit	• In a single arm-trial of tafasitamab in combination with lenalidomide for patients with a diagnosis of relapsed or refractory DLBCL and not eligible for autologous stem cell transplantation, the Independent review committee (IRC) assessed best overall response rate (ORR) in 71 patients with DLBCL confirmed by central pathology was 55% (95% CI 43%, 67%); 37% of patients had a complete response. The median duration of response (DOR) was 21.7 months (range, 0-24 months). • The ORR in the 35 patients with relapsed or refractory DLBCL enrolled on MOR208C201 who received single agent tafasitamab was 26.0% and provides supportive evidence of efficacy of single agent tafasitamab. • The efficacy data from the L-MIND trial was considered in the	• Based on the ORR and durable DOR, tafasitamab in combination with lenalidomide has meaningful treatment benefit in the intended patient population with relapsed or refractory DLBCL. • A post marketing requirement to confirm the benefit of tafasitamab in patients with (b) (4) DLBCL will be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	context of the ORR of 32% noted with single agent lenalidomide in the RE-MIND retrospective observational study and literature data.	
Risk and Risk Management	• The 81 patients enrolled and treated with tafasitamab at the intended dose and regimen in the L-MIND trial are the primary safety population. • A total of 46 patients (56.8%) were exposed to tafasitamab for > 6 months, a total of 34 patients (42.0%) were exposed for greater than 1 year and a total of 19 patients (23.5%) were exposed for > 2 years. • Fatal adverse reactions occurred in 5% of patients. The rates of permanent treatment discontinuation of tafasitamab due to adverse reactions was 15%. • Important safety risks include infusion related reactions, myelosuppression and infections. • TEAEs that occurred in more than 20% of patients on the L-MIND trial included neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, peripheral edema, pyrexia, respiratory tract infection, and decreased appetite.	• Tafasitamab+ lenalidomide has an acceptable safety profile in the intended population. • Toxicities were manageable with appropriate treatment interruption and discontinuation. • Infusion-related reaction, myelosuppression, and serious or opportunistic infections will be included in the Warnings and Precautions. • The USPI includes toxicity management guidelines for hematologic and non-hematologic adverse reactions. • The safe use of tafasitamab and lenalidomide can be managed through labeling and routine oncology care.

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:	N/A
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO)	
☐	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	
☐	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.	

Bindu Kanapuru, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Non-Hodgkin lymphomas (NHLs) account for approximately 5% of all new cancer cases and comprise a heterogeneous group of lymphoproliferative malignancies, which in 90% of cases are derived from B-cells. Diffuse large B-cell lymphoma (DLBCL), the most common high-grade NHL, accounts for approximately 40% of NHLs (Armitage and Weisenburger, 1998; Smith 2015; Swerdlow et al., 2008) and comprises 60% of all new lymphomas in the elderly population (Thieblemont and Coiffier, 2007). According to data from the United States (U.S.) Surveillance, Epidemiology, and End Results (SEER) program, it is estimated that in 2019, there were 74,200 new NHL cases in the U.S., which constitute approximately 4.2% of all new cancer cases. Additionally, there were an estimated 19,970 deaths from NHL in 2019 (<https://seer.cancer.gov/statfacts/html/nhl.html>). The median age at the diagnosis of DLBCL is 64 years, and the majority of patients present with advanced disease.

The standard of care for first-line therapy for DLBCL regardless of stage is R-CHOP; however, approximately 30% of patients relapse despite having achieved complete remission (CR), and a further 20% of patients are refractory to R-CHOP (Coiffier and Sarkozy 2016; Sehn and Gascoyne, 2015). Patients with disease that has relapsed or is refractory to R-CHOP have a poor prognosis with short survival times, ranging 6-12 months (Coiffier and Sarkozy, 2016; Smith et al., 2015, Crump et al 2017, Farooq et al., 2017). For the minority of patients who are fit for high-intensity therapy, it may be possible to achieve cure using intensive re-induction immunochemotherapy, followed by high-dose chemotherapy (HDC) with subsequent autologous stem cell transplantation (ASCT). In transplant-eligible R/R DLBCL patients, cure is achieved in approximately 10% of cases. The remaining 90% will eventually relapse again and succumb to their disease (Van Den Neste et al., 2016).

The majority of patients with relapsed/refractory (R/R) DLBCL are not eligible for intensive immunochemotherapy and ASCT, generally due to advanced age or co-morbidities. The NCCN guidelines recommend that these or patients who relapse after ASCT participate in a clinical trial or receive third-line systemic therapies, palliative involved-site radiotherapy or best supportive care treatments, indicating a lack of effective treatment options. The development of novel therapies is required due to the continued unmet medical need in patients with R/R DLBCL.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment above.

2.2. Analysis of Current Treatment Options

R-CHOP is the standard of care for all newly-diagnosed patients; approximately 40% of patients will ultimately relapse or progress (Vitolo et al., 2017). In patients whose disease progresses or relapses after first-line treatment, salvage chemotherapy options such as DHAP (cisplatin, cytarabine, dexamethasone), DHAX (dexamethasone, cytarabine, oxaliplatin), ICE (ifosfamide, carboplatin, etoposide), or GDP (gemcitabine, dexamethasone, cisplatin/carboplatin), with or without the anti-CD20 mAb rituximab followed by HDC with ASCT offer the potential for cure. HDC/ASCT significantly improves disease-free survival and overall survival (OS) in patients with relapsed / refractory DLBCL (Gisselbrecht et al., 2010; Philip et al., 1995).

However, HDC/ASCT may not be appropriate, especially in patients who are chemorefractory, have comorbidities or are older, and this applies to a significant proportion of patients with R/R DLBCL. Approximately 25% of patients with R/R DLBCL undergo HDC/ASCT . For the remaining patient population, several second-line combination therapies such as B-R, R-GemOx, R-Lenalidomide and other therapies as per NCCN guidelines are used with variable success.

Recently, three new therapies have been approved for DLBCL patients who have progressed after second-line therapy. These comprise two chimeric antigen receptor (CAR) T-cell therapies (CAR-T therapies), axicabtagene ciloleucel (Yescarta™) and tisagenlecleucel (Kymriah™) as well as the antibody-drug conjugate polatuzumab vedotin, in combination with bendamustine and rituximab (Pola + BR). Both CAR-T cell therapies target CD19, the same antigen as tafasitamab, whereas polatuzumab vedotin targets the CD79b antigen.

Table 1: FDA-Approved Therapy for Relapsed/Refractory DLBCL

Product Name	Relevant Indication	Year and type of approval	Efficacy Information*	Important Safety and Tolerability Issues
FDA Approved Treatments				
Yescarta (axicabtagene ciloleucel)	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	18 Oct 2017 Regular approval	ORR 72% CR 51% mDoR 9.2 months	Cytokine Release Syndrome Neurologic toxicity

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Product Name	Relevant Indication	Year and type of approval	Efficacy Information*	Important Safety and Tolerability Issues
Kymriah (tisagenlecleucel)	Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma	1 May 2018 Regular approval	ORR 50% CR 32% mDoR not reached	Cytokine Release Syndrome Neurologic toxicity
Polivy (Polatuzumab vedotin)	In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.	10 Jun 2019 Accelerated approval	ORR 63% CR 50% mDoR not reached	Peripheral neuropathy

*Data extracted from US labels

The Applicant’s Position:

The CAR-T cell therapies may produce durable CRs, but their use has limitations because of the toxicity profile, which requires rigorous selection criteria and inpatient administration, and restricted availability in tertiary care facilities. Additionally, the waiting period associated with CAR-T manufacture may be prohibitive in patients with symptomatic or rapidly progressing disease. Polatuzumab vedotin received accelerated approval for use in combination with bendamustine and rituximab (pola-BR). All three recently approved products are licensed for use in the third-line setting (after failure of two or more prior systemic therapies). There is no FDA-approved therapy for patients with R/R DLBCL after failure of one prior therapy, or for patients who are unable to receive CAR-T therapy.

The FDA’s Assessment:

There is no FDA approved therapy for patients with R/R DLBCL after one prior therapy or ineligible for autologous stem cell transplant. FDA also agrees that although these CAR-T cell therapies can produce durable CRs, their use has limitations in the general R/R DLBCL population. FDA also notes that other combination salvage regimens include platinum, etoposide, and/or cytarabine based combination regimens and gemcitabine-based regimens. FDA notes the following:

The proposed intended population for tafasitamab is different than the populations for tisagenlecleucel and axicabtagene ciloleucel mentioned by the Applicant in Table 1. The proposed indication for tafasitamab is in combination with lenalidomide followed by MONJUVI monotherapy for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for, ^{(b) (4)} ASCT usually due to advanced age or co-morbidities. The intended population for tafasitamab and polatuzumab vedotin are similar, as trials supporting the approval of drugs have enrolled patients not a candidate for SCT, however polatuzumab vedotin received accelerated approval in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies. Additionally, selinexor received accelerated approval in June 2020, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (RR DLBCL), not otherwise specified, who have received at least 2 prior therapies. The IRC assessed ORR was 29% (95% CI: 22, 38) and CR rate was 13% according to Lugano criteria

3 Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Tafasitamab is not currently marketed in the U.S.

The FDA's Assessment:

The clinical reviewer agrees with above.

3.2.Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The key U.S. pre-submission activities are outlined in Table 2. Tafasitamab has been studied under IND 114856 (since 2012) and IND (b) (4) (since 2019) (b) (4)

Table 2: Key Regulatory Interactions Related to BLA 761163

Date	Regulatory Interaction
29 Jan 2010	Original IND (b) (4) submitted by prior sponsor Xencor, Inc.
21 Sep 2012	IND 114856 submitted
29 Oct 2014	Fast track designation granted
01 Dec 2014	Orphan drug designation granted for the treatment of diffuse large B-cell lymphoma.
23 Oct 2017	Breakthrough therapy designation granted in combination with lenalidomide for the treatment of patients with relapsed or refractory diffuse Large B-Cell Lymphoma (DLBCL) who are not eligible for high-dose chemotherapy and autologous stem-cell transplantation.
24 Jan 2018	Multidisciplinary Type B meeting following BTD to discuss overall development plan for CMC comparability, non-clinical and clinical development plan, including initial discussion of data MorphoSys could provide to demonstrate lenalidomide monotherapy activity in this disease setting.
01 Aug 2018	Type B clinical meeting to discuss data sources for lenalidomide monotherapy; RWE introduced as possible source, but Agency recommended another meeting with full proposal for RWE.
09 Nov 2018	Type C meeting to discuss with FDA on RWD to provide evidence for lenalidomide monotherapy cohort, including using a matching approach.
12 Mar 2019	FDA Advice Letter agreeing to timing of DS PPQ submission to BLA.

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Date	Regulatory Interaction
15 Apr 2019	FDA response and comments on RWD proposal for observational retrospective cohort of lenalidomide (LEN) monotherapy.
01 Jul 2019	Pre-BLA meeting to agree on content and format of BLA submission.
29 Jul 2019	FDA Advice Letter to propose schedule for manufacturing site inspections.

The FDA's Assessment:

Relevant discussions from prior meetings are summarized below:

Type C Meeting December 2, 2014

The focus of this meeting was a randomized trial comparing tafasitamab + bendamustine versus rituximab + bendamustine. The population proposed for this trial was patients who are not eligible for intensive therapy including SCT. It was discussed that patients who are eligible for standard therapy but are unwilling or refuse to undergo SCT should not be included in a registrational trial. The Agency had concerns with the dosing regimen and recommended before beginning a planned pivotal trial that integrated dose-response and exposure response analyses should occur.

Type A Meeting August 10, 2015

This meeting was to discuss non-agreement on a Special Protocol Assessment for a protocol of titled "A Phase III, Randomized, Multicenter Study of MOR00208 with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL) Who Are Not Eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT). While this is not the trial submitted in support of this Application, some of the discuss that occurred is relevant and summarized below:

- At this time, the Agency did not agree with a dose of 12 mg/kg as an optimal dose for single agent use as an integrated dose-response analysis for safety and activity to should be done. It was discussed the Applicant should investigate the trend of exposure-weight relationship in order to determine whether weight based dosing or flat dosing was the optimal dosing regimen.
- Regarding the proposed criterion for ineligibility for SCT it was discussed that age >60 is not a contraindication to SCT. It was also discussed that some criteria assessed by the treating physician are nondescript and would be problematic for labeling.

Type C Meeting June 28, 2017

This meeting occurred to discuss a Special Protocol Assessment of the trial entitled "A Phase III, Randomized, Multicenter Study of MOR00208 with Bendamustine versus Rituximab with

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Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Are Not Eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell-Transplantation (ASCT)". During this meeting the Agency expressed concerns regarding continued monotherapy treatment with monoclonal antibodies tafasitamab or rituximab in patients with DLBCL. The Agency suggested a second randomization prior to maintenance.

Type B Meeting January 24, 2018

The Applicant requested this meeting to discuss further development and filing for tafasitamab. At this time the Agency had concerns regarding an initial application based on the L-MIND trial, a single arm trial that evaluates tafasitamab in combination with lenalidomide. For approval, the Applicant was informed evidence of the activity of single agent tafasitamab would be needed, as the contribution of tafasitamab to the efficacy of the combination could not be determined in the L-MIND trial. Also following concerns were also mentioned:

- Time to event endpoints such as PFS, TTP, and OS are not interpretable from single arm trials.
- Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

Type B Meeting August 1, 2018

The purpose of this meeting was to discuss further clinical development and filing strategy. At this meeting, the Applicant notified the Agency of the strategy to compare the combination of tafasitamab and lenalidomide to lenalidomide monotherapy by a comparative network meta-analysis with published data of clinical trials with lenalidomide monotherapy in R/R DLBCL and to compare the combination of tafasitamab and lenalidomide with all published data of regimens listed in NCCN guidelines for the treatment of patients with r/r DLBCL not eligible for SCT. The Agency did not agree with this approach. The Agency reiterated the need for person level data for patients in the historical control. The Agency also stressed the importance of measuring endpoints the same way between patients in L-MIND and the RWE patients.

Type C Meeting September 12, 2018

This meeting was to discuss a planned protocol amendment for clinical study MOR208C204 entitled, "A Phase III, randomized, multicenter study of MOR00208 with Bendamustine versus Rituximab with Bendamustine in patients with relapsed or refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL) who are not eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT)". This meeting was focused on a trial not submitted with this Application, NKCC high vs NKCC low testing, co primary endpoints and hierarchical testing.

Type C Meeting November 9, 2018

This meeting was focused on the use of Real World Data included with this submission. During this meeting the following concerns were discussed:

- The data quality from the L-MIND study may differ from the lenalidomide monotherapy cohort. There may be differences in type of data, missing data and different follow up. The Applicant was instructed to provide summary data such as the amount of missing data and duration of follow up to demonstrate comparability. For each data element the Applicant should provide evidence that the data can be captured adequately, accurately and non-differentially.
- The lenalidomide monotherapy cohort should resemble patients in the L-MIND study. It was recommended a matching approach be used rather than the overlap weights approach. The lenalidomide monotherapy cohort should be induced by matching patients from the database to patients in the L-MIND study. The Agency acknowledged that this could lead to sample size attrition. However, the Applicant was informed that substantial attrition is indicative of two very different populations, such that, it may not be reasonable to compare them.
- The concern of covariates, measured or unmeasured, may affect the outcome was also discussed. The Applicant was informed that when conducting observational studies, matching on as many reasonable covariates should occur. The Applicant had listed age, Ann-Arbor stage, IPI score, refractoriness to previous line of therapy, number of prior lines of therapy, history of primary refractoriness, and prior ASCT. It was mentioned other covariates such as laboratory values prior to index date should be included.
- The Applicant was informed at this time the Agency does not accept imputation of missing covariates for the purpose of estimating propensity scores.
- Concern regarding the collection of response data for assessment of the ORR endpoint was raised. Data from the clinical notes alone may not allow assessment of different aspects of response criteria. It was recommended the Applicant consider a validation study in patients who have clinical notes and imaging to ensure robustness of the data.
- Outcome misclassification was also discussed. Is a reported response an actual response? Is a reported lack of response an actual lack of response? The response rate in the lenalidomide monotherapy cohort may not be identifiable as it can be contaminated by the misclassification process. The Applicant was also informed that misclassification can affect covariates such as medical history, disease, staging, prior therapies at the time of the lenalidomide monotherapy index date. It was critical that values at the time of the index date were accurately captured.
- For an accurate assessment of the endpoints a minimum duration of follow up of 6 months for each patient included in the monotherapy cohort was recommended.
- Only patients with in initial dose of 25 mg of lenalidomide at the index date in the lenalidomide monotherapy cohort should be included.

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- The sponsor expressed concerns regarding the exclusion of patients with missing baseline covariates, which the Agency acknowledged, however, it was discussed that the goal is to learn about lenalidomide monotherapy activity in patients whose characteristics closely resemble those in the L-MIND trial.
- The Agency had concerns regarding the ability to capture duration of response in the external databases.

Type C Meeting February 4, 2019

This meeting was to obtain agreement of the biomarker drives protocol amendment of the ongoing B-MIND trial. This trial is currently ongoing and not submitted with this application.

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

4.1. Office of Scientific Investigations (OSI)

A single clinical investigator site, Johannes Duell, M.D., (b)(4), the contract research organization [CRO] for Study MOR208C203, (b)(4) CRO for Study MOR208C206 (b)(4), and MorphoSys (sponsor) were part of a remote site data investigation in support of BLA 761163.

A remote site investigation for study MOR208C203 was done for Johannes Duell, M.D. in Wurzburg, Germany. A total of 7 patients were screened and enrolled at this site. Based on the investigation, the study data derived from Dr. Duell's clinical site was considered reliable. The primary efficacy endpoint, as assessed by the principal investigator was verifiable at this site. This clinical investigator appeared to be in compliance with Good Clinical Practice.

A remote site investigation for The Applicant, MorphoSys in Germany was conducted. This investigation involved review of organizational charts, transfer of obligations, investigator agreements, and financial disclosures with the sponsor. At the end of the audit, some observations and concerns were raised. This included inadequate monitoring, monitors failed to identify noncompliance for subject ineligibility and investigational product dosing errors. There were patients who failed to meet inclusion and/or exclusion criteria prior to randomization and were not identified during the periodic monitoring, see Table 3. The OSI reviewer notes the sponsor's monitoring obligations were transferred to the CRO. The OSI reviewer also states the violation may not have significantly impact on the safety and welfare of the patients and they do not appear to impact data reliability or safety as they were isolated.

Table 3: Patients Who Failed to Meet Criteria and Were Not Identified During Monitoring

Subject#	Inclusion/Exclusion Criteria
(b)(6)	Exclusion criteria 1b
	Exclusion criteria 1b
	Exclusion criteria 1b
	Exclusion criteria 1b
	Exclusion criteria 1b and inclusion criteria 4a
	Inclusion criteria 3
	Exclusion criteria 2d

Key to inclusion/exclusion criteria

Exclusion criteria 1b: primary refractory DLBCL

Inclusion criteria 3: tumor sample sent to the central pathology lab greater than 3 months

Inclusion criteria 4a: relapsed/refractory disease criteria not met

Inclusion criteria 2d: IV antibiotics administered within 14 days of treatment C1D1

The OSI reviewer also notes isolated dosing errors for patients who were not identified during the periodic monitoring and that a site monitor failed to ensure the clinical investigator obtained pregnancy prevention plans from each patient prior to enrollment at each visit. The OSI reviewer noted the Applicant acknowledged the above observations and provided adequate written response. The monitoring obligations had been transferred to the CRO. Although the CRO failed to conduct adequate monitoring, based on the OSI review and the Applicant's response, the finding was considered unlikely to impact data reliability nor compromise the rights, safety and welfare of patients in the study.

Also noted during the remote site investigation for The Applicant, MorphoSys, it was discovered the Applicant failed to recognize accurate status of drug and there was inadequate drug accountability. This responsibility was transferred to (b) (4). The OSI reviewer notes, based on review and sponsor's response, all patients appeared to have adequate drug accountability. This finding, based on the OSI reviewer comments, was unlikely to impact study data reliability, nor did it compromise the rights, safety and welfare of patients.

The CRO, (b) (4) was also remotely investigated. This investigation evaluated the compliance with the sponsor's transferred responsibilities regarding trial MOR208C203. At the conclusion of this investigation, one concern was raised, which was, failure to follow the monitoring plans for the trial. The investigation also detected additional eligibility violations which were not previously detected.

A remote site investigation was also done for (b) (4) the CRO for study MOR208C206, the observational retrospective study. The OSI reviewer concluded that (b) (4) (b) (4) appeared to have adequate oversight of study MOR208C206 and clinical trial monitoring appeared to be adequate.

Reviewer Comments:

The above was taken from Clinical Inspection Summary dated June 30, 2020 from Anthony Orencia M.D., F.A.C.P., Medical Officer, Min Lu, M.D., M.P.H., Team Leader and Kassa Ayalew, M.D., M.P.H., Branch Chief

As a result of the OSI remote audit inspections, the Applicant submitted a response to address the observations raised by the OSI review. The Applicant's response document was reviewed and the responses were considered adequate. In this document the Applicant provided potential underlying reasons, improvement measures that have been implemented and a plan to further strengthen the oversight systems.

4.2.Product Quality

Novel excipients: No

Any impurity concern: None

See CMC review for details related to product quality.

4.3.Clinical Microbiology

See Clinical Microbiology review for details.

4.4.Devices and Companion Diagnostic Issues

A device or companion diagnostic was not part of this review.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Tafasitamab (also known as MOR00208, MOR208, and XmAb5574) is a humanized IgG1/2 hybrid Fc-modified monoclonal antibody that targets CD19, a cell surface protein expressed on B cells and follicular dendritic cells of the hematopoietic system and on several B-cell malignancies including DLBCL^{1,2}.

Tafasitamab bound to human CD19 antigen with an average dissociation constant (K_D) of approximately 0.4 nM. Comparable binding of tafasitamab was observed to CD19-expressing lymphocytes of human, cynomolgus monkey, and rhesus monkey, and low-affinity binding to dog, rabbit, rat, and mouse lymphocytes. Tafasitamab exhibited similar binding affinities to human and monkey Fc gamma receptor (FcγRs). There was no off-target binding of tafasitamab detected in tissue panels from the human and cynomolgus monkey. Tafasitamab bound to mononuclear leukocytes in the majority of tissues examined, lymphocytes in blood, and hematopoietic precursor cells in the bone marrow in both species. Based on these findings, the cynomolgus monkey was chosen as the relevant toxicology species.

The in vitro activity of tafasitamab was assessed in human B-cell lines, as well as primary cells derived from patients with hematological malignancies. Upon binding to CD19, tafasitamab mediates B-cell lysis of tumor cells through apoptosis, mainly antibody dependent cellular cytotoxicity (ADCC), and antibody-dependent cell-mediated phagocytosis (ADCP). Tafasitamab showed ADCC activity in several CD19+ lymphoma cell lines including DLBCL; with NK-mediated lysis of 25 to 90% of lymphoma cells, a half-maximal concentration (EC_{50}) values of 1 to 10 ng/mL was observed. Tafasitamab induced macrophage-mediated ADCP in CD19+ ALL cell lines with a maximal phagocytosis of 30-40% at tafasitamab concentrations of 1 to 10 ng/mL. In in vitro studies, treatment of DLBCL cells with the combination of tafasitamab and lenalidomide resulted in increased ADCC activity compared to tafasitamab or lenalidomide alone. In the absence of effector cells, tafasitamab induced apoptosis in DLBCL cells (SU-DHL-6). The apoptotic activity was greater with tafasitamab compared to control antibodies containing the same CD19-binding domain but non-modified Fc domain (anti-CD19 IgG1 analog) or Fc-knockout (anti-CD19 Fc-KO). The in vivo anti-tumor activity of tafasitamab at doses ranging from 1 to 10 mg/kg was demonstrated in xenograft models bearing human lymphoma tumors.

The safety of tafasitamab was evaluated in GLP-compliant 8- and 13-week general toxicology studies in cynomolgus monkeys. Monkeys received tafasitamab by intravenous (i.v.) infusion

¹ Tedder, T. F., Isaacs, C. M. Isolation of cDNAs encoding the CD19 antigen of human and mouse B lymphocytes: a new member of the immunoglobulin superfamily. J. Immun. 143: 712-717, 1989.

² Olejniczak SH et al 2006. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry: Immunol Invest. 2006;35(1):93-114.

once every two weeks at 2, 10 or 50 mg/kg in the 8-week study, or once every week at 0, 10, 30 or 100 mg/kg in the 13-week study. Monkeys were observed for 90 days and 132 days for recovery following the dosing periods in the 8-week and 13-week studies, respectively. In the 8-week study, tafasitamab caused marked B-cell depletion at all doses tested, consistent with its pharmacological activity; the effects were reversible. Decreases in B-cell were associated with decreased white blood cell counts and absolute lymphocytes, decreased spleen weights, and altered spleen histology (decreased cellularity of the splenic germinal center). ADAs were detected in 47% of tafasitamab-treated monkeys, resulting in enhanced clearance of tafasitamab in the 8-week study. In the 13-week toxicology study, reductions in lymphocytes, WBC, and neutrophils were less pronounced compared to the results observed in the 8-week study. The results may suggest presence of neutralizing ADAs that were not detected due to high circulating tafasitamab levels. In the 13-week study, neurological behavioral changes including tremors and changes in body temperature were observed. The number of animals affected and the number of incidences of the tremors were higher at the high dose. The tremors resolved following the termination of dosing. Statistically significant differences in body temperature (100-102°F) were observed mainly at 100 mg/kg during dosing that recovered in the recovery period. There were no effects on menstrual cycle length in females and no histopathology/ microscopic changes in male and female reproductive organs. Mean maximum serum concentration (C_{max} observed after the 13th dose) and exposure (AUC_{0-144h}) in cynomolgus monkeys dosed at 100 mg/kg in the 13-week study were 4595 $\mu\text{g/mL}$ and 8375 $\mu\text{g}\cdot\text{day/mL}$, respectively. This is approximately 8 to 9-fold the corresponding values in humans observed in clinical study (Study No. MOR208C201) with weekly dosing at 12 mg/kg (mean C_{max} = 547.4 $\mu\text{g/mL}$; Mean AUC_{0-last} = 914.3 $\mu\text{g}\cdot\text{day/mL}$).

Based on a prior agreement with the FDA, the Applicant did not conduct reproductive and developmental toxicity studies with tafasitamab since tafasitamab is administered in combination with lenalidomide, a known teratogen and embryo-fetal toxicant. The Applicant submitted other information in the weight-of-evidence (WOE) reproductive risk assessment on the potential effects of tafasitamab (monotherapy) on embryofetal development, consistent with the Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry. Based on the WOE risk assessment, treatment of pregnant women with tafasitamab may result in depletion of B cells and thus dysfunction of immune response in a newborn. This risk has been communicated in the tafasitamab label. Normal B-cell counts and immunologic function may be restored based on reversibility of effects in animal studies. The contraception duration listed in the label is until at least 3 months after the last dose and covers a period of at least 5 half-lives for tafasitamab ($T_{1/2}$ = 17 days). Additionally, lactating women are advised not to breastfeed during treatment and for 3 months after the last dose.

Carcinogenicity studies are not necessary to support the marketing of therapeutics intended to treat patients with advanced cancer as discussed in the ICH S9 guidance document.

Genotoxicity studies are generally not necessary to support marketing of biotechnology-derived pharmaceuticals such as tafasitamab as discussed in the ICH S6 guidance document.

The nonclinical studies submitted to this BLA provide sufficient information to support the use of tafasitamab (Monjuvi), in combination with lenalidomide, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). From the nonclinical pharmacology and toxicology perspective, tafasitamab (Monjuvi) is recommended for approval.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for tafasitamab.

5.3. Pharmacology

Primary Pharmacology

The FDA agrees with the primary pharmacology data summarized by the Applicant that describes tafasitamab's pharmacological effects including ADCC, ADCP activities, apoptosis of tumor cells and the increased anti-tumor activities in combination with lenalidomide. Tafasitamab does not mediate complement-dependent cytotoxicity (CDC).

Binding affinity of tafasitamab to human CD19 was measured in cell-based formats (study #TR07098). Tafasitamab bound to CD19-expressing human embryonic kidney (HEK) 293 cells transfected with a human CD19 expression plasmid in a concentration-dependent manner with an observed half-maximal concentration (EC_{50}) of 0.72 $\mu\text{g}/\text{mL}$, or 4.8 nM. CD19-expressing human tumor cell lines (Raji and RS4;11), were used to determine the steady-state cell binding by measuring the equilibrium dissociation constant (K_D) by flow cytometry. The steady-state cell binding assays indicated that tafasitamab binds cell-surface CD19 in the range of 0.29 to 0.46 nM, resulting in an average K_D of approximately 0.4 nM.

Binding of tafasitamab to CD19-expressing lymphocytes from multiple mammalian species was assessed to identify the relevant species for toxicological evaluation (study #XC9-23209). Whole blood samples from human donors, cynomolgus and rhesus monkeys, dogs, rabbits, rats, and mice were evaluated in flow cytometric studies using fluorescein isothiocyanate conjugated (FITC) tafasitamab. Binding of tafasitamab-FITC to human, cynomolgus monkey and rhesus monkey lymphocytes was comparable. Tafasitamab showed lower binding to rat and mouse, and no binding to dog and rabbit lymphocytes.

Tafasitamab binding characteristics to human, cynomolgus monkey, and mouse FcγRs were determined using a surface plasmon resonance (SPR)-based method (study # TR08137). Antibodies were immobilized on a protein A/G chip surface and injected with serially diluted recombinant FcγR proteins. The affinity of tafasitamab increased relative to IgG1 (native IgG1 control) for all FcγRs with the strongest increase observed for the FcγRIIIa variants for human and monkey. In addition, tafasitamab exhibited similar binding affinities to human and monkey FcγRs; the human-to-monkey fold difference in K_D was 0.4 for FcγR1, 1.1 for FcγRIIa, 1.4 for FcγRIIb, and 2.5 for FcγRIIIa. These studies support the use of the cynomolgus monkey as a pharmacologically relevant test model.

In vitro activity of Tafasitamab against tumor cell lines

In vitro and in vivo pharmacology studies with tafasitamab used several controls antibodies (mAbs) for comparison purposes. See details in the table below.

Table 4: Control Antibodies Used in the Pharmacology Studies with Tafasitamab

Name	mAb	Characteristics
XENP5603 (also known as IgG1, 5603_IgG1, IgG1 analog, Xmab5603, non-Fc-enhanced Xmab5603)	Anti-CD19 IgG1	Possesses the same CD19 binding domain as tafasitamab but carries a non-engineered human IgG1 Fc-domain.
XENP6187 (also known as Fc-KO, 6187_KO)	Fc-Knockout	Possesses the same CD19 binding domain as tafasitamab, but carries G236R/L328R mutations in the human IgG1 Fc-domain, which are intended to abrogate interactions with Fc gamma receptors
XENP4614 (also known as IgG1 control, negative control IgG1 antibody)	XmAb isotype control	Possesses no binding to CD19 antigen

Antiproliferation activity

The antiproliferative and apoptosis properties of tafasitamab related to direct interaction between the target antigen, CD19, and the variable region (Fv) of tafasitamab were evaluated (Study # TR08138). These assays were carried out using DLBCL derived SU-DHL-6 cells in the presence of tafasitamab or control antibodies crosslinked by FcγRIIIa-GST. Secondary crosslinking of FcγRIIIa-GST tag was used to simulate in vivo effects, but there were no effector cells present in these assays (e.g., no PBMCs). The antiproliferative activity of tafasitamab (assessed by ATP levels) was compared with those of control antibodies, an anti-CD19 IgG1 analog (XENP5603 or IgG1), and an anti-CD19 Fc-KO (Fc-knockout; XENP6187) that knocks

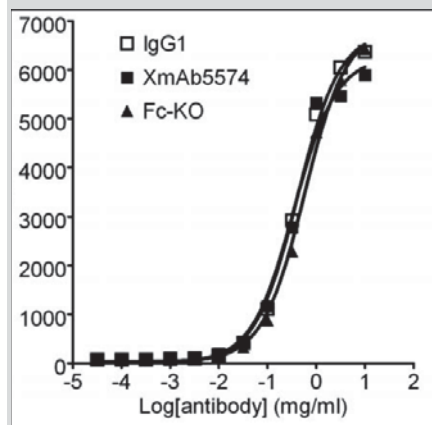
binding to FcγRs. These antibodies have the identical Fv region and equal affinity to CD19 binding, thus any differences in proliferation may represent differences in the Fc domain. In addition, an isotype XmAb control (XENP4614) was included as a negative control that does not bind to CD19. The crosslinked antibodies were incubated with SU-DHL-6 cells for 72 hours and cell titers were analyzed using a cell viability assay. Tafasitamab exhibited relatively higher antiproliferative activity compared to the control antibodies (IgG1 analog and Fc-KO), suggesting that modifications to the Fc domain may have contributed to this mode of action.

Apoptosis

Assay conditions were the same as described above for antiproliferative activity. Caspase activation and annexin V staining were used to detect apoptosis. The crosslinked antibodies and SU-DHL-6 cells were incubated for 48 hours. Caspase activity was quantitated using a fluorometric assay (Panel B in figure below). For the annexin V assay, cells were labeled with annexin V-PE and 7-amino-actinomycin D, and fluorescence was analyzed by flow cytometry.

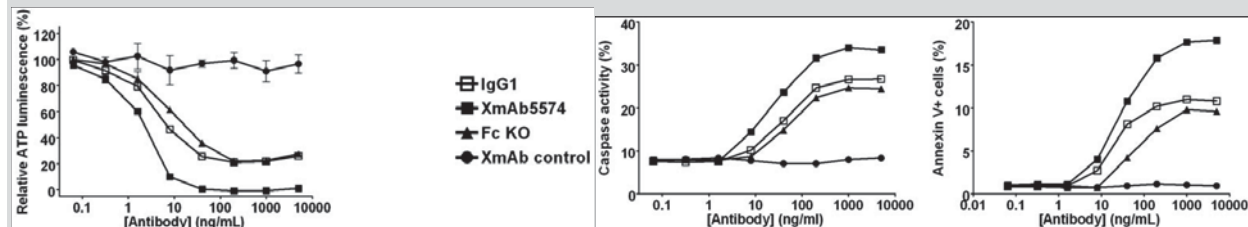
Tafasitamab exhibited relatively higher apoptosis activity compared to the control antibodies (IgG1 analog and Fc-KO). Since no effector cells were present, results suggest that antiproliferative activity may be through induction of apoptosis and modifications to the Fc domain. In this study, tafasitamab-induced apoptosis in a DLBCL cell line (SU-DHL-6) with a maximum percentage of caspase activity of ~34% and Annexin-V-positive cells of ~17%.

Figure 1: Binding of Tafasitamab and Its IgG1 and Fc-KO Analogs to CD19+ Cells



Binding of antibodies to CD19+ RS4;11 cells (ALL cell line) was tested by flow cytometry.

Figure 2: Anti-Proliferative Activity and Caspase-Mediated Apoptosis Activity of Tafasitamab



Studies were performed on SU-DHL-6 cells using a human FcγRIIIa-GST fusion receptor to provide antibody crosslinking. Cross-linked antibodies were used to assess both anti-proliferative and apoptotic activity of tafasitamab in comparison with control antibodies.

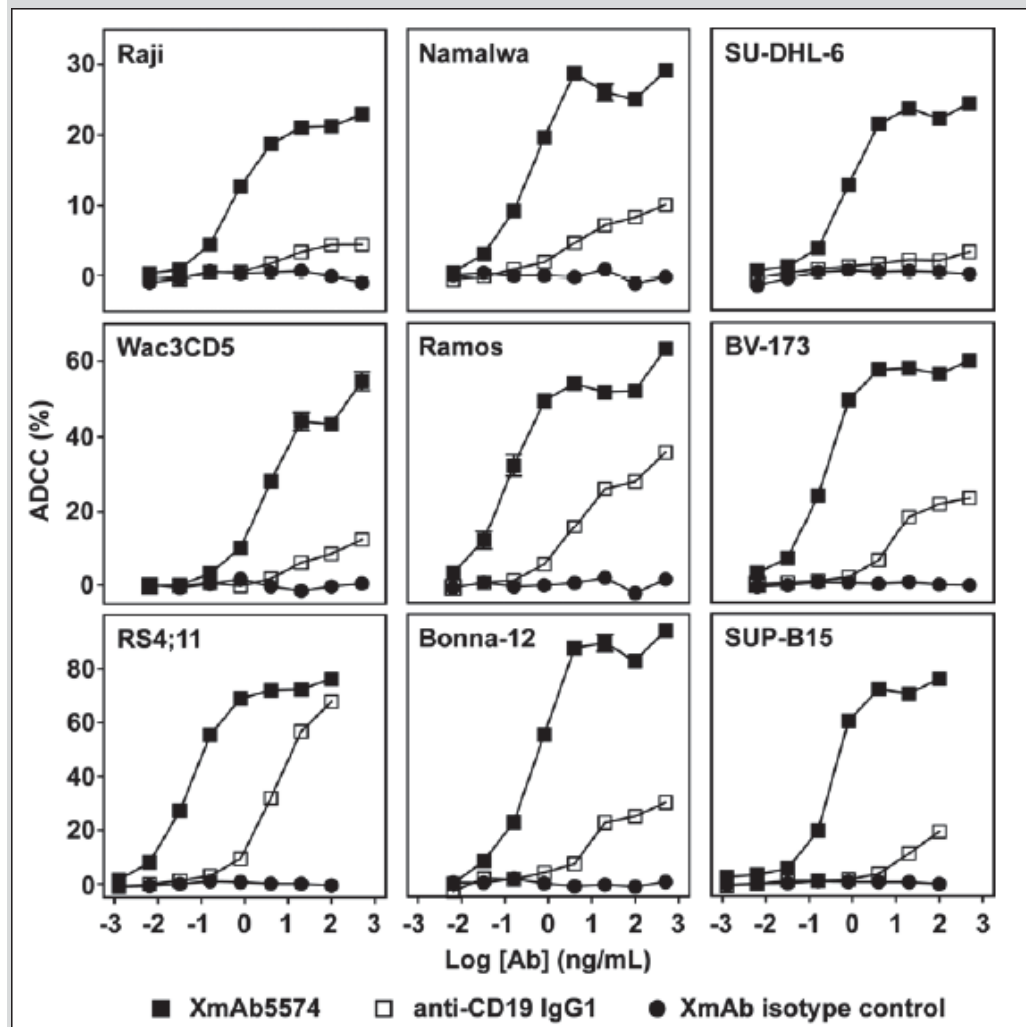
Effector function

The Fc-mediated immune effector function properties including ADCC, and ADCP activities of tafasitamab were evaluated in cell based assays in vitro against multiple CD19+ expressing tumor cell lines and primary tumors (Study # TR08139, MOR208L029).

Antibody-dependent cell-mediated cytotoxicity

For the ADCC assay (Study # TR08139), isolated interleukin-2 (IL-2)-activated natural killer (NK) cells were used as effector cells. Target cells included CD19+ tumor cell lines with varying levels of CD19 antigen (15,000 to 105,000 molecules/cell). XENP5603, an anti-CD19 IgG1, and XENP4614, an XmAb isotype, were used as control antibodies. Tumor cells were incubated with antibodies at different concentrations for opsonization. Effector cells and target were co-cultured and lactate dehydrogenase (LDH) activity was measured using the cytotoxicity detection kit. Tafasitamab induced immune cell mediated ADCC (cell lysis) of 25% to 90% with no correlation with cell surface CD19 expression level; the EC₅₀ ranged from 0.1 to 1 ng/mL. The ADCC effect was 100- to 1000-fold over the anti-CD19 IgG1 control antibody likely related to modifications made to Fc region of tafasitamab.

Figure 3: NK Cell Mediated ADCC Activity of Tafasitamab (XmAb5574) Against Multiple Tumor Cell Lines



The ADCC activity of the tafasitamab mediated by $\gamma\delta$ T-cells (immune effector cells) derived from donors was also evaluated (Study #MOR208L029). T-cells ($\gamma\delta$) appear to recognize malignant cells, infiltrate tumors, and induce cytotoxic and pro-inflammatory activities³. T-cells ($\gamma\delta$) were isolated from donors and used as effector cells at different effector-to-target (E:T) cell ratios. Five lymphoma and leukemia cell lines as well as patient-derived (CLL, MCL and B-ALL) cells were used as target cells. Target cells were stained with carboxyfluorescein succinimidyl ester (CFSE) and treated with tafasitamab, Xmab5603 (non-Fc-modified antibody) or an IgG1 negative control antibody. Effector cells were added to the stained target cells and incubated for 4 hours. The lysis of target cells was determined using FACS analysis. Tafasitamab showed

³ Hoeres, T., et al., (2018): Improving the Efficiency of V γ 9V δ 2 T-Cell Immunotherapy in Cancer. In *Frontiers in immunology* 9, p. 800.

increased cell killing activity compared to control antibodies (tafasitamab >Xmab5603>IgG1 control) in five cell lines and in patient-derived cells.

The in vitro ADCC of tafasitamab in combination with lenalidomide (LEN) against DLBCL cell lines was investigated (MOR208L039). The immunomodulatory drug lenalidomide activates T cells to release the cytokines interferon gamma (IFN- γ) and interleukin-2 (IL-2), which stimulate NK cell activity and lead to increased NK cell numbers^{4,5}. Consequently, treatment in combination with lenalidomide appears to increase tafasitamab-mediated NK-cell activation and ADCC activity⁶.

The antitumor activity of tafasitamab, LEN or the combination of both was determined with peripheral blood mononuclear cells (PBMCs) isolated from healthy donors as effector cells and DLBCL cell lines (SU-DHL-2, -4, -6 and U-2932) as target cells. PBMCs were preincubated for 72 hours in the presence of 10 μ M LEN or DMSO (vehicle control). Subsequently, the pre-incubated cells were utilized in a FACS-based cytotoxicity assay in the presence or absence of tafasitamab to compare the cytotoxic effects of single agent or combination. Cytotoxicity was measured by quantification of dead and viable cells using the fluorescent DNA binding dye 4',6-diamidino-2-phenylindole (DAPI).

Tafasitamab-mediated ADCC activity in DLBCL cells was increased after lenalidomide pre-treatment of PBMCs, resulting in an average increase of up to 10% (See table below) compared to LEN or tafasitamab alone. The results show that the combination of tafasitamab with lenalidomide resulted in increased cytotoxicity on DLBCL cell lines over single agent in vitro. Similar experiments conducted with NK cells isolated from six healthy donors showed enhancement of ADCC (~8%) for the combination (tafasitamab and LEN) compared to treatment with single-agent tafasitamab, in four out six donors.

⁴ Kotla V, et al (2009). Mechanism of action of lenalidomide in hematological malignancies. J Hematol Oncol. 2009 Aug 12;2:36.

⁵ Gribben JG, et al (2015). Mechanisms of action of lenalidomide in B-Cell Non-Hodgkin Lymphoma. J Clin Oncol. 2015 Sep 1;33(25):2803-11.

⁶ Awan, FT. (2010): CD19 targeting of chronic lymphocytic leukemia with a novel Fc-domain-engineered monoclonal antibody. In Blood 115 (6), pp. 1204–1213.

Table 5: Tumor Lysis Activity of Tafasitamab, LEN, or Combination of Both

Cell line	Donor	Internal donor ID	Experiment	Sample	Replicate	E:T	Cytotoxicity [%]	Mean [%]	Mean (MOR208/LEN) - Mean (MOR208) [%]		
SU-DHL-4	Donor 1	312	115APO07	MOR208	1	10:1	25.1	26.3	15.6	Average: 10.2 %	
SU-DHL-4	Donor 1	312	115APO07	MOR208	2	10:1	27.4				
SU-DHL-4	Donor 1	312	115APO07	LEN	1	10:1	2.9	2.9			
SU-DHL-4	Donor 1	312	115APO07	LEN	2	10:1	2.9				
SU-DHL-4	Donor 1	312	115APO07	MOR208/LEN	1	10:1	41.7	41.8			
SU-DHL-4	Donor 1	312	115APO07	MOR208/LEN	2	10:1	41.9				
SU-DHL-4	Donor 2	140	115APO11	MOR208	1	5:1	20.7	18.6			
SU-DHL-4	Donor 2	140	115APO11	MOR208	2	5:1	16.5				
SU-DHL-4	Donor 2	140	115APO11	LEN	1	5:1	5.4	7.2			
SU-DHL-4	Donor 2	140	115APO11	LEN	2	5:1	9.0				
SU-DHL-4	Donor 2	140	115APO11	MOR208/LEN	1	5:1	27.3	27.6			
SU-DHL-4	Donor 2	140	115APO11	MOR208/LEN	2	5:1	27.90				
SU-DHL-4	Donor 3	309	115APO13	MOR208	1	10:1	28.1	29.1			
SU-DHL-4	Donor 3	309	115APO13	MOR208	2	10:1	30.1				
SU-DHL-4	Donor 3	309	115APO13	LEN	1	10:1	0.3	0.1			
SU-DHL-4	Donor 3	309	115APO13	LEN	2	10:1	-0.1				
SU-DHL-4	Donor 3	309	115APO13	MOR208/LEN	1	10:1	35.9	35.0			
SU-DHL-4	Donor 3	309	115APO13	MOR208/LEN	2	10:1	34.1				
SU-DHL-6	Donor 2	140	115APO11	MOR208	1	10:1	26.0	27.3			
SU-DHL-6	Donor 2	140	115APO11	MOR208	2	10:1	28.6				
SU-DHL-6	Donor 2	140	115APO11	LEN	1	10:1	-0.9	0.4			
SU-DHL-6	Donor 2	140	115APO11	LEN	2	10:1	1.7				
SU-DHL-6	Donor 2	140	115APO11	MOR208/LEN	1	10:1	37.8	36.4			
SU-DHL-6	Donor 2	140	115APO11	MOR208/LEN	2	10:1	34.9				
SU-DHL-2	Donor 4	001	115APO14	MOR208	1	10:1	10.4	12.7			
SU-DHL-2	Donor 4	001	115APO14	MOR208	2	10:1	14.9				
SU-DHL-2	Donor 4	001	115APO14	LEN	1	10:1	-2.2	-1.1			
SU-DHL-2	Donor 4	001	115APO14	LEN	2	10:1	0.1				
SU-DHL-2	Donor 4	001	115APO14	MOR208/LEN	1	10:1	23.5	22.7			
SU-DHL-2	Donor 4	001	115APO14	MOR208/LEN	2	10:1	21.9				
U-2932	Donor 4	001	115APO14	MOR208	1	10:1	11.2	11.7			
U-2932	Donor 4	001	115APO14	MOR208	2	10:1	12.1				
U-2932	Donor 4	001	115APO14	LEN	1	10:1	10.4	10.4			
U-2932	Donor 4	001	115APO14	LEN	2	10:1	10.3				
U-2932	Donor 4	001	115APO14	MOR208/LEN	1	10:1	19.9	20.5			
U-2932	Donor 4	001	115APO14	MOR208/LEN	2	10:1	21.0				

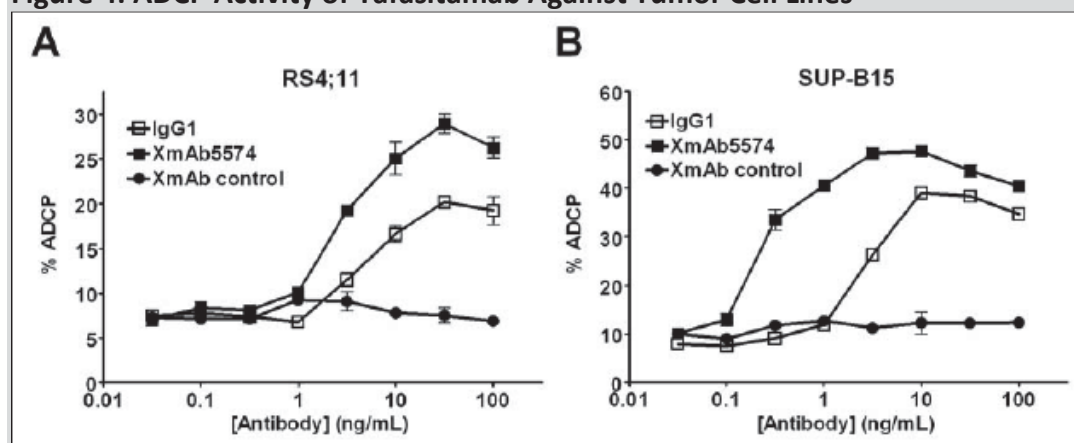
Phagocytosis

CD14+ cell (macrophage) mediated phagocytosis (ADCP) was determined by flow cytometry (Study # TR08139). Monocyte derived macrophages were generated by cultivation of purified CD14+ monocytes from PBMCs in the presence of macrophage colony-stimulating factor (M-CSF). Two CD19 positive tumor cell lines, RS4;11 and SUP-B15, were labeled with the fluorescent dyes (PKH67 or CFSE). Tafasitamab, and control antibodies (IgG1 analog or XmAb isotype) at 0.1, 1, 10, and 100 ng/mL were added to the tumor cells and incubated with macrophages. Cells were then stained with fluorescent-labeled antibodies against macrophage cell surface-specific markers, anti-CD11b-APC and anti-CD14-APC. Phagocytosis was evaluated using flow cytometry with percent phagocytosis calculated as the number of PKH67 or CFSE

(tumor cells)/APC (macrophages) double positive cells divided by the total number of tumor cells.

Both tafasitamab and the IgG1 analog increased phagocytosis in a dose-dependent manner from 1 ng/mL; however, tafasitamab induced phagocytosis activity approximately 10-fold higher relative to the IgG1 analog.

Figure 4: ADCP Activity of Tafasitamab Against Tumor Cell Lines



Tafasitamab in vivo anti-tumor activity

The anti-tumor activity of tafasitamab was demonstrated in severe combined immune deficiency mutation *Prkdc^{scid}* (SCID) mice engrafted with human lymphoma cells (Raji, or RAMOS cells; study #s XC9-05407, XC9-05607, XC9-07607, and XC9-10008). Mice bearing subcutaneously injected Raji or RAMOS tumor cells given tafasitamab at 1, 3 or 10 mg/kg by intraperitoneal injection on Days 3, 6, 10 and 13 exhibited a statistically significant reduction in tumor growth compared to the PBS control group or XENP4614 (isotype control). In addition, at a dose of 10 mg/kg, 33% of the mice remained tumor-free.

Figure 5: Anti-Tumor Activity of Tafasitamab in SCID Mice Bearing Raji Cell Xenografts

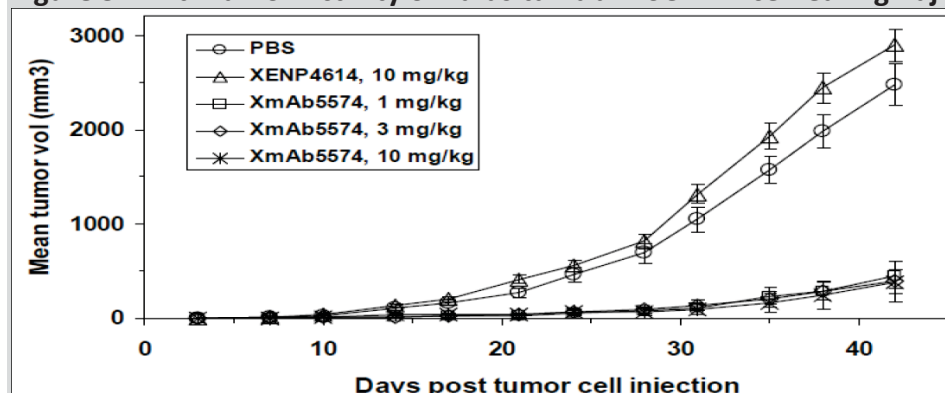
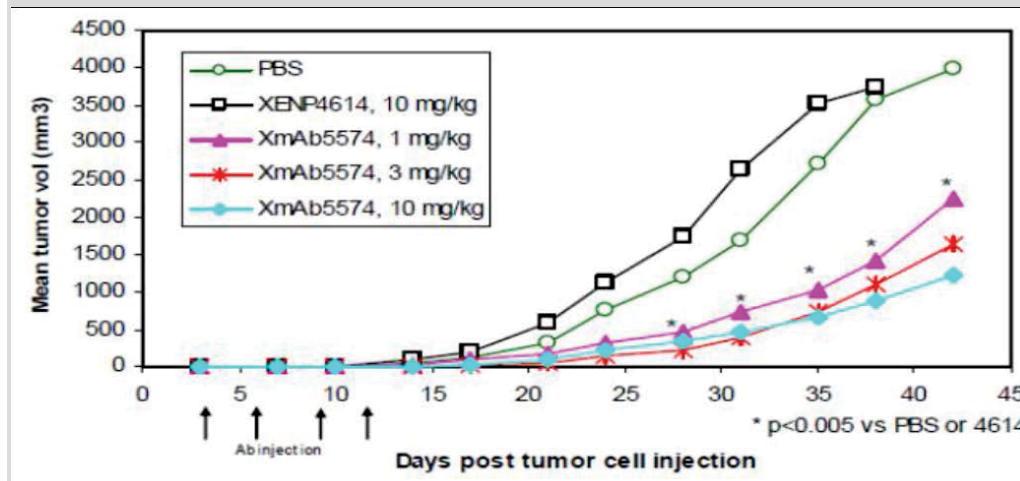


Figure 6: Anti-Tumor Activity of Tafasitamab in SCID Mice Bearing RAMOS Xenografts



The lifespan of animals after treatment with tafasitamab in combination with lenalidomide was evaluated in a disseminated RAMOS non-Hodgkin lymphoma survival model (Study #MOR208P009). RAMOS tumor cells were injected on Day 0 via tail vein injection to mice randomized into 6 six groups (see table below for group designation). Starting on Day 3 after inoculation, tafasitamab was administered at 3 mg/kg by i.v. twice weekly for three weeks and lenalidomide (100 or 200 mg/kg) was administered by oral gavage daily for 28 consecutive days. For the combination treatment, lenalidomide/tafasitamab were administered at 100/3 or 200/3 mg/kg as described above. Vehicle control: Ora-Plus:Ora-Sweet SF (1:1) was administered orally for 28 days, and the isotype control antibody Ref_mAb_33 was administered i.v. twice weekly for three weeks. Following the completion of treatment, the animals were monitored for survival for five weeks post-inoculation. The lifespan was increased in the combination groups compared to the respective mono-therapy groups.

Table 6: Survival Benefit of Single Agent or Combination Treatment of Tafasitamab and Lenalidomide in RAMOS SCID Mouse Model

Group	Treatment	Median Survival (Days Post- Inoculation) (MS)	% Increase in Lifespan (ILS) [§]
1	Tafasitamab (3 mg/kg)	38.0 ^a	72.73
2	Lenalidomide (100mg/kg)	23.0	4.55
3	Lenalidomide (200 mg/kg)	25.0	13.64
4	Lenalidomide/Tafasitamab (100/3 mg/kg)	45.0 ^{a,b}	104.55
5	Lenalidomide/Tafasitamab (200/3 mg/kg)	42.5 ^{a,c}	93.18
6	Vehicle Control	22.0	NA

The Applicant's Position:

Tafasitamab is an Fc-enhanced monoclonal antibody that targets the CD19 antigen. Two amino acid modifications were introduced into the Fc-domain of tafasitamab leading to increased affinity to Fcγ receptors, resulting in more potent immune effector cell mechanisms including enhanced ADCC and ADCP, compared with an antibody with an unmodified Fc-domain.

In vitro assays demonstrated that upon binding to CD19, tafasitamab mediates B-cell lysis through: 1) engagement of immune effector cells, like NK cells, γδ T cells and phagocytes; and, 2) direct induction of cell death (apoptosis). Tafasitamab does not mediate CDC.

The *in vivo* antitumor activity of tafasitamab monotherapy was evaluated using subcutaneous xenograft models in severe combined immunodeficiency (SCID) mice engrafted with human Raji and RAMOS lymphoma cells. Tafasitamab treatment resulted in reduction in tumor growth.

Lenalidomide exerts its antitumor activity by inhibition of proliferation and apoptosis as well via its immunostimulatory function to activate T- and NK cells (REVLIMID USPI). As NK cells are an important effector cell population for tafasitamab mediated ADCC, the combination of tafasitamab and lenalidomide was investigated preclinically. Increased anti-tumor activity in *in vitro* ADCC assays and increased survival in a xenograft *in vivo* model of disseminated RAMOS cells, compared with both monotherapy regimens, were observed. These data provided the rationale to investigate the combination of tafasitamab and lenalidomide in MOR208C203 (L-MIND).

Secondary Pharmacology

No secondary pharmacodynamic effect unrelated to CD19 binding were observed, thus no dedicated secondary pharmacodynamics studies have been conducted.

Tafasitamab cross-reacts with CD19 on cynomolgus monkey B-lymphocytes. In cynomolgus monkeys, tafasitamab mediated B-cell depletion from peripheral blood as a secondary pharmacodynamic effect at doses ranging from 0.3 mg/kg to 100 mg/kg was observed. Histopathological changes to several lymphatic organs (decreased cellularity of the germinal centers in lymphoid follicles of spleen, mesenteric and mandibular lymph nodes) were observed. B-cell depletion in peripheral blood was reversible upon discontinuation of tafasitamab in cynomolgus monkeys.

The Applicant's Position:

The reduced peripheral B-cell counts and changes to lymphatic organs are considered exaggerated pharmacodynamic effects related to B-cell depletion.

The FDA's Assessment:

The FDA agrees with the Applicant that tafasitamab-related changes to lymphatic organs are exaggerated pharmacodynamic effects related to B-cell depletion. In the GLP tissue-cross reactivity studies with human and cynomolgus monkey tissues, tafasitamab binds only B-cells (as expected based on the expression profile of CD19).

Safety Pharmacology

The Applicant's Position:

No stand-alone safety pharmacology studies were conducted. The safety pharmacology parameters were assessed within the pivotal 8-week and 13-week repeat-dose toxicity studies in cynomolgus monkey (XC-9-14408, MOR208P008) and did not reveal any unwanted effects on vital organ functions (cardiovascular, respiratory, central nervous system) at doses up to 100 mg/kg.

The FDA's Assessment:

The neurobehavioral assessments in the 13-week repeat-dose toxicology study in monkeys revealed severe tremors of the whole body observed occasionally in one out five females at the high dose during the tafasitamab 60-minute infusion as well as slight tremors for several animals at the control, low-dose and high-dose. The number of animals affected and the number of incidences of tremors were higher at the high-dose. The tremors resolved following the termination of dosing. In addition, statistically significant differences in body temperature

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(100-102°F) were observed in males at 100 mg/kg and females at 30 and 100 mg/kg during dosing, that recovered in the recovery period. These data demonstrate tafasitamab-related adverse effects at 100 mg/kg.

5.4.ADME/PK

The Applicant's Position:

Following i.v. administration in five separate studies in cynomolgus monkey at dose levels from 0.3 – 100 mg/kg, tafasitamab exhibited a typical 2-compartment PK profile. Tafasitamab showed consistent PK parameters across studies and study groups (volume of distribution at steady state (V_{ss}) 52.6 mL/kg - 124.3 mL/kg, Clearance (CL) 4.31 mL/day/kg - 7.37 mL/day/kg, mean terminal elimination half-life 7.7 days - 14.2 days). Dose linearity was observed between 2-100 mg/kg, and no gender differences were determined. Exposure values (AUC and C_{max}) at NOAEL (100mg/kg) were 8-9 fold higher than corresponding values in humans. As expected for a humanized monoclonal antibody in non-human primates, the development of anti-drug antibodies (ADA) was observed, which was associated with increased tafasitamab clearance but not with any other safety relevant laboratory or clinical findings. An additional exploratory PK study in mice was performed confirming the 2-compartment PK profile and demonstrating PK parameters as expected for humanized therapeutic antibodies in mice without TMDD.

The FDA's Assessment:

An 8-week toxicity study of XmAB® 5574 administered by intravenous infusion every two weeks to cynomolgus monkeys, with a 90- day recovery period/XC9-14408	T_{1/2}=10-14 days Accumulation in C_{max} and AUC was observed during the treatment phase (from the first to the last dose). The percent increase in C_{max} was 26%, 42% and 38% for Groups 2, 3 and 4, respectively, and the percent increase in AUC was 44-46%. Increases in C_{max} and AUC₀₋₅₆ were approximately dose proportional across the dosing range. Immunogenicity: Approximately 47% (14/30) of tafasitamab-treated animals developed ADA responses that were associated with clearing of tafasitamab plasma concentrations. ADA-positive animals with decreased tafasitamab exposure were excluded from the PK analysis.																																																																																																																																
	TK parameters for treated animals without evidence of ADA (Dosing once every two weeks) <i>(Table excerpted from the BLA)</i> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="3">Group 2 (2 mg/kg)</th> <th colspan="3">Group 3 (10 mg/kg)</th> <th colspan="3">Group 4 (50 mg/kg)</th> </tr> <tr> <th>Mean</th> <th>SD</th> <th>%CV</th> <th>Mean</th> <th>SD</th> <th>%CV</th> <th>Mean</th> <th>SD</th> <th>%CV</th> </tr> </thead> <tbody> <tr> <td>Tmax (days) (Min-Max)</td> <td>33.7</td> <td>12.5</td> <td>37.2</td> <td>36.8</td> <td>7.2</td> <td>19.7</td> <td>32.7</td> <td>9.9</td> <td>30.3</td> </tr> <tr> <td></td> <td colspan="3">(14.1-42.1)</td> <td colspan="3">(28.1-42.1)</td> <td colspan="3">(14.1-42.2)</td> </tr> <tr> <td>Cmax 1st (µg/mL)</td> <td>53.5</td> <td>6.1</td> <td>11.5</td> <td>256.2</td> <td>37.0</td> <td>14.4</td> <td>1239.3</td> <td>260.3</td> <td>21.0</td> </tr> <tr> <td>Cmax 4th (µg/mL)</td> <td>67.4</td> <td>6.2</td> <td>9.2</td> <td>364.4</td> <td>41.9</td> <td>11.5</td> <td>1709.4</td> <td>393.3</td> <td>23.0</td> </tr> <tr> <td>Cmax all (µg/mL)</td> <td>72.6</td> <td>9.5</td> <td>13.1</td> <td>376.7</td> <td>48.2</td> <td>12.8</td> <td>1842.8</td> <td>349.8</td> <td>19.0</td> </tr> <tr> <td>AUC0-14 <i>First</i> (day*µg/mL)</td> <td>269</td> <td>49</td> <td>18.1</td> <td>1323</td> <td>189</td> <td>14.3</td> <td>6505</td> <td>1483</td> <td>22.8</td> </tr> <tr> <td>AUC42-56 <i>Last</i> (day*µg/mL)</td> <td>391</td> <td>56</td> <td>14.4</td> <td>1936</td> <td>466</td> <td>24.1</td> <td>9375</td> <td>1910</td> <td>20.4</td> </tr> <tr> <td>AUC0-56 (day*µg/mL)</td> <td>1413</td> <td>188</td> <td>13.3</td> <td>7208</td> <td>1364</td> <td>18.9</td> <td>33689</td> <td>4872</td> <td>14.5</td> </tr> <tr> <td>AUC0-84 (day*µg/mL)</td> <td>1637</td> <td>285</td> <td>17.4</td> <td>8643</td> <td>1741</td> <td>20.1</td> <td>37485</td> <td>8555</td> <td>22.8</td> </tr> <tr> <td>AUC0-146 (day*µg/mL)</td> <td>1657</td> <td>289</td> <td>17.4</td> <td>8930</td> <td>1940</td> <td>21.7</td> <td>38779</td> <td>8700</td> <td>22.4</td> </tr> <tr> <td>AUC0-last (day*µg/mL)</td> <td>1657</td> <td>289</td> <td>17.5</td> <td>8930</td> <td>1940</td> <td>21.7</td> <td>38779</td> <td>8700</td> <td>22.4</td> </tr> </tbody> </table> Total number of qualifying animals was 5 (2F/3M), 8 (3F/5M) and 9 (4F/5M) for Groups 2, 3 and 4, respectively. The number of Recovery animals in each group was 2, 3 and 3 for Groups 2, 3 and 4. AUC0-84, AUC0-146 and AUC0-last are from recovery animals only. Tmax was computed over the entire sampling period.	Parameter	Group 2 (2 mg/kg)			Group 3 (10 mg/kg)			Group 4 (50 mg/kg)			Mean	SD	%CV	Mean	SD	%CV	Mean	SD	%CV	Tmax (days) (Min-Max)	33.7	12.5	37.2	36.8	7.2	19.7	32.7	9.9	30.3		(14.1-42.1)			(28.1-42.1)			(14.1-42.2)			Cmax 1 st (µg/mL)	53.5	6.1	11.5	256.2	37.0	14.4	1239.3	260.3	21.0	Cmax 4 th (µg/mL)	67.4	6.2	9.2	364.4	41.9	11.5	1709.4	393.3	23.0	Cmax all (µg/mL)	72.6	9.5	13.1	376.7	48.2	12.8	1842.8	349.8	19.0	AUC0-14 <i>First</i> (day*µg/mL)	269	49	18.1	1323	189	14.3	6505	1483	22.8	AUC42-56 <i>Last</i> (day*µg/mL)	391	56	14.4	1936	466	24.1	9375	1910	20.4	AUC0-56 (day*µg/mL)	1413	188	13.3	7208	1364	18.9	33689	4872	14.5	AUC0-84 (day*µg/mL)	1637	285	17.4	8643	1741	20.1	37485	8555	22.8	AUC0-146 (day*µg/mL)	1657	289	17.4	8930	1940	21.7	38779	8700	22.4	AUC0-last (day*µg/mL)	1657	289	17.5	8930	1940	21.7	38779	8700
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13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys With a 132-Day Recovery Period (MOR208P008)	$T_{1/2}$=12-14 days, with a mean value of 12.7 days The average accumulation ratios over all dose levels were approximately 2 for C_{max} and AUC_{0-144}, during the dosing period. Increases in C_{max} and AUC_{0-144} were approximately dose proportional across the dosing range. Immunogenicity: Two samples from one male animal at 10 mg/kg were ADA positive; however, there was no impact on exposure due to ADAs in this animal.																											
	Mean PK Parameters in Cynomolgus Monkeys (Dosing Once weekly) <i>(Table excerpted from the BLA)</i> <table border="1"> <thead> <tr> <th>Dose (mg/kg)</th> <th>N Total / N Recovery</th> <th>C_{max} (µg/mL)</th> <th>AUC_{0-144h} (µg·day/mL)</th> <th>CL (mL/day/kg)</th> <th>Accumulation ratio</th> <th>$T_{1/2}$ term (days)</th> </tr> </thead> <tbody> <tr> <td>10</td> <td>10 / 4</td> <td>486</td> <td>737.5</td> <td>7.37</td> <td>2.52</td> <td>12.3</td> </tr> <tr> <td>30</td> <td>10 / 4</td> <td>1505</td> <td>2297.9</td> <td>6.89</td> <td>2.49</td> <td>14.0</td> </tr> <tr> <td>100</td> <td>10 / 4</td> <td>4595</td> <td>8375.0</td> <td>6.80</td> <td>1.96</td> <td>11.8</td> </tr> </tbody> </table> C_{max} was determined following the 13th dose. $T_{1/2}$ term (terminal elimination half-life) was computed only for recovery animals. AUC_{0-144h} and CL were estimated from the 1st dose. Accumulation ratio was calculated as [AUC_{0-144h} from the 13th dose / AUC_{0-144h} from the first dose]. For calculation of PK parameters, no animal was excluded due to suspected ADA-mediated clearance. Note that the values presented here are calculated as mean from male and female animals and transformed from hours to days.	Dose (mg/kg)	N Total / N Recovery	C_{max} (µg/mL)	AUC_{0-144h} (µg·day/mL)	CL (mL/day/kg)	Accumulation ratio	$T_{1/2}$ term (days)	10	10 / 4	486	737.5	7.37	2.52	12.3	30	10 / 4	1505	2297.9	6.89	2.49	14.0	100	10 / 4	4595	8375.0	6.80	1.96
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5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

The toxicological assessment was performed in cynomolgus monkeys and included pivotal 8-week (XC-9-14408) and 13-week (MOR208P008) repeat-dose IV infusion toxicity studies. In summary, tafasitamab was well tolerated after weekly IV administration to cynomolgus monkeys at doses up to 100 mg/kg for 13 weeks, with no target organ toxicities or mortalities. Administration of tafasitamab was not associated with electrocardiographic evidence of cardiotoxicity, arrhythmogenesis, or effects on blood pressure when evaluated as part of the pivotal toxicity studies. Importantly, no evidence of an increased susceptibility to infections was noted after tafasitamab administration to cynomolgus monkeys for 13 weeks.

The B-cell clearance observed in these pivotal toxicity studies represents the desired pharmacologic mechanism of action for the proposed therapeutic intervention in B-cell malignancies.

The FDA's Assessment:

In general, we agree with the Applicant's assessment; see additional information provided below for the 13-week and 8-week repeat-dose studies-

Study title/ Study number: MOR00208: 13-week intravenous infusion toxicity study in the cynomolgus monkey with a 132 day recovery period/MOR208P008

Key Study Findings

- Slight to severe tremors were observed during the tafasitamab infusion. In addition, significant changes were noted in body temperature.
- Tafasitamab caused marked decreases in peripheral blood CD20+ B cells at all doses.
- Tafasitamab caused reductions in T-cell dependent antibody response (TDAR) as assessed by immune response to keyhole limpet hemocyanine (KLH) and Tetanus Toxoid vaccine (TT).
- Lack of germinal centers in lymphoid follicles was observed in several lymphatic organs (spleen, mesenteric and mandibular lymph node) in all tafasitamab-treated groups during the treatment period.
- There were no effects on menstrual cycle length in females and no histopathology/microscopic changes to male and female reproductive organs.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (control), 10, 30, or 100 mg/kg (tafasitamab batch # MOR208-B3G-044). Administered once weekly.
Route of administration:	Intravenous infusion for one hour
Formulation/Vehicle:	Buffer: 25 mM sodium citrate, 200 mM trehalose, 0.02% (w/v) polysorbate 20, pH 6.0
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	5 animals/sex/dose level
Age:	4 to 6 years
Deviation from study protocol affecting interpretation of results:	None that affected the overall interpretation of study findings nor compromised the integrity of the study

Observations and Results: changes from control

Parameters	Major findings																																																																		
Mortality	There were no unscheduled deaths during the study.																																																																		
Clinical Signs	Whole body (WB) tremors were observed at low-dose, high-dose and control animals during the dosing period. The number of animals effected and the number of incidences of tremors were higher at the high-dose. The slight whole body tremors occurred on single occasions in low-dose and control males, while the high-dose animals experienced tremors on 2-5 occasions during dosing. In addition, one female at the high-dose experienced severe whole body tremors during the first dose on Day 1 of dosing. Summary of whole body tremors observed during dosing <table border="1"> <thead> <tr> <th>Group/sex</th> <th>Dose/mg/kg</th> <th>Animal #</th> <th>Tremors</th> <th>Period</th> <th>Days</th> </tr> </thead> <tbody> <tr> <td>1/M</td> <td>0</td> <td>18902M</td> <td>slight WB</td> <td>Dosing</td> <td>43</td> </tr> <tr> <td>1/M</td> <td>0</td> <td>18907M</td> <td>slight WB</td> <td>Dosing</td> <td>36</td> </tr> <tr> <td>2/M</td> <td>10</td> <td>18880M</td> <td>slight WB</td> <td>Dosing</td> <td>57</td> </tr> <tr> <td>2/M</td> <td>10</td> <td>18889M</td> <td>slight WB</td> <td>Dosing</td> <td>43</td> </tr> <tr> <td>4M</td> <td>100</td> <td>18705M</td> <td>slight WB</td> <td>Dosing</td> <td>15, 22, 36, 43, 64</td> </tr> <tr> <td>4F</td> <td>100</td> <td>19051F</td> <td>slight WB</td> <td>Dosing</td> <td>1, 8, 15</td> </tr> <tr> <td>4F</td> <td>100</td> <td>19208F</td> <td>slight WB</td> <td>Dosing</td> <td>8,15, 36, 78</td> </tr> <tr> <td>4F</td> <td>100</td> <td>19230F</td> <td>slight WB</td> <td>Dosing</td> <td>8, 15, 78</td> </tr> <tr> <td>4F</td> <td>100</td> <td>19255F</td> <td>Severe WB</td> <td>Dosing</td> <td>1</td> </tr> <tr> <td>4F</td> <td>100</td> <td>19255F</td> <td>slight WB</td> <td>Dosing</td> <td>8, 15, 78</td> </tr> </tbody> </table>	Group/sex	Dose/mg/kg	Animal #	Tremors	Period	Days	1/M	0	18902M	slight WB	Dosing	43	1/M	0	18907M	slight WB	Dosing	36	2/M	10	18880M	slight WB	Dosing	57	2/M	10	18889M	slight WB	Dosing	43	4M	100	18705M	slight WB	Dosing	15, 22, 36, 43, 64	4F	100	19051F	slight WB	Dosing	1, 8, 15	4F	100	19208F	slight WB	Dosing	8,15, 36, 78	4F	100	19230F	slight WB	Dosing	8, 15, 78	4F	100	19255F	Severe WB	Dosing	1	4F	100	19255F	slight WB	Dosing	8, 15, 78
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Neurobehavioral Observations	Statistically significant differences in body temperature (100-102°F) were observed in males at 100 mg/kg and females at 30 and 100 mg/kg during dosing that recovered in the recovery period.																																																																		
Body Weights	Unremarkable																																																																		
Ophthalmoscopy	Unremarkable																																																																		
ECG	Unremarkable																																																																		
Blood Pressure	Unremarkable																																																																		
Respiratory Rate	Unremarkable																																																																		
Hematology	Hematology changes included transiently decreased absolute neutrophils. There were no dose-dependent or appreciable changes observed in absolute lymphocytes and white blood cells compared to control. The results suggest presence of neutralizing antibodies and/or target saturation. See table below.																																																																		

Changes in hematology parameters compared to predose									
Dose mg/kg/ sex	Predose ¹	Day 22		Day 50		Day 85		Recovery Day 129	
		10E9/L	%Δ	10E9/L	%Δ	10E9/L	%Δ	10E9/L	%Δ
Abs. lymphocytes									
0/M	3.55	5.71	61	5.04	42	4.82	36	5.56	57
10/M	3.45	4.56	32	3.69	7	3.81	10	3.46	0
30/M	5.5	5.91	7	5.41	-2	5.46	-1	4.37	-21
100/M	4.2	4.5	7	4.05	-4	4.5	7	3.31	-21
0/F	3.16	4.54	44	4.61	46	4.13	31	2.48	-22
10/F	4.48	4.03	26	4.29	34	3.5	9	4.2	31
30/F	4.67	5.44	16	5.35	15	4.33	-7	5.45	17
100/F	2.76	3.55	29	4.57	66	3.66	33	3.52	28
WBC									
0/M	9.77	13.02	33	10.31	6	11.42	17	10.11	3
10/M	8.88	13.24	49	10.42	17	10.29	16	10.29	16
30/M	11.35	10.80	-5	12.05	6	13.89	22	11.58	2
100/M	11.40	10.26	-10	9.15	-20	12.33	8	9.31	-18
0/F	8.82	9.86	12	9.78	11	9.18	4	12.94	47
10/F	8.23	7.45	-9	9.14	11	7.72	-6	9.74	18
30/F	9.91	8.30	-16	9.35	-6	8.31	-16	10.58	7
100/F	9.09	6.56	-28	9.05	0	7.52	-17	9.76	7
Abs. neutrophils									
0/M	5.93	6.78	14	4.81	-19	6.35	7	4.1	-31
10/M	4.86	7.74	59	6.07	25	5.97	23	6.44	33
30/M	5.46	4.29	-21	6.04	11	8	47	6.73	23
100/M	6.9	5.06	-27	4.64	-33	7.44	8	5.69	-18
0/F	5.4	4.88	-10	4.72	-13	4.78	-11	9.88	83
10/F	4.7	2.94	-37	4.32	-8	3.83	-19	5.04	7
30/F	4.89	2.24	-54	3.5	-28	3.59	-27	5.68	16
100/F	6	2.58	-57	4.03	-33	3.47	-42	5.86	-2
¹ Predose samples for hematology were from Predose Day 35 (males) or Predose Day 36 (females).									
Clinical Chemistry				The only notable changes were decreases in IgG and IgM levels. See table below; only Day 85 data are presented.					

Changes in clinical chemistry parameters compared to predose¹

Dose mg/kg/ sex	Predose ¹	Day 85		Recovery Day 129	
	10E9/L	10E9/L	%Δ	10E9/L	%Δ
IgG g/L					
0/M	10.63	10.25	-4	11.29	6
10/M	10.27	8.63	-16	9.86	-4
30/M	10.61	8.57	-19	8.81	-17
100/M	11.74	9.88	-16	9.74	-17
0/F	10.15	10.2	0	10.1	0
10/F	10.67	8.37	-22	9.79	-8
30/F	11.31	8.83	-22	10.75	-5
100/F	9.7	6.77	-30**	9.85	2
IgM g/L					
0/M	0.96	0.97	1	1.22	27
10/M	0.99	0.92	-7	0.83	-16
30/M	0.64	0.62	-3	0.77	20
100/M	1.01	0.97	-4	1.43	42
0/F	1.52	1.50	-1	1.20	-21
10/F	1.48	1.37	-7	1.62	9
30/F	1.74	1.52	-13	0.98	-44
100/F	1.10	0.86	-22	0.95	-14

¹Predose samples for clinical chemistry from Predose Day 35 (males) or Predose Day 36 (females). ** P<=0.01

Urinalysis	Unremarkable
Anti-drug-antibodies	Two samples from one animal at 10 mg/kg were confirmed positive for ADA at Week 1 (predose) and Week 18 of the recovery period. There was no impact of ADAs on system exposure or clearance in these animals. It is likely that high levels of the investigational product interfered with the detection of ADAs.
Cytokine Analysis	Female animals of each tafasitamab dose group showed an increase in interleukin-6 (IL-6) values at 4 hours after the end of the infusion for the first dose (Day 1) and the third dose (Day 15). The increase was less pronounced after the third dose.
Immunophenotyping	All doses depleted peripheral B cells (CD3- CD20+) throughout the dosing period; effects were reversible as assessed at the end of the recovery period (Week 19). Absolute NK cells decreased during the first week in several animals, and returned to the range of predose for the rest of the dosing period. Consistent with B-cell depletion observed in peripheral blood, reductions in CD20+ B cells in bone marrow, lymph node and spleen were observed, and were reversible.

BLA Multi-disciplinary Review and Evaluation BLA 761163
 Monjuvi (tafasitamab-cxix)

Changes in CD20+ B-cell numbers									
Dose mg/kg/sex	Predose ¹	Day 14		Day 42		Day 92		Recovery ²	
		10E9/L	%Δ	10E9/L	%Δ	10E9/L	%Δ	10E9/L	%Δ
0/M	1.48	1.73	17%	1.71	16%	1.6	8%	1.77	20%
10/M	1.58	0.11 ***	-93%	0.11 **	-93%	0.12 **	-92%	1.16	-27%
30/M	2.54	0.08 ***	-97%	0.12 **	-95%	0.11 **	-97%	0.87	-66%
100/M	1.52	0.12*	-92%	0.11 **	-93%	0.08**	-95%	0.85	-44%
0/F	1.09	1.12	3%	1.22	12%	1.03	6%	0.71	-35%
10/F	0.96	0.07 **	-93%	0.10 ***	-90%	0.05 ***	-95%	0.62	-35%
30/F	1.64	0.11 *	-93%	0.16 ***	-90%	0.08 *	-95%	0.94	-47%
100/F	1	0.07 **	93%	0.10 ***	-90%	0.06 **	-94%	0.65	-35%

Changes in CD16+ NK-cells									
Dose mg/kg/sex	Predose ¹	Day 14		Day 42		Day 92		Recovery ²	
		10E9/L	%Δ	10E9/L	%Δ	10E9/L	%Δ	10E9/L	%Δ
0/M	0.63	1.2	90%	0.96	52%	0.8	30%	0.73	16%
10/M	0.4	0.39	-2.50%	0.45	13%	0.44	10%	0.33	-18%
30/M	1.08	0.67	-38%	0.88	-19%	1.09	1%	0.87	19%
100/M	0.71	0.57	-20%	0.68	-4%	0.58	-18%	0.77	8%
0/F	0.47	0.61	30%	0.63	34%	0.49	4%	0.54	15%
10/F	0.6	0.36	-40%	0.61	2%	0.38	-37%	0.33	-45%
30/F	0.75	0.56	-51%	0.66	-12%	0.57	-24%	0.69	-8%
100/F	0.4	0.37	-8%	0.44	10%	0.28	-30%	0.46	15%

¹ Predose samples for immunophenotyping from Predose Day 14 (males) or Predose Day 15 (females); ² Recovery week 19
 * - p<0.05 ** - p<0.01 *** - p<0.001

Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology	Lack of germinal centers in the spleen, mesenteric and mandibular lymph nodes in the terminal period were observed. These findings were not observed in the recovery period.

Incidence of tafasitamab-related microscopic findings
 (Excerpted from Applicant's BLA)

Sex	Males				Females			
	0	10	30	100	0	10	30	100
Dose Level (mg/kg)								
Number Examined	3	3	3	3	3	3	3	3
<u>Spleen</u>								
Lack of Germinal Centers	-	2	-	1	-	3	2	2
<u>Mesenteric Lymph Node</u>								
Lack of Germinal Centers	-	-	-	-	-	-	2	-
<u>Mandibular Lymph Node</u>								
Lack of Germinal Centers	-	-	-	-	-	1	-	-

T-cell Dependent Antibody Response (TDAR) Evaluation	All animals were vaccinated with Anti-KLH on Day 36 (1st immunization) after B-cell depletion during the dosing period and all recovery animals on Day 195 (2nd immunization) in Week 15 of the recovery period. Blood samples were collected at several time points at pre- and each post-immunization. The levels of anti-KLH IgG and anti-LLH IgM in the samples were determined. Anti-KLH IgM and IgG: The mean peak anti-KLH IgM and IgG responses to KLH vaccine were reduced in all dose groups by 60% to 85% in a non-dose dependent manner, as compared to the mean peak titer for the controls on Day 36. These effects were reversible. Anti-TT IgG: All animals were vaccinated with TT on Day -35 (1st immunization) of the predose period, on Day 28 (2nd immunization) in Week 5 of the dosing period, and on Day 188 (3rd immunization) in Week 14 of the recovery period. The mean peak anti-TT IgG responses were reduced in all dose groups by 60% to 90% in a non-dose dependent manner, as compared to the control group mean peak titer on Day 28. These effects were reversible.
Toxicokinetics	
See the section 1.4 ADME/PK for the toxicokinetic data.	

General toxicology; additional studies

Tafasitamab was also assessed in three non-GLP single-dose studies (study #XC9-05707, #XC9-07907, #XC0-08007), and a GLP 8-week repeat-dose study (XC9-14408), each in cynomolgus monkeys. The results are summarized below. In general, findings were comparable to those observed in the 13-week toxicology study and expected based on the pharmacology of the product. See additional information below related to the 8-week toxicology, Study XC9-14408:

In a GLP-compliant study, groups of 5/sex cynomolgus monkeys received 2, 10, or 50 mg/kg of tafasitamab by i.v. infusion once every 2 weeks x 4. Three animals/sex were necropsied at termination of dosing (Day 57) and 2/sex were sacrificed after 90 days of recovery (Day 147).

Key Study Findings:

- Tafasitamab caused marked decreases in peripheral blood B cells associated with decreased absolute lymphocytes, decreased white blood cell counts, decreased spleen weights, and altered spleen histology (decreased cellularity of the splenic germinal center). By the end of recovery (Day 90), depleted B cells at the low- and mid-dose had fully recovered but the high-dose had only partially recovered (to 53% of baseline).
- The splenic change was observed at all doses, and the severity increased with increasing dose. Recovery was apparent; one high-dose animal (1/4, a male) continued to exhibit decreased cellularity of the germinal center on Day 147.

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- ADAs were detected in 47% of tafasitamab treated monkeys (8/10 at 2 mg/kg, 3/10 at 10 mg/kg, and 3/10 at 50 mg/kg). ADAs enhanced the clearance of tafasitamab.

5.5.2. Genetic Toxicology

The Applicant's Position:

No studies were conducted to evaluate the genotoxicity of tafasitamab. According to ICH guideline S6(R1), the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed for tafasitamab. In addition, it is not expected that tafasitamab would interact directly with DNA or other chromosomal material.

The FDA's Assessment:

The FDA concurs with the Applicant.

5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies in animals were not conducted with tafasitamab. ICH guideline S9 outlines that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, and as such no carcinogenicity studies are required.

The FDA's Assessment:

The FDA concurs with the Applicant.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

In accordance with ICH S9, no embryofetal development or (enhanced) pre- and postnatal development studies were conducted, as the drug is given in the intended patient population in combination with a drug known to be teratogenic or causing embryo-fetal lethality (lenalidomide). The approach was agreed upon with FDA.

Potential effects of tafasitamab on male and female fertility were examined by standard histopathology evaluation of the reproductive tract and by menstrual cycle assessment in females during the pivotal 13-week, repeat-dose, toxicity study in sexually mature cynomolgus monkeys (MOR208P008); no drug-related changes were observed.

The FDA's Assessment:

The FDA concurs with the Applicant that no embryo-fetal development (EFD) studies are needed when tafasitamab is given in combination with lenalidomide, a known teratogen and embryo-fetal toxicant.

To address the potential effects of tafasitamab on embryo-fetal development, the Applicant submitted an assessment for reproductive and developmental risk using a weight-of-evidence approach and with the Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry. The relevant information is summarized below and supports that the main reproductive risk for tafasitamab is B-cell depletion in neonates.

The WOE risk assessment include the following information; references cited were provided by the Applicant:

- 1) As CD19 expression is mainly restricted to cells of the B-cell lineage, and dendritic cells, the main reproductive risk for tafasitamab is immune related. While the impact of tafasitamab on fetal development is unknown; data in CD19 knockout mice and SCID mouse deficient in T and B cells, suggest that CD19 is not essential for developmental processes during embryofetal development ^{7,8,9}. Tafasitamab is an IgG monoclonal antibody, and as a class, IgG monoclonal antibodies have the potential to cross the placental barrier permitting direct fetal exposure. Based on its mechanism of action and pharmacodynamic effects seen in animals, tafasitamab may cause depletion of B cells and impair the immune response after birth due to fetal exposure to tafasitamab.
- 2) As described in toxicology studies in monkeys, the main toxicities of tafasitamab treatment were to the immune system with no evidence of off-target toxicity, including effects to the male and female reproductive organs.
- 3) The dosing regimen for the intended patient population (relapsed or refractory diffuse large B-cell lymphoma) consists of the combination of tafasitamab and lenalidomide. Lenalidomide is a teratogenic drug.

⁷ Rickert RC, Rajewsky K, Roes J. (1995). "Impairment of T-cell-dependent B-cell responses and B-1 cell development in CD19-deficient mice." *Nature*. 1995 Jul 27;376(6538):352-5

⁸ Gärdby E, Chen XJ, Lycke NY. (2001). "Impaired CD40-signalling in CD19-deficient mice selectively affects Th2-dependent isotype switching." *Scand J Immunol*. 2001 Jan;53(1):13-23

⁹ Kitamura D, Roes J, Kühn R, Rajewsky K. (1991). "A B cell-deficient mouse by targeted disruption of the membrane exon of the immunoglobulin mu chain gene." *Nature*. Apr 4;350(6317):423-6

5.5.5. Other Toxicology Studies

The Applicant's Position:

To identify tissues with the potential to be associated with tafasitamab systemic toxicities, the binding of FITC labelled tafasitamab to cynomolgus monkey and human tissue panels was evaluated using immune-histochemical staining in frozen sections of normal tissues.

Tafasitamab-FITC bound both to lymphocytes in the blood, and to mononuclear leukocytes which are presumed to be B-lymphocytes based on morphology and/or location, in numerous tissues. Some hematopoietic precursor cells in the bone marrow also stained. Under the conditions of the study, it was not possible to determine the stage of B-cell development for these precursor cells. No off-target binding was detected in tissue cross-reactivity studies on normal tissues from human and cynomolgus monkey.

Staining in cynomolgus monkey tissues closely paralleled that seen in human tissues. The cell types stained, and the subcellular localization of the stain were similar although the staining intensity and frequency were not clear but may be attributable to the antigenic structure or distribution differences between species.

The FDA's Assessment:

The FDA agrees with Applicant.

Compared to the human tissue cross-reactivity study, the binding intensity was reduced for the monkeys, likely due to a difference in binding affinity to the epitope.

Ramadevi Gudi
Primary Reviewer

Brenda Gehrke
Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

Tafasitamab is a Fc-modified monoclonal antibody that binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes, and on several B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL). The Applicant is seeking approval of tafasitamab in combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for, (b) (4) autologous stem cell transplant (ASCT). The proposed dosage of tafasitamab is 12 mg/kg administered by intravenous infusion according to the following schedule (1 cycle = 28 days):

- **Cycle 1:** Days 1, 4, 8, 15, and 22
- **Cycle 2-3:** Days 1, 8, 15, and 22
- **Cycle 4 and beyond:** Days 1 and 15

Tafasitamab is proposed to be administered in combination with lenalidomide 25 mg on Days 1-21 of each cycle for a maximum of 12 cycles, followed by tafasitamab monotherapy until disease progression or unacceptable toxicity.

The Clinical Pharmacology section of the BLA is supported by analyses of single and multiple dose pharmacokinetics (PK) of tafasitamab in patients with DLBCL, immunogenicity, population pharmacokinetics (popPK), and exposure-response (E-R) relationships.

RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the information and data submitted in BLA 761163. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized in **Table 7** below.

Table 7: Key Clinical Pharmacology Review Issues

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal Study MOR208C203 (L-MIND) in the target population. An ORR of 60% (42% CR, 18% PR) was demonstrated out of 80 evaluable patients.
General dosing instructions	The proposed dosing regimen is 12 mg/kg tafasitamab administered by intravenous infusion on Days 1, 4, 8, 15, 22 in Cycle 1, Days 1, 8, 15, 22 in Cycles 2-3, Days 1, 15 in Cycles 4 and beyond) in combination with 12 mg lenalidomide on Days 1-21 of each 28-day cycle for up to 12 cycles is acceptable for approval. Body weight has a clinically significant effect on the PK of tafasitamab, with higher clearance and volume of distribution

	expected with higher body weight. Flat E-R relationships for ORR, PFS, and safety (Grade $\geq$ 3 treatment emergent adverse events [TEAEs] and most evaluated TEAEs of special interest) were observed for tafasitamab in combination with lenalidomide. Population PK and E-R analyses support the proposed dosing regimen.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustment is needed in patient subgroups. The effect of severe renal impairment to end-stage renal disease (CLCr < 30 mL/min) and moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN, any AST) is not known.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement with the FDA revisions to the labeling.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Pharmacodynamics

In patients with R/R-DLBCL, tafasitamab led to a reduction in peripheral blood B cell counts. The reduction relative to baseline B cell count reached 97 % after eight days of treatment in the L-MIND study (MOR208C203). Nadir with a reduction of 100% was reached within 16 weeks of treatment.

Pharmacokinetics

Based on a population pharmacokinetic analysis of tafasitamab in combination with lenalidomide, tafasitamab average serum trough concentrations ($\pm$ standard deviation) were determined at 179 ($\pm$ 53) μ g/mL during weekly intravenous administrations at 12 mg/kg including an additional dose at Day 4 of Cycle 1. During bi-weekly administrations from Cycle 4 onwards average trough serum concentrations of 153 ($\pm$ 68) μ g/mL were determined. Overall maximum tafasitamab serum concentrations were determined at 483 ($\pm$ 109) μ g/mL.

Distribution

The total volume of distribution for tafasitamab was determined at 9.3 L.

Elimination

The general clearance of tafasitamab was determined at 0.41 L/day and terminal elimination half-life at 16.9 days. Following long-term observations, tafasitamab clearance was found to decrease over time to a value of 0.19 L/day after two years.

Metabolism

The exact pathway through which tafasitamab is metabolized has not been characterized. As a humanized IgG monoclonal antibody, tafasitamab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Immunogenicity

Overall, no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed. Pre-existing anti-tafasitamab antibodies in 17/245 (6.9%) patients had no impact on pharmacokinetics, efficacy, or safety of tafasitamab.

The Applicant's Position:

The Pharmacology and Clinical Pharmacokinetics program supports the BLA for the intended indication.

The FDA's Assessment:

FDA agrees with the Applicant's position. To reflect the intended patient population, FDA updated the incidence and potential effect of immunogenicity to state that no clinically meaningful differences in the PK, efficacy, or safety profile of tafasitamab were observed in 2.5% (2/81) of patients with relapsed or refractory (R/R) DLBCL with pre-existing anti-tafasitamab antibodies.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The recommended dose of tafasitamab is 12 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule:

- Cycle length: 28 days.
- Cycle 1: Administer tafasitamab on Day 1, 4, 8, 15 and 22.
- Cycles 2 - 3: Administer tafasitamab on Day 1, 8, 15 and 22 of each cycle.
- Cycle 4 until disease progression: Administer tafasitamab on Days 1 and 15.

Patients should self-administer lenalidomide capsules at the recommended starting dose of 25 mg daily on Days 1 - 21 of each cycle. Tafasitamab plus lenalidomide in combination are given up to twelve cycles. Lenalidomide dose adaptations are permitted as per prescribing information. Refer to the lenalidomide prescribing information for dosing guidelines and recommendations.

After a maximum of twelve (12) cycles of combination therapy, stop treatment with lenalidomide and continue tafasitamab infusions as single agent on Days 1 and 15 of each 28-day cycle, until disease progression.

DER analysis for efficacy performed for MOR208C203/L-MIND showed that tafasitamab exhibited a flat exposure-response relationship (see section 6.3.2.2).

The Applicant's Position:

The recommended dose and dosing schedule for the intended indication is supported by dose-exposure response analysis for efficacy and safety.

The FDA's Assessment:

FDA agrees with the Applicant's proposed dosing regimen, which was evaluated in Study MOR208C203 (L-MIND) and is supported by popPK and E-R analyses for efficacy and safety.

6.2.2.2. Therapeutic Individualization

In a population PK analysis for tafasitamab (see also below in 0), age (16 to 90 years), body weight, sex, tumor size, disease type, B-cell or absolute lymphocyte counts, anti-drug antibodies, lactate dehydrogenase, serum albumin, hepatic (AST, ALT, ALKP, GGT) and renal function (CrCL) had no clinically significant effect on the PK of tafasitamab. The influence of race and ethnicity is unknown. Lenalidomide co-administration was not found to influence tafasitamab PK in the Population PK analysis.

The Applicant's Position:

No dose adjustments are recommended based on intrinsic or extrinsic factors.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustments are recommended based on intrinsic or extrinsic factors. The popPK analyses showed that body weight (40 to 163 kg) has a clinically significant effect on the PK of tafasitamab, which supports body weight-based dosing for tafasitamab. No clinically meaningful differences in the PK of tafasitamab were observed based on age (16 to 90 years), sex, mild to moderate renal impairment (CLcr 30-89 mL/min, estimated by the Cockcroft-Gault equation) and mild hepatic impairment (total bilirubin $\leq$ ULN and AST $>$ ULN, or total bilirubin 1 to 1.5 times ULN and any AST). The effect of severe renal impairment to end-stage renal disease (CLcr $<$ 30 mL/min), moderate to severe hepatic impairment (total bilirubin $>$ 1.5 times ULN and any AST), and race/ethnicity on tafasitamab PK is unknown (although no effect is expected).

6.2.2.3. Outstanding Issues

The Applicant's Position:

There are no outstanding issues.

The FDA's Assessment:

FDA agrees that there are no outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Table 8: Overview Clinical Pharmacology Characteristics Tafasitamab

General Information	
Chemical Structure	Disulfide-linked glycosylated protein tetramer with two identical 451 amino acid heavy chains and two identical 219 amino acid kappa light chains Fc part: human IgG1/2 with two single amino acid exchanges (S239D and I332E) Molecular weight: approximately 150 kDa
Mechanism of Action	Tafasitamab binds to the human B-cell surface antigen cluster of differentiation (CD) 19. The engineered Fc part possesses significantly increased binding to Fc gamma receptors (FcγR) leading to enhanced in vitro antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Tafasitamab also mediates direct cytotoxic effects (apoptosis) on tumor cells relative to the unmodified antibody. Tafasitamab does not mediate complement-dependent cytotoxicity (CDC).
Bioanalysis	

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Bioanalysis PK	Tafasitamab concentrations in human plasma or serum were quantified by validated ligand binding assays (PK assay). The first-generation PK assay (enzyme-linked immunosorbent assay - ELISA) employed capture with a mouse monoclonal anti-tafasitamab idiotypic antibody and detection with an anti-human IgG Fc antibody. The second-generation PK assay (electrochemiluminescence assay) employed capture with a human monoclonal anti-idiotypic antibody (Fab fragment) and detection with a mouse monoclonal anti-tafasitamab idiotypic antibody. The lower limit of quantification (LLOQ) in undiluted samples was 80 ng/mL and 50 ng/mL in the 1st and 2nd generation PK assay, respectively.
Bioanalysis ADA	Anti-tafasitamab antibodies were determined using a validated homogenous bridging electrochemiluminescence based ligand-binding assay. For the pivotal study L-MIND a Solid-Phase Extraction Followed by Acid Dissociation (SPEAD) approach was added for sample pre-treatment to increase drug tolerance. Study samples were analyzed using a multi-tiered testing approach consisting of a screening, a conformation, a specificity and a titer determination assay. For the pivotal study L-MIND confirmed positive samples were further tested in a validated cell based ADCC neutralizing antibody (NAb) assay.
Pharmacokinetic (PK) Characteristics	
Pop-PK Model	For the population PK analysis incl. covariate assessments results from four different clinical studies were used (XmAb5574-01, MOR208C201, MOR208C202 and MOR208C203). The PK of tafasitamab following IV administration was well characterized by a 2-compartment linear disposition model. A time-dependent clearance term ($CL \exp(t^y / (T50^y + t^y))$) was included in the model to describe the increasing trough concentrations observed in the L-MIND study (MOR208C203) beyond one year of treatment.
Drug Exposure	Based on the population pharmacokinetic analysis, tafasitamab average serum trough concentrations ($\pm$ standard deviation) in the L-Mind study were determined to be 179 ($\pm$ 53) μ g/mL during weekly intravenous administrations at the 12 mg/kg dose level including an additional dose at Day 4 of Cycle 1 in combination with lenalidomide. During bi-weekly administrations from Cycle 4 onwards, average trough serum concentrations of 153 ($\pm$ 68) μ g/mL were determined. Overall, maximum tafasitamab serum concentrations were determined to be 483 ($\pm$ 109) μ g/mL.
Dose Linearity	Dose linearity was assessed in the Phase I dose escalation study XmAb5574-01. For dose levels below 3 mg/kg nonlinear pharmacokinetics were observed in patients with R/R CLL/SLL. Employing dose levels of 3 – 12 mg/kg, AUC and Cmax increased in a dose proportional manner.
Absorption	No bioavailability studies were performed as tafasitamab is administered IV.
Distribution	The total volume of distribution for tafasitamab was determined at 9.3 L.

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Elimination	The general clearance of tafasitamab was determined at 0.41 L/day; terminal elimination half-life at 16.9 days. Following long-term observations, tafasitamab clearance was found to decrease over time to a value of 0.19 L/day after two years.	
Metabolism	The metabolic pathway of tafasitamab has not been characterized. As a human monoclonal antibody, tafasitamab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.	
Excretion	The excretion of tafasitamab has not been studied. Tafasitamab is a human monoclonal IgG1/2 antibody and has a molecular weight of approximately 150 kDa; therefore, intact tafasitamab is unlikely to be filtered by the kidney or excreted in the urine.	
Immunogenicity		
Incidence	Pre-existing ADA	Overall 17/245 subjects (6.9%) were tested ADA-positive before start of tafasitamab treatment
	Treatment-boosted or treatment-emergent ADA	No treatment related boost of pre-existing ADAs, and no treatment-emergent ADAs were observed
Impact on PK, efficacy, safety	The presence of ADAs had no obvious impact on the pharmacokinetics of tafasitamab. Following a descriptive analysis, the presence of ADAs had no obvious impact on the clinical efficacy and safety of tafasitamab.	
Pharmacodynamic (PD) characteristics		
B-cell depletion	Peripheral B-cell depletion was demonstrated in whole blood samples within clinical studies MOR208C203 (L-MIND), MOR208C201, MOR208C202, MOR208C205 and XmAb5574-01. In most studies, substantial B-cell depletion was observed at the earliest consistently tested time point, Cycle 1 Day 8 (C1D8). The magnitude of the maximal reduction seen at nadir relative to baseline count ranged from -80% (MOR208C201) to -100% (MOR208C203, the pivotal study), exceeding -95% in all but one study (MOR208C201), which had a method related background limitation. The time to reach the nadir ranged from 6 to 16 weeks after treatment start.	
QT effects	As tafasitamab is a human monoclonal antibody no “Thorough QT/QTc Study” was performed. Instead, periodic ECG monitoring was implemented in all company-sponsored clinical studies to capture potential ECG changes. Results showed that tafasitamab did not have a clinically relevant effect on cardiac repolarization or result in clinically significant cardiac AEs.	

The Applicant’s Position:

The Pharmacology and Clinical Pharmacokinetics program supports the BLA for the intended

indication.

The FDA's Assessment:

FDA agrees with the Applicant's position. To reflect the intended patient population, FDA updated the incidence and potential effect of immunogenicity to state that no clinically meaningful differences in the PK, efficacy, or safety profile of tafasitamab were observed in 2.5% (2/81) of patients with R/R DLBCL with pre-existing anti-tafasitamab antibodies.

6.3.2. Clinical Pharmacology Questions

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

In clinical studies XmAb5574-01, MOR208C201, MOR208C202, L-MIND, and MOR208C205, tafasitamab treatment led to a reduction in peripheral B-cells in subjects suffering from CLL, MCL, MZL, ALL and DLBCL with a maximum reduction that generally exceeded -95% vs. baseline. Substantial B-cell depletion was usually observed after 8 days, reaching a median nadir within 6 to 16 weeks after treatment start. The depletion was lasting under continued tafasitamab treatment.

For the dose-exposure-response (DER) analysis for efficacy and safety of tafasitamab, refer to section 6.3.2.2.

The Applicant's Position:

Depletion of peripheral B-cells is consistent with the proposed mode of action of tafasitamab as a mediator of ADCC, ADCP and direct cytotoxicity towards CD19 expressing cells. The dose-exposure response analysis for efficacy provides evidence for effectiveness.

The FDA's Assessment:

FDA agrees with the Applicant's position on the time course of pharmacodynamics response. The primary evidence of effectiveness comes from pivotal Study MOR208C203 (L-MIND) in the target population that showed an ORR of 60% (42% CR, 18% PR) in 80 evaluable patients.

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

The dosing regimen for the combination therapy uses the maximum previously applied monotherapy doses for each agent in R/R DLBCL.

Tafasitamab

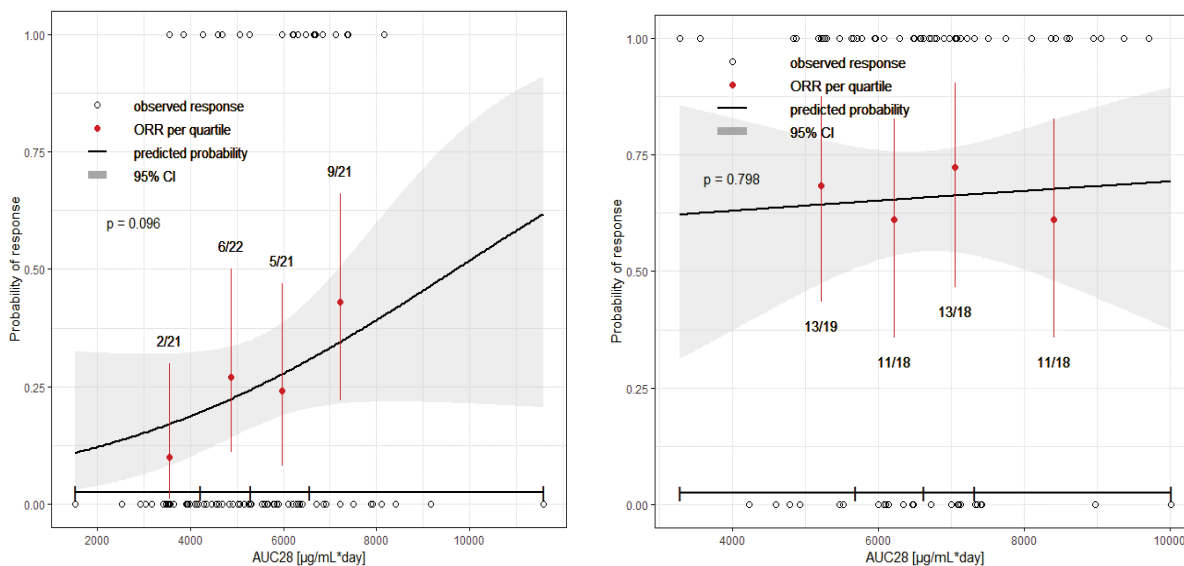
A dose-exposure-response (DER) analysis for efficacy and safety of tafasitamab was performed, with tafasitamab exposure metrics derived by simulation for each subject from the Pop-PK model. The individual exposure metrics were separated into exposure quartiles and analyzed against PFS and ORR, or against treatment-emergent adverse events (TEAEs) and each AE of special interest (AESI). Furthermore, logistic regression analysis was performed in order to assess the impact of tafasitamab exposure on safety and efficacy.

Exposure-Response Relationship for Clinical Efficacy

A post-hoc assessment of the DER relationship for efficacy (study MOR208L035) was performed for clinical trials MOR208C203/L-MIND, MOR208C201, and XmAb5574-01 with the following conclusions:

- An exposure-response relationship was observed for tafasitamab monotherapy in clinical studies XmAb5574-01 (subjects with R/R CLL/SLL) and MOR208C201 (subjects with R/R NHL/DLBCL, see Figure 7). Within these studies, higher exposure to tafasitamab was associated with higher ORRs and prolonged median PFS.
- In combination with lenalidomide (MOR208C203), tafasitamab exhibited a flat exposure-response relationship (see Figure 7). Based on the results of the exposure-response analysis, increasing exposure to tafasitamab is unlikely to result in higher response rates or longer PFS when tafasitamab is used in combination with lenalidomide.
- Switching the dosing frequency of tafasitamab in combination with LEN from initially Q1W to Q2W, after three treatment cycles, as implemented in MOR208C203, had no pronounced effect on PFS based on this analysis.

Figure 7: Analysis of Objective Response Versus AUC28 for Clinical Study MOR208C201 (Left, Tafasitamab Monotherapy) and MOR208C203/L-MIND (Right, Tafasitamab in Combination with Lenalidomide)



Black solid line and grey shaded areas represent logistic model-predicted relationship and 95% confidence interval based on the sensitivity analysis population (N=73 for L-MIND; N=85 for MOR208C201). Quartile borders of AUC28 quartiles are displayed at the bottom. Quartile-wise ORR (red dots) and 95% Clopper-Pearson confidence intervals (red vertical lines) are overlaid for information. Number of responders versus total number of subjects per quartile are displayed at the top/bottom of 95% CIs. Black circles on top and bottom represent actual observations used for regression. Note that only subjects receiving all planned doses during Cycle 1 were included in this analysis in order to avoid bias of an early drop-out leading to low AUC28. Abbreviations: ORR = objective response rate; AUC28 = AUC from 0-28 days. Source: Report MOR208L035 Figure 5 and Figure 11.

Exposure-Response Relationship for Clinical Safety

A post-hoc assessment of the DER relationship for safety was performed for clinical trials MOR208C203/L-MIND and MOR208C201. Overall, there were no obvious trends for an increase in AEs or TEAEs in any System Organ Class (SOC) (including the Blood and Lymphatic Disorders and Cardiac Disorder SOCs) with increasing values for AUC28 or C_{max}, as the numbers and percentages of subjects with such events were equally or randomly distributed across the 4 exposure quartiles. This was also confirmed using logistic regression. For details, refer to m2.7.4.2.1.5.2.

Lenalidomide

The LEN starting dose was 25 mg daily. This dose was selected on the basis of published data and the recommended starting dose for patients with myeloma and MCL (REVLIMID USPI, 2019). Published studies indicate a consistent and manageable safety profile for this dose of

LEN monotherapy in patients with R/R DLBCL ([Wiernik et al., 2008](#); [Witzig et al., 2011](#); [Czuczman et al., 2017](#)). Similar doses (20-25 mg) have also been used when lenalidomide was combined with rituximab (RTX) ([Zinzani et al., 2011](#); [Wang et al., 2013](#); [Vose et al., 2013](#); [Ivanov et al., 2014](#)) or R-CHOP ([Nowakowski et al., 2011](#); [Nowakowski et al., 2015](#)).

Treatment with LEN is limited to 12 cycles (12 months), based on benefit-risk considerations. In terms of benefit, a similar duration of LEN treatment (12 months) was defined in a previous study in patients with R/R DLBCL ([Zinzani et al., 2011](#)) which demonstrated an ORR of 35%, a CR rate of 30%, and 1-year DFS rate 35%, 18-month OS rate 55%. Limiting treatment duration was introduced to avoid further cumulative risk though prolonged exposure to lenalidomide, e.g. the incidence of second primary malignancies with LEN seen in some clinical trials (REVLIMID USPI, 2019).

The Applicant's Position:

The dosing regimen of LEN applied in the MOR208C203 (L-MIND) study is consistent with the USPI in other hemato-oncological indications (REVLIMID USPI, 2019). The duration of LEN therapy (approximately 12 months) is similar to that in many other combination studies including LEN in aggressive and indolent lymphoma and is therefore considered appropriate. The dose and regimen of tafasitamab is supported by exposure-response analysis for efficacy and safety.

The FDA's Assessment:

FDA agrees with the Applicant's position that the proposed dosing regimen is supported by popPK and E-R analyses for efficacy and safety.

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

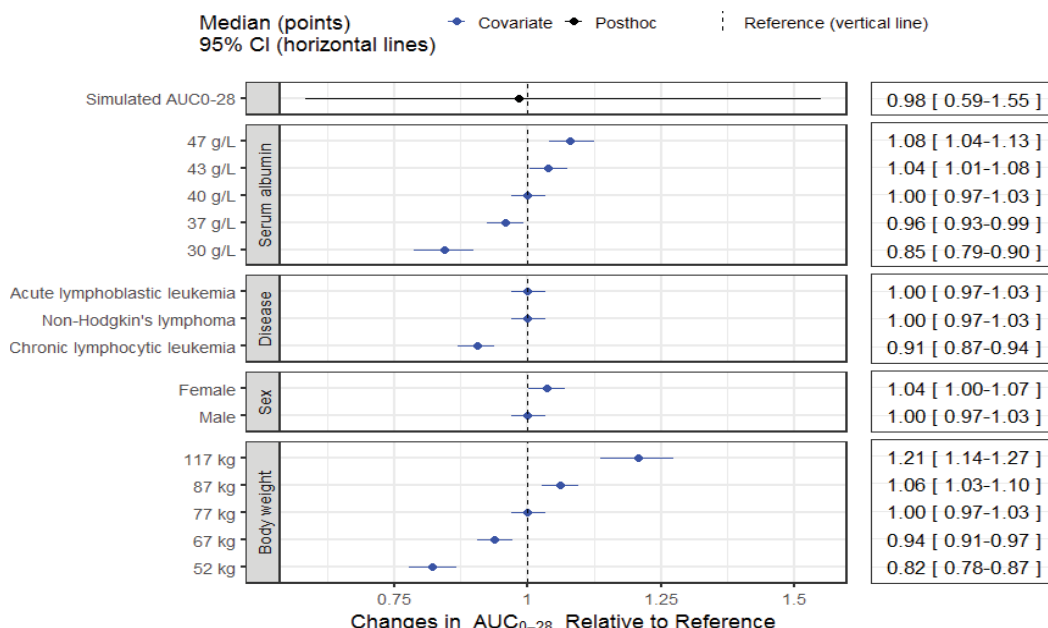
Intrinsic patient factors for tafasitamab exposure were evaluated during population PK analysis. As determined by stepwise covariate model building, body weight at baseline (WTB) was found to have a significant effect on CL and V. In addition, covariate effects of albumin (ALB) on clearance, sex and of the type of disease (NHL/ALL or CLL/SLL) on central volume were also included in the final Pop-PK model. Covariate effects were moderate in size (5th or 95th percentile of the respective covariate range caused a change of < 50% of the respective primary PK parameter or derived exposure parameter, for most exposure parameters even < 25%, see also Figure 7 for AUC₀₋₂₈ as an exemplary exposure metric). In a dose/exposure assessment for clinical effectiveness of tafasitamab, (MOR208L035, see also section 6.3.2.2), tafasitamab exhibited a flat exposure-response relationship in combination with lenalidomide in R/R DLBCL subjects (MOR208C203, all subjects dosed at 12 mg/kg). In a dose/exposure response assessment for safety of tafasitamab, no obvious increase in safety events could be observed with increasing exposure.

Thus, based on exposure-response analysis and based on the moderate size of PK covariate effects, the latter were considered to be clinically not relevant and not warranting dose adjustments for subpopulations.

Table 9: Summary of Covariate Assessment in the Population PK Analysis

	Covariates investigated within the Population PK analysis	Results of Population PK analysis
Intrinsic Factors	Demographics: sex, age, and body weight	Body weight at baseline (WTB) was found to have a statistically significant effect on tafasitamab CL and central volume of distribution (V). Other statistically significant covariates identified were serum albumin (inverse correlation with clearance), sex (lower V in females), and disease type (subjects with NHL or ALL had a lower V than subjects with CLL/SLL). The influence of race and ethnicity on the pharmacokinetics of tafasitamab could not be tested due to limited diversity in the patient population evaluated.
	Disease-specific / disease-related: disease type (ALL, CLL/SLL, NHL), NHL subtypes (FL, MCL, DLBCL, other indolent lymphomas (iNHL)), tumor size (sum of area of indicator lesions, SPD), lactate dehydrogenase (LDH), cancer stage, ECOG performance status, B-cell count and absolute lymphocyte count (ALC).	
	Immunological: presence/absence of anti-drug antibodies (ADA)	
	Clinical chemistry: total protein, albumin, liver enzymes (ALT, AST, GGT, ALKP), creatinine clearance	
	Renal or Hepatic Impairment	No significant effect of renal function (creatinine clearance), or hepatic function (AST, ALT, ALKP, GGT) on tafasitamab PK could be detected.

Figure 8: Univariate Impact of Covariates on Tafasitamab Exposure Metrics



Source: Population PK Report MOR208L032 Figure 15

Note: Selected covariate values (y-axis) represent p5, 1st quartile, median, 3rd quartile and p95 of the respective covariate in the dataset. The parameter point estimate and error bars for each covariate level are the median and 95% CI of 998 bootstrap replicates. Note that the error bars (in blue) represent uncertainty in the population estimates, not IIV. Simulated exposure metrics (top row, in black: median and 95% CI) are derived from the post-hoc PK parameter estimates and thus include IIV.

Reference values: ALB=40 g/L, WTB=76.6 kg, DIS=2 (Non-Hodgkin's lymphoma), and SEX=0 (Male). Regimen used for simulation: weekly dosing at 12 mg/kg during Cycles 1-3 (plus a loading dose at Cycle 1 Day 4) as employed in the clinical study L-MIND. The following values were used as reference values: Median AUC0-28

(6814.121 mg.day/L), median MaxCmax (465.3103 mg/L).

Abbreviations: ALB = serum albumin, AUC0-28 = area under the serum concentration-time curve for the first treatment cycle (28 days), CI = confidence interval, IIV = inter-individual variability, p5 = 5th percentile, p95 = 95th percentile.

The Applicant's Position:

No dose adjustments are recommended based on intrinsic patient factors.

The FDA's Assessment:

FDA agrees with the Applicant's position. The effect of severe renal impairment to end-stage renal disease (CLcr < 30 mL/min) and moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN, any AST) is unknown (although no effect is expected).

FCGR (Fc Fragment of IgG Receptor) Polymorphisms and Tumor Response: The Applicant explored whether germline FCGR2A and FCGR3A polymorphisms affect the response to tafasitamab (Appendix 19.4). The analyses were limited by small sample size and missing data and no conclusions could be drawn. More data are required to assess the role of FCGR polymorphisms on tafasitamab response. The applicant should continue to conduct FCGR genotyping in ongoing or planned trials.

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

No dedicated food-drug or drug-drug interaction studies were performed.

The Applicant's Position:

As tafasitamab is given as an i.v. infusion, there is no potential for food effects on bioavailability (BA).

As tafasitamab does not undergo extensive hepatic metabolism and the pharmacological modes of action do not offer the potential for a direct (anti-)inflammatory activity possibly modifying Cytochrome P450 function, no specific drug-drug interaction studies were performed.

Considering the combination of tafasitamab and lenalidomide, the potential impact of lenalidomide on the PK of tafasitamab was evaluated during covariate analysis of the population PK analysis (extrinsic factor) with no effect of lenalidomide on tafasitamab PK.

As LEN is reported to be excreted > 90% without being metabolized via renal filtration and is not subject to any Phase 1 or 2 metabolism, no risk for a potential drug-drug interaction of tafasitamab on the lenalidomide PK is expected.

BLA Multi-disciplinary Review and Evaluation BLA 761163
Monjuvi (tafasitamab-cxix)

The FDA's Assessment:

FDA agrees with the Applicant's position.

Vicky Hsu
Primary Reviewer

Ruby Leong
Team Leader

Ruojing Li
Pharmacometrics Reviewer

Lian Ma
Pharmacometrics Team Leader

Katarzyna Drozda
Pharmacogenomics Reviewer

Rosane Charlab Orbach
Pharmacogenomics Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

All studies pertinent to the evaluation of efficacy and safety are summarized in Table 10.

Table 10: Listing of Clinical Trials Relevant to This BLA

Trial	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
<i>Pivotal</i>							
MOR208C203	PH2, SA, OL, P, MC	Tafa: 12 mg/kg IV C1:D1,4, 8, 15, 22 C2-C3: D1, 8, 15, 22 C4+ until progression: D1,15 LEN: starting dose 25mg/day, administered for up to 12 cycles	1°: ORR 2°: DCR, DoR, PFS, OS, TTP, TTNT, safety, PK, immunogenicity	DCO: 30 NOV 2018 Median treatment duration: 9.2 months Median duration of PFS follow-up: 17.3 months Median duration of OS follow-up: 19.6 months	81	R/R DLBCL	56 centers; 10 countries
<i>Additional Supportive Studies to Support the Indication</i>							
MOR208C206	R, Obs	N/A (LEN Monotherapy)	1°: ORR 2°: DoR, PFS, OS, TTNT, EFS, DCR	DCO: 25 Aug 2019 Median treatment duration (MAS25): 7.8 months (Tafasitamab+LEN) and 3.9 months (LEN monotherapy) Median duration of follow-up (for OS, MAS25):	490	R/R DLBCL	4 countries (for LEN monotherapy)

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Trial	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				21.5 months (Tafasitamab+LEN) and 20.9 months (LEN monotherapy)			
MOR208C201	PH2, OL, MC	Tafa: 12 mg/kg IV C1-C2:D1,8,15,22 C3:D1, D15 or (if SD or better) D1,8,15,22 C4+ (if PR or better): D1,15 OR once every 4 weeks	1°: ORR 2°: PFS, TTP, DCR, Safety, PK, immunogenicity	DCO: 28 SEP 2018 Median treatment duration: 31.6 weeks Median duration of PFS follow-up: not reported	92	R/R DLBCL, FL, MZL, NHL	26 centers; 7 countries
Additional Supportive Studies Evaluating the Monotherapy							
XmAB5574-01	PH1, OL, MD, SA, DE	Tafa: 0.3, 1, 3, 6, 9, or 12 mg/kg IV C1:D1,4, 8, 15, 22, C2:D1,8,15,22 <u>Extension:</u> Tafa:12 mg/kg IV C3-7:D1	Identify MTD, Safety and tolerability of IV dosing PK, PD, and Immunogenicity Preliminary efficacy	DCO: 24 JAN 2013 Median treatment duration: 9 doses (infusions) across all treated patients (n=27) Median duration of follow-up: not reported	27	R/R CLL or SLL	3 centers; 1 country (US)
MOR208C202 (B-ALL)	PH2, OL, SA, MC	Tafa: 12 mg/kg IV C1:D1,4, 8, 15, 22, C2-4:D1,8,15,22	1°: ORR 2°: DoR, Time to hematological	DCO: 12 MAR 2015	22	R/R B-ALL	3 centers; 1 country (US)

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 Monjuvi (tafasitamab-cxix)

Trial	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		C4+:D1,15	relapse, Safety, MRD, immunogenicity, PK	Median treatment duration: 3.1 weeks Median duration of follow-up: not reported			
<i>Additional Supportive Studies Evaluating Other Combination Therapies</i>							
MOR208C204 (B-MIND)	PH2/3, OL, RA	Tafa: 12 mg/kg IV C1:D1,4, 8, 15, 22, C2-C4:D1,8,15,22 C4+ until progression:D1,15 Combination / with BEN or RTX+BEN	PFS, ORR, DoR, OS, DCR, TTP and TTNT Safety, QoL, PK and immunogenicity	DCO: not applicable (study ongoing) Median treatment duration: not applicable (study ongoing) Median duration of follow-up: not applicable (study ongoing)	Enrolled as of DCO: 283 Planned: ~450	R/R DLBCL	Ongoing
MOR208C205 (COSMOS)	PH2, OL, MC	Tafa: 12 mg/kg IV C1:D1,4, 8, 15, 22, C2-C4:D1,8,15,22 C4+:D1,15 Combination / with idelalisib (Cohort A) or venetoclax (Cohort B)	1°: Incidence and severity of (TEAEs) 2°: ORR, PK and immunogenicity	DCO: 09 NOV 2018 Median treatment duration: not reported Median duration of follow-up (Time on study): Cohort	24	R/R CLL or SLL	34 centers; 7 countries

BLA Multi-disciplinary Review and Evaluation BLA 761163
 Monjuvi (tafasitamab-cxix)

Trial	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				A: 9.9 months; Cohort B: 12 months			
Other studies (ongoing / planned)							
MOR208C107 (FIRST-MIND)	PH1, OL, RA	Tafa: 12 mg/kg IV C1-6: D1,8,15 Combination/R-CHOP or R-CHOP+LEN	1°: Incidence and severity of (TEAEs) 2°: ORR, CR, incidence and severity of AEs, PFS, EFS, OS, TTNT, immunogenicity	Planned treatment duration: 18 weeks (study ongoing)	Enrolled as of 31Jan2020: 2 Planned: ~60	Patients with newly diagnosed DLBCL	Ongoing
(b) (4)							Planned
(b) (4)							Planned

AE = adverse event; ALL = acute lymphoblastic leukemia; ASCT = Autologous stem-cell transplantation; BTK = Bruton’s Tyrosine Kinase; CLL = chronic lymphocytic leukemia; DCR = disease control rate; DE= dose escalation; DoR = duration of response; EFS = Event-free survival; FL = follicular lymphoma; HDC = High-dose chemotherapy; IV = intravenous; LEN = Lenalidomide; DLBCL = diffuse large cell B cell lymphoma; mAbs = monoclonal antibodies; MC= multicenter; MCL = mantle cell lymphoma; MD= Multiple dose; MRD = minimal residual disease; MZL = marginal zone lymphoma; Obs= Observational; OL= Open label; ORR = overall/objective response rate; OS = overall survival; P= prospective; PH= Phase; PK = pharmacokinetics; PFS = progression free survival; QOL = quality of life; R/R = relapsed or refractory; R= Retrospective; RA= Randomized; RTX = Rituximab; SA= single arm; SLL = small lymphocytic lymphoma; Tafa = Tafasitamab; TBD = to be determined; TEAEs = treatment-emergent adverse events; TTNT = time to next treatment; TTP = time to progression

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The Applicant's Position:

All studies listed above are relevant to the evaluation of efficacy and/or safety of tafasitamab to support the proposed indication.

Other studies (ongoing or planned studies MOR208C107, (b) (4)) are not pertinent for the current evaluation of efficacy and safety of tafasitamab to support the proposed indication (no data available).

The FDA's Assessment:

Study MOR203 was the pivotal study supporting efficacy of tafasitamab in patients with relapsed or refractory DLBCL. Studies MORC201 and MORC206 are relevant to the evaluation of efficacy. The safety evaluation focused on the pivotal trial MOR208C203 supported by a pooled evaluation of tafasitamab monotherapy in trials MOR208C201, MOR208C202, and XmAb5574-01.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Data supporting the overall efficacy of 12 mg/kg IV tafasitamab in combination with lenalidomide (LEN) in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) are based on 3 studies, MOR208C203 (L-MIND), MOR208C206 (RE-MIND), and MOR208C201 (Table 10). MOR208C203 studied the efficacy of tafasitamab in the intended regimen (in combination with LEN), the proposed dosing regimen, the proposed indication (adult patients with R/R DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for, (b) (4) autologous stem cell transplant) and utilizes the intended commercial drug formulation. The contribution of each of the single agents in the combination was determined via 1) MOR208C201, which demonstrated the activity of tafasitamab monotherapy in DLBCL patients; and 2) MOR208C206, in which the efficacy of LEN monotherapy was statistically assessed in a matching observational cohort to the combination in MOR208C203 study

8.1.1. MOR208C203, L-MIND

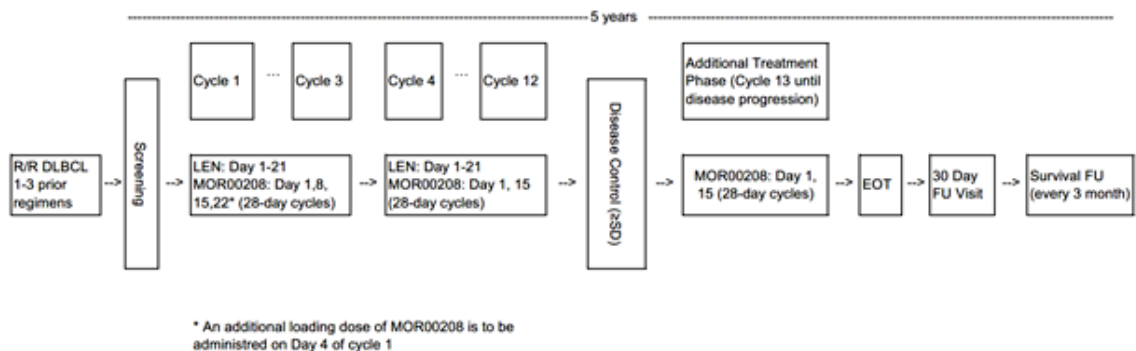
Trial Design

The Applicant's Description:

This is an ongoing Phase 2, single-arm, open-label, multicenter study conducted at sites in the

U.S. and Europe designed to evaluate the efficacy and safety of tafasitamab + LEN in patients with R/R DLBCL. The study included patients who had relapsed after or were refractory to at least 1, but no more than 3 previous systemic regimens (one therapy line must have included a CD20-targeted therapy such as rituximab [RTX]), and who were not candidates for HDC and subsequent ASCT (or relapsed after ASCT). The study design is depicted in Figure 9.

Figure 9: Trial Design of Clinical Study MOR208C203



EOT=end of treatment; FU=follow-up; LEN=lenalidomide; R-R DLBCL=relapsed or refractory diffuse large B-cell lymphoma; SD=stable disease.

Tafasitamab was administered via IV infusion at a dose of 12.0 mg/kg. For the first 3 cycles (Cycles 1-3), tafasitamab was administered on Day 1, Day 8, Day 15, and Day 22 of each 28-day cycle, with an additional loading dose on Day 4 of Cycle 1. Thereafter, tafasitamab was administered on Day 1 and Day 15 of each 28-day cycle. LEN was self-administered by patients daily with a starting dose of 25 mg orally on Days 1 to 21 of each 28-day cycle. LEN was administered in combination with tafasitamab up to 12 cycles in total. In patients with at least SD after 12 cycles of combination therapy, tafasitamab was administered until disease progression, unacceptable toxicity or discontinuation for any other reason, whichever came first.

The FDA's Assessment:

FDA agrees with the above description. Further details of the trial are provided below.

Patient population

Inclusion criteria (summarized)

- Age >18 years
- Diagnosis of DLBCL not otherwise specified, T cell/histiocyte rich large B-cell lymphoma, Epstein-Barr positive DLBCL of the elderly, Grade 3B follicular lymphoma, composite lymphoma with a DLBCL component with a subsequent DLBCL relapse. Diagnosis was

according to the Revised European American Lymphoma/World Health Organization classification. Patients with transformation from previous low grade lymphoma to DLBCL with a subsequent relapse of DLBCL were also eligible.

- Fresh tumor for central pathology review was to be provided, if not possible, archival tissue ≤ 3 years prior must be available.
- Patients must have
 - Relapsed and/or refractory disease
 - At least one bidimensional measurable disease site
 - Received at least 1 but no more than 3 previous systemic regimens for the treatment of DLBCL. A CD20 targeted therapy must have been included in one therapy line
 - ECOG performance status of 0 to 2
- Patients not considered eligible, or unwilling to proceed with, intensive salvage therapy including ASCT. Documentation of the reason was to be provided.
- Laboratory values at screening including:
 - ANC $\geq 1.5 \times 10^9/L$ (unless due to bone marrow involvement)
 - Platelet count $\geq 90 \times 10^9/L$ (unless due to bone marrow involvement)
 - Total serum bilirubin $\leq 2.5 \times ULN$ unless Gilbert's syndrome or liver involvement by lymphoma then total bilirubin $\leq 5 \times ULN$
 - ALT, AST and alkaline phosphatase $\leq 3 \times ULN$ or $< 5 \times ULN$ if documented liver involvement
 - Serum creatinine clearance must be ≥ 60 mL/min using Cockcroft Gault formula
- Able to receive adequate prophylaxis for thromboembolic events
- Give written informed consent

Exclusion criteria (summarized)

- Other types of lymphoma including primary mediastinal (thymic) large B-cell or Burkitt lymphoma
- Primary refractory DLBCL
- History of double/triple hit genetics with detection of MYC with BCL2 and/or BCL6 translocations defined by FISH. MYC, BCL2, BCL6 testing prior to enrollment was not required.
- Patient within 14 days prior to first dose:
 - Not discontinued CD20 targeted therapy, chemotherapy, radiotherapy or other lymphoma specific therapy
 - Major surgery or significant trauma
 - Received a live vaccine
 - Required parenteral antimicrobial therapy for an active infection
- Patients who:
 - Have not recovered from toxic effects of prior therapy
 - Previously treated with CD19 targeted therapy or IMiDs

- Undergone ASCT within 3 months of signing the informed consent. Patients with a history of ASCT must have full hematologic recovery.
- Previous allogenic transplantation
- History of deep vein thrombosis/embolism or at a high risk for thromboembolic event and not able to take prophylaxis
- Patients with a medical history of:
 - Positive hepatitis B and/or hepatitis C serology
 - Known seropositivity for HIV
 - CNS lymphoma involvement
 - Clinically significant cardiovascular, CNS and/or other systemic disease that prohibit trial participation
 - History of rare hereditary problems of galactose malabsorption
 - Severe hepatic impairment (total bilirubin > 3 mg/dL), jaundice unless due to Gilbert's syndrome or documented liver involvement by lymphoma

Treatment was administered as stated above. The investigator was to decide if the patient should continue therapy in case of disease progression.

Prior to proceeding with a new cycle, the patient was to have met the following criteria:

- ANC $\geq 1.000/\text{mm}^3$ (unless due to bone marrow involvement)
- Platelets $\geq 50000/\text{mm}^3$ (unless due to bone marrow involvement)
- No serious organ or other toxicity present

For this trial primary refractory disease was defined as disease progressing in the course of the first line of treatment according to International Working Group response criteria and/or a response of less than a PR to first line treatment or disease recurrence/progression within ≤ 6 months from the completion of first line treatment. Disease refractory to last treatment was defined as less than a partial response to the most recent therapy.

Relapsed/progression/recurrent disease was defined as any new lesions or increase by $\geq 50\%$ according to International Working Group response criteria.

Dose Modifications:

Dose reductions for tafasitamab were not allowed during the trial.

Dose modification for hematologic toxicities are displayed in Figure 10 and dose modification guidelines for other toxicities considered related to lenalidomide are displayed in Figure 11. The dose reduction guidelines for lenalidomide are displayed in Figure 12.

Figure 10: Dose Modification for Hematologic Toxicities

Grade 3/4 thrombocytopenia judged to be related to study drugs	PLTs fall to <50000/ μ l	Interrupt MOR00208* and LEN dosing) Follow CBC every 7 days
	PLTs return to $\geq$ 50000/ μ l	Provided all other criteria are fulfilled, resume dosing of MOR00208 and/or LEN. LEN should be administered at the next lower dose level (Table 4)
Grade 3/4 neutropenia judged to be related to study drugs	ANC falls to <1000/ μ l for at least 7 days or ANC falls to <1000/ μ l with an associated body temperature $\geq$ 38.5°C or ANC falls to <500/ μ l	Interrupt MOR00208* and LEN dosing Follow CBC every 7 days Growth factors (G-CSF) and antimicrobial prophylaxis is to be used, as per local guidelines
	ANC return to $\geq$ 1000/ μ l	Provided all other criteria are fulfilled, resume dosing of MOR00208 and/or LEN. LEN should be administered at the next lower dose level (Table 4)
Other clinically significant toxicities judged to be related to study drugs	Grade 3/4	Interrupt the administration of the study drug(s)* to which the toxicity is judged to be related to.
	Toxicities resolve to grade $\leq$ 2	Provided all other criteria are fulfilled, resume dosing of study drug(s). LEN should be administered at the next lower dose level (Table 4)

Abbreviations: ANC=absolute neutrophil count; CBC=complete blood count; G-CSF=granulocyte colony-stimulating factor; LEN=lenalidomide; PLT=platelets.

Source: Applicant submission: Final protocol MOR208C203 Amendment 3 Version 6 page 53]

Figure 11: Other Toxicities Judged to be Related to Lenalidomide

Thromboembolic events	Grade 3/4	Interrupt LEN dosing Start anticoagulation as per local guidelines Continue MOR00208 treatment as per protocol
	Toxicities resolve to grade ≤ 2	Restart LEN at investigator's discretion (maintain dose level) Continue MOR00208 treatment as per protocol
Allergic reaction or hypersensitivity grade 3/4 (including but not limited to Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative or bullous rash, angioedema)	Grade 3/4	Discontinue LEN permanently Continue MOR00208 treatment as per protocol
Allergic reaction or hypersensitivity	Grade >2	Interrupt LEN dosing Follow at least every 7 days Continue MOR00208 treatment as per protocol
	Resolved to $\leq$ grade 2 severity or at least the baseline value (for pre-existing conditions; at screening)	Restart LEN (next lower dose level)
Desquamating (blistering) rash $\geq$ grade 3 or nondesquamating rash grade 4 considered to be related to LEN		Discontinue LEN permanently Continue MOR00208 treatment as per protocol
Nondesquamating rash	Grade 3/4	Interrupt LEN dosing Continue treatment with MOR00208 as per protocol
	Resolve to grade ≤ 1	Restart LEN at next lower dose level
Tumour flare reaction	Grade 3/4	Interrupt LEN dosing Provide symptomatic treatment as per local guidelines Continue treatment with MOR00208 as per protocol

	Resolve to grade ≤ 1	Restart LEN (maintain same dose level)
Tumour flare reaction	Grade 1/2	Provide symptomatic treatment as per local guidelines Continue LEN without dose modification or interrupt LEN dosing at investigator's discretion Continue treatment with MOR00208 as per protocol

Source: Applicant submission, Final protocol MOR208C203 Amendment 3 Version 6 page 54-55]

Figure 12: Lenalidomide Dose Reduction Guidelines

Starting dose	25 mg daily on Days 1–21, every 28 days
Dose Level - 1	20 mg daily on Days 1–21, every 28 days
Dose Level - 2	15 mg daily on Days 1–21, every 28 days
Dose Level - 3	10 mg daily on Days 1–21, every 28 days
Dose Level - 4	5 mg daily on Days 1–21, every 28 days

Source: Applicant submission, Final protocol MOR208C203 Amendment 3 Version 6 page 55]

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint of this study was Best Objective Response Rate (ORR), defined as the proportion of complete and partial responders ($ORR = CR + PR$), as assessed by Independent Radiology/Clinical Review Committee (IRC) according to the International Working Group revised response criteria for malignant lymphoma ([Cheson et al., 2007](#)).

Additional efficacy endpoints included:

- Disease control rate (DCR), defined as the proportion of patients having CR or PR or SD ($DCR = ORR + SD$);
- Duration of response (DoR), defined as the time between the initial time point of tumor response and the first time point where a change in response to progression or relapse was detailed;
- Progression-free survival (PFS), defined as the time between first study drug dosing and tumor progression or death from any cause, whichever occurs first;
- Time to progression (TTP), defined as the time from first study drug dosing until time of progression;
- Overall survival (OS), defined as time from first study drug dosing to the date of death;
- Time to next treatment (TTNT).

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints. The endpoints that FDA used to determine the benefit of tafa+LEN in the context of the single arm trial are ORR and DOR. The primary efficacy endpoint, as prespecified, was to be based on an independent, central radiographic review. Two independent radiologists reviewed the imaging findings with adjudication of discrepant responses. The disease assessments incorporated review by a clinical reviewer to determine the overall disease status.

Statistical Analysis Plan and Amendments

The Applicant's Description:

For the determination of a suitable sample size, it was assumed that the combination treatment could improve the ORR of LEN from a value of 20% (under monotherapy) to 35% (under combination therapy). For an exact binomial test with a two-sided significance level of 5% and a power of 85% the calculated sample size was 73 patients. With an assumed drop-out rate of 10%, a total sample size of about 80 patients was estimated.

The initial SAP Version 1.0 was amended after DCO for primary analysis but before database lock of the primary analysis (April 18, 2019), resulting in SAP Version 2.0 (April 8, 2019).

SAP Version 2.0 was subject to an addendum (Addendum 1.0) after the database lock of the primary analysis. Changes to the SAP versions are summarized in the following table:

Table 11: Summary of Changes to SAP

SAP Version	Date	Changes to the previous SAP version
Version 1.0	November 09, 2015	Not applicable
Version 2.0	April 08, 2019	• Paragraphs were rephrased to detail analysis strategies. • Multiple subgroup and sensitivity analyses were added.
Addendum 1.0 to SAP Version 2.0	August 09, 2019	• Efficacy and safety analyses were added.

Primary and secondary endpoints were not affected by these modifications, and the analysis strategies as initially specified in SAP Version 1.0 remained unchanged.

The data cut-off (DCO) date for the analysis of MOR208C203 (i.e. approximately 12 months after the last patient has been enrolled) was Nov 30, 2018. The full analysis set (FAS) was defined as all patients who received ≥ 1 dose of tafasitamab and ≥ 1 one dose of LEN.

For the primary endpoint (ORR), the number and percentage of patients classified as having best overall response of CR or PR as determined by IRC with 95% confidence limits (using the

Clopper-Pearson exact method) was calculated. DCR (ORR+SD) was evaluated using the same methods as ORR. For the time-to-event endpoints DoR, TTP, PFS, OS, and TTNT, Kaplan-Meier methodology was applied. With the exception of OS and TTNT, all endpoints were analyzed based on both IRC and investigator response assessments. No formal statistical hypothesis testing was performed.

Additional sensitivity assessments were conducted on the per protocol population (PPS), as well as on the FAS based on the Investigator assessment, and excluding patients with no post-baseline assessment of response.

The FDA's Assessment:

FDA agrees with the Applicant's general description. The L-MIND study was designed to rule out an ORR of 20%. The populations for analysis were defined as:

- The full analysis set was all patients who received at least one dose of tafasitamab and one dose of lenalidomide.
- The safety analysis set was all patients who received at least 1 dose of tafasitamab or lenalidomide.
- The per protocol set was all patients in the full analysis set without any major protocol non-compliances. Patients without any post-baseline assessment of DLBCL response or having major protocol deviations were to be excluded from the per protocol set.

The primary analysis of the primary efficacy endpoint was based on the full analysis set. To address the potential for outcome-dependent sampling where eligible patients who initiated study therapy may be more likely to respond than eligible patients who did not initiate study therapy, the Agency extended FAS to include one patient who was dosed with tafasitamab but not lenalidomide, hereafter referred to in this document as the enrolled set. As with FAS, any patient in the enrolled set without disease assessments are classified as non-responders.

Protocol Amendments

The Applicant's Description:

The initial protocol was amended 3 times prior to the DCO for the primary analysis. These changes are not expected to have had an impact on the integrity of the trial or interpretation of the results. Key changes were as follows:

- Amendment 1 (May 27, 2015): Amendment 1 included updates to correct minor inconsistencies and organizational changes made since release of the original protocol and updates/clarification made to eligibility criteria, patient compliance, and safety assessments.
- Amendment 2 (June 27, 2016): Changes were made to the eligibility criteria to allow up to three prior lines for DLBCL treatment (previously two prior lines), set an upper age

limit on treatment (80 years), as well as to provide additional specifications for other inclusion/exclusion criteria. The definition of primary refractory DLBCL was revised to less than a PR to first-line therapy or progression within 6 months from completion of first-line therapy and removed the need to have DLBCL relapse/progression after at least 3 months from completion of prior CD20-containing therapy. This definition of primary refractory DLBCL matched the commonly applied period (6 months) for determining rituximab refractoriness, and was consistent with the scientific advice received from regulatory agencies.

- Amendment 3 (Oct 23, 2017): The primary change involved extension of tafasitamab therapy beyond Cycle 24 until disease progression, based on the decision of the treating investigator.

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments.

8.1.2. Study Results

Patient Disposition

A total of 81 patients were enrolled, of whom 80 (98.8%) received both tafasitamab and LEN. One patient received tafasitamab only and was excluded from the FAS. Overall, 30 of the 81 patients enrolled (37.0%) successfully completed the combination treatment phase on both study drugs (12 cycles). Fifty-one out of the 81 patients enrolled (63.0%) did not complete the combination treatment phase (Cycle 1 to Cycle 12), primarily due to progressive disease (32 patients, 39.5%). Ten patients did not complete the combination phase due to an adverse event, two due to patient withdrawal, and one due to other reasons. The primary reason for discontinuation of tafasitamab monotherapy beyond Cycle 12 was progressive disease (4 patients), followed by adverse event (1 patient), and patient withdrawal (1 patient). Twenty eight (34.6%) patients were still on treatment with tafasitamab monotherapy at the primary DCO of Nov 2018.

The Applicant's Position:

A substantial number of patients were able to complete the combination phase and continued tafasitamab monotherapy beyond 12 months. The most common cause of discontinuation of study drug was disease progression.

The FDA's Assessment:

FDA agrees with the Applicant's description.

Protocol Violations/Deviations

Key protocol deviations included deviations associated with prohibited concomitant medication (6.2%), informed consent forms (25.9%), eligibility criteria (24.7%), laboratory assessment (35.8%), procedure or test (76.5%), study drug and treatment (38.3%), visit schedule and assessment (1.2%), and other (27.2%). Three protocol deviations in the FAS were considered major protocol violations, leading to patient exclusion from the PPS. Two patients were excluded due to prohibited concomitant medication use, and one patient was excluded due to failing an inclusion criterion [PET-positive measurable disease could not be confirmed as a part of screening assessments].

The Applicant's Position:

The most frequently reported protocol violations were those relating to study procedures or tests. No patient was excluded from the FAS due to a protocol violation. Although a total of 191 protocol deviations occurred, none materially altered the assessment of safety or efficacy.

The FDA's Assessment:

There was high rate of protocol deviations reported in the L-MIND trial. Of the 81 patients, a total of 73 patients had at least 1 major protocol deviation. The categories of major protocol deviations are displayed in Table 12.

An Information Request was sent to the Applicant regarding the high rate of protocol deviations on the L-MIND trial. The Applicant noted a conservative approach to protocol deviations and a potential over-reporting of deviations. The majority of the deviations were considered by the Applicant to not impact the integrity of the trial data. Protocol deviations and violations were also noted during the remote OSI inspections See Section 4.1. for reviewer comments regarding protocol deviations. Patients without any post-baseline assessment of DLBCL response or having major protocol deviations were to be excluded from the per protocol set.

Table 12: Major Protocol Deviations

Deviation	N	% (N=81)
Procedures/tests	62	76.5
Study drug	31	38.3
Laboratory	29	35.8
Other	22	27.2
ICF issues	21	25.9
Inclusion/exclusion criteria	20	24.7
Concomitant medications	5	6.17
Visit schedule	1	1.23

Source: FDA analysis

Demographic Characteristics

The majority of patients were male (53.8%) and white (90.0%). The median age was 72.0 years (min, max: 41, 86); the majority (71.3%, 57/80) were ≥65 years of age.

Table 13: Demographic Characteristics (FAS) (MOR208C203)

Demographic Characteristics		Tafasitamab + LEN (N = 81)
Age (years)	Mean (StD)	69.3 (9.53)
	Median	72.0
	Q1, Q3	62.0, 76.0
	Min, max	41, 86
Age group (years) n (%)	< 60	17 (21.0)
	≥ 60	64 (79)
	< 65	23 (28.4)
	≥ 65	58 (71.6)
	≤ 70	36 (44.4)
	> 70	45 (55.6)
Sex n (%)	Male	44 (54.3)
	Female	37 (45.7)
Race n (%) ^a	Asian	2 (2.5)
	White	72 (88.9)
	Other	1 (1.2)
	Missing	6 (7.4)*

Abbreviations: FAS = full analysis set; LEN = lenalidomide; StD = standard deviation; Q1 = lower quartile; Q3 = upper quartile

*Data on race was not collected from certain sites, e.g., in France.

^a More than one race could be checked (categories were not mutually exclusive).

The Applicant's Position:

Overall, the patient population enrolled in this study was representative of the proposed target population of adult patients with R/R DLBCL in US, including DLBCL arising from low grade lymphoma, and who are not eligible for or refuse, ASCT.

The FDA's Assessment:

The Agency agrees with the Applicants demographic characteristics of the patient population. However, Table 13 characterized patients in the enrolled set (n=81), not patients in FAS (n=80). FDA notes that the median age of the patients enrolled, 72 years, is higher than the median age of patients diagnosed with DLBCL in the US population reflecting the population who are likely ineligible to receive autologous stem cell transplantation due to age or comorbidities.

FDA does not agree with the statement that the enrolled patients were representative of the proposed target population of adult patients with R/R DLBCL in the US for the following reasons: 1) the precise definition (taking into consideration the eligibility criteria and other comorbidities) of the target population was never specified and 2) there was no random selection of patients from the target population into the L-MIND trial. For example, the L-MIND study consisted mostly of Whites. Furthermore, patients in clinical practice may have more comorbidities that may not be reflected in the L-MIND trial.

The patient population for the MOR208C203 was 88.9% white, 2.5% Asian, missing 7.4% and 1.2% other. A total of 6 patients in the L-MIND trial were enrolled in the U.S. As a result of a lack of diversity in the patient population a PMC will be issued to further evaluate the efficacy and safety of tafasitamab in the underrepresented racial subgroups. Refer to Section 13.

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

Table 14 provides an overview of important baseline characteristics for the study population.

Table 14: Baseline Characteristics (FAS) (MOR208C203)

Baseline Characteristics	Tafasitamab + LEN (N = 81)
Number of prior systemic treatment lines (DLBCL medications) n (%)	
1	40 (49.4)
2	35 (43.2)
3	5 (6.2)
4	1 (1.2)
≥ 2	41 (50.6)
Time since first DLBCL diagnosis (months)	
n	81
Mean (StD)	39.6 (34.8)

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Baseline Characteristics	Tafasitamab + LEN (N = 81)
Median	26.9
Q1, Q3	16.9, 50.1
Min, max	7.8, 189.3
Time since discontinuation of last prior anti-DLBCL medication or ASCT (months)	
n	81
Mean (StD)	17.0 (21.8)
Median	9.2
Q1, Q3	4.9, 20.2
Min, max	0.6, 121.9
Time between first DLBCL diagnosis and first documented relapse or progression n (%)	
≤12 months	19 (23.5)
>12 months	61 (75.3)
Unknown	1 (1.2)
ECOG performance status n (%)	
0	29 (35.8)
1	45 (56.6)
2	7 (8.6)
Ann Arbor Disease Staging dichotomized n (%)	
Stage I and II	20 (24.7)
Stage III and IV	61 (75.3)
IPI Category n (%)	
Low risk and low-intermediate risk (IPI Score 0-2)	40 (49.4)
High risk and intermediate-high risk (IPI Score 3-5)	41 (50.6)
LDH levels at baseline n (%)	
Within reference range	36 (44.4)
Beyond reference range	44 (55.6)
Cell of origin based on immuno-histochemistry/central pathology n (%)**	
GCB	38 (46.9)
Non-GCB	21 (25.9)
Missing	22 (27.2)
Rituximab refractoriness n (%)	
Yes	34 (42)
No	46 (56.8)
Unknown	1 (1.2)
Refractoriness to last prior therapy n (%)	
Yes	36 (44.4)
No	45 (55.6)
Primary refractoriness n (%)	
Yes	15 (18.5)
No	66 (81.5)
Prior ASCT n (%)	
Yes	9 (11.1)
No	72 (88.9)

The Applicant's Position:

Overall, the patient population enrolled in this study was representative of the proposed target population of adult patients with R/R DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for or refuse, ASCT.

The FDA's Assessment:

The presentation of baseline disease characteristics in Table 14 is not entirely accurate. As with Table 13, the results pertain to the enrolled set (n = 81), not FAS (n = 80). With respect to elevated LDH in the enrolled set, 36 (44%) did not have elevated LDH at baseline while 45 (56%) had elevated LDH at baseline. FDA does not agree with the statement that the patients in the L-MIND study were representative of the target population as the precise definition of the target population was never specified and there was no random selection of patients from the target population into the L-MIND study. Additionally, there were limited representation of other racial subgroups other than whites.

Although patients with primary refractory disease were enrolled in the L-MIND trial, they should have been excluded as this was an exclusion criterion. Per the protocol, the demographics for the primary refractory patient population will not be presented in the USPI. However, the FDA notes that patients with primary refractory disease have a very poor prognosis and have limited effective treatment options. The median time since last discontinuation of last DLBCL treatment or ASCT was 9 months reflects the treatment paradigm for DLBCL therapies where treatment with combination chemoimmunotherapy is stopped after a defined number of treatment cycles. The median time to initiation of tafasitamab and lenalidomide since last progression or relapse was 1.4 months (FDA analysis) which indicates that the L-MIND trial enrolled a patient population with an immediate need for treatment.

Patients on trial MOR208C203 were enrolled and treated based on local pathology, however, retrospective central pathology review was done. Based on central pathology a total of 9 patients were non-DLBCL and 2 were unknown. Table 15 lists the patients with confirmed DLBCL and Table 16 lists the patients who were confirmed with a lymphoma type other than DLBCL. Patients with a diagnosis other than DLBCL were excluded from the efficacy analysis for the U.S. Prescribing Information. FDA also notes that DLBCL not otherwise specified was the predominant subtype in the L-MIND study. In response to an IR, the Applicant provided data from 9 patients who had a previous diagnosis of indolent lymphoma transformed to DLBCL. The indication for the U.S. Prescribing Information will reflect the lymphoma subtypes enrolled.

Table 15: Patients with Confirmed DLBCL

Diagnosis	Number of patients N=81 n (%)
Composite lymphoma with DLBCL component	9 (11.1)
DLBCL	56 (69.1)
DLBCL (double hit lymphoma)	1 (1.2)
DLBCL (triple hit lymphoma)	1 (1.2)
EBV-positive DLBCL	2 (2.5)
T cell/histiocyte rich large B cell lymphoma	2 (2.5)

Source: Applicant’s response to FDAs information request

Table 16: Patients with Lymphoma Type Other Than DLBCL Based on Central Pathology Review

Diagnosis	Number of patients N=81 n(%)
Follicular lymphoma (grade 2 +3A)	1 (1.2)
Follicular lymphoma (grade 2)	2 (2.5)
Mantle cell lymphoma, classic type	1 (1.2)
Marginal zone lymphoma	4 (4.9)
unknown	1 (1.2)

Source: Applicant’s response to FDAs information request.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was summarized per single infusion (for tafasitamab) and per cycle (for both tafasitamab and LEN). Compliance was reached if $\geq 80\%$ and $\leq 120\%$ of the dose was administered. Planned dose reductions (LEN) and planned interruptions (LEN, tafasitamab) due to medical reasons were accounted for the determination of treatment compliance. The median compliance for both tafasitamab and LEN for each cycle was 100% until Cycle 34.

All patients in the FAS reported the use of concomitant medications. The most frequently ($\geq 20\%$) reported concomitant medications were paracetamol (45.0%), filgrastim (38.8%), allopurinol (32.5%), acetylsalicylic acid (30.0%), enoxaparin sodium ([28.8%), Bactrim and ciprofloxacin (26.3%), acyclovir, amoxicillin/clavulanic acid, and furosemide (23.8%) and levofloxacin (21.3%). Protocol deviations due to the use of prohibited medications were reported in 5 (6.2%) patients.

The Applicant's Position:

Treatment compliance for tafasitamab was ensured as it was infused under the direct supervision of study personnel. Also for LEN, a high overall compliance to the treatment as prescribed by the protocol was recorded.

Due to the patient population (primarily elderly with advanced disease), the proportion of patients taking concomitant medications is expected. There were a few cases of prohibited concomitant medication usage, the majority of which were associated with corticosteroid (prednisone) use. Two of these prohibited concomitant medication deviations were considered major deviations, resulting in patients' exclusion from the PPS (one patient had concomitant administration of corticosteroids in excess of a dose specified as per protocol; one patient received radiotherapy due to disease progression but did not stop study drug as per protocol).

The FDA's Assessment:

The U.S. Prescribing Information will reflect the use of premedication's to minimize infusion-related reactions, especially during the first three infusions.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The best ORR based on IRC was 60% (95% CI: 48.4, 70.8), and CR rate was 42.5% (95% CI: 31.5, 54.1); 30/34 CRs were PET confirmed. A best response of PR was observed in 17.5% (95% CI: 9.9, 27.6), SD in 11 (13.8%), PD in 13 (16.3%) patients, and 8 (10.0%) patients were not evaluable. There was an 88.2% concordance between IRC and Investigator assessments in the FAS for best ORR. A sensitivity analysis on the per protocol set (PPS, N=70), excluding patients with no post-baseline assessment of response (n=8) or who received prohibited concomitant therapy (n=2) or did not have measurable disease at baseline (n=1), demonstrated robustness of the results with an ORR of 65.7% (95% CI: 53.4, 76.7) and CR for 33 (47.1%) patients.

Table 17: Best Objective Response Rate Summary in Patients with R/R DLBCL

Results per IRC	Tafasitamab + LEN N = 80
Best Objective Response Rate, n (%) (95% C.I.)*	48 (60) (48.4, 70.8)
Complete response rate, n (%) (95% C.I.)*	34 (42.5) (31.5–54.1)
Partial response rate, n (%) (95% C.I.)*	14 (17.5) (9.9–27.6)

(*) Binomial exact CI using Clopper Pearson method

The Applicant’s Position:

18.5% of patients had primary refractory DLBCL, 50% of patients had $\geq$ two prior lines of therapy, and over 10% of patients had relapsed after HSCT. Thus, the patient population had disease that was both heavily pre-treated and demonstrated decreased sensitivity to standard of care chemotherapy regimens. The combination of tafasitamab and LEN demonstrated substantial efficacy in ASCT-ineligible R/R DLBCL patients with only limited therapeutic options.

The FDA’s Assessment:

Not all patients in the L-MIND study had confirmed DLBCL at baseline. Out of the 81 patients in the enrolled set, 71 had confirmed DLBCL, hereafter referred to as the confirmed enrolled set. During the review, further information was requested from the Applicant regarding the adjudication of the response determination. As a result of this review by the FDA and the Applicant, it was determined an error was made as one patient who was previously considered to be a CR should have been a best response of SD. This will be reflected in the USPI. Among the 71 patients in the confirmed enrolled set, 39 (55%; 95% CI:43%, 67%) responded:

- CR. 26 (37%; 95% CI: 25%, 49%)
- PR. 13 (18%; 95% CI: 10%, 29%)

Note that results per FDA’s analyses are similar to those presented by the Applicant. Note also that 1 of the 71 patients in the confirmed enrolled set was dosed with tafasitamab but not with lenalidomide. Per the SAP, the primary analysis set was FAS which was defined as consisting of patients who were dosed with both drugs at least once. This suggests that FDA’s analyses should include only 70 patients in the denominator. However, as stated earlier, excluding patients who met eligibility criteria but were not treated is susceptible to outcome-dependent sampling in the sense that patients not dosed has the potential to be less likely to respond than those who were dosed. Therefore, FDA’s analysis uses all 71 eligible patients in the denominator.

A difference in the response rate was noted in patients who had DLBCL confirmed by central pathology vs patents who had an alternative diagnosis as per central pathology (Figure 13). Patients with an alternative diagnosis per central pathology were excluded from the efficacy

Figure 13: Efficacy Outcomes (IRC) and OS by Local and Central Pathology

	DLBCL as per Local Pathology (FAS)	DLBCL as per Central Pathology	Alternative Diagnosis as per Central Pathology
	(N = 80)	(N = 70)	(N = 8)
BORR^a (95% CI^b)	60% (48.4, 70.8)	57.1% (44.7, 68.9)	75% (34.9, 96.8)
CR rate (95% CI)	42.5% (31.5, 54.1)	38.6% (27.2, 51.0)	75% (34.9, 96.8)
Median DoR, months (95% CI)	21.7 (21.7 - NR)	21.7 (21.7 - NR)	NR (NR - NR)
Median PFS, months (95% CI)	12.1 (5.7-NR)	9.1 (4.7 - NR)	NR (0.6 - NR)
Median OS (95% CI)	NR (18.3 - NR)	NR (14.8-NR)	NR (0.6 - NR)

Source: From Applicant submission; Response to FDA Request dated April 03, 2020 page 10

Efficacy Results – Secondary and other relevant endpoints

Twenty-eight (34.6%) of 80 patients were ongoing with treatment and in remission at the primary DCO. Median time to initial response was 2.0 months (range: 1.7–16.8); and median time to CR was 7.1 months (range: 1.7–17.0).

The table below summarizes the overall duration of response and the duration of response by best response category.

Table 18: Duration of Response in Patients with R/R DLBCL

Results per IRC (months)	Tafasitamab + LEN N = 80
Number of responders	48
Overall DoR	
Median ^a (95% C.I.)	21.7 months (21.7 – not reached)
12 months DoR % ^a (95% C.I.)	71.6% (55.1, 82.9)

Results per IRC (months)	Tafasitamab + LEN N = 80
Number of responders	48
18 months DoR % (95% C.I.)	71.6% (55.1, 82.9)
DoR if Best Response is CR	
Median ^a (95% C.I.)	Not reached (21.7 – not reached)
12 months DoR % ^a (95% C.I.)	93.2 % (75.4, 98.3)
18 months DoR % (95% C.I.)	93.2 % (75.4, 98.3)
DoR if Best Response is PR	
Median ^a (95% C.I.)	4.4 months (2.0, 9.1)
12 months DoR % ^a (95% C.I.)	14.4 % (1.1, 43.7)
18 months DoR % (95% C.I.)	not estimable not estimable

^a Kaplan Meier estimates

With a median follow-up of 17.3 months, median PFS was 12.1 (95% CI: 5.7, NR) months. With a median follow-up of 19.6 months, the median for OS was not reached (95% CI: 18.3, NR). The Kaplan-Meier estimates of achieving OS at 12, 18, and 24 months were 73.7%, 63.6% and 56.6%, respectively. The median TTP was 16.2 months and the median TTNT was 15.4 months. Overall, 59 of 80 patients demonstrated a clinical benefit, 48 were responders and 11 showed SD as best response, resulting in a DCR of 73.8% (95% CI: 62.7, 83.0).

The Applicant’s Position:

Secondary endpoints corroborate findings from the primary efficacy analysis, showing that the combination of tafasitamab and LEN demonstrates substantial efficacy in NTE patients with R/R DLBCL. DoR results show that patients who achieve a CR have a high probability to remain in remission for an extended period of time, with 93.2% of patients in response at 18 months. In contrast, patients achieving only a PR as best response tend to progress within the next 6 months. The time-to-event endpoints from this single-arm study are considered descriptive.

The FDA’s Assessment:

There were 39 responders among DLBCL-confirmed patients. Estimated median DOR (in months) and its associated 95% confidence interval among these 39 responders is 21.7 (95% CI: 21.7, NE). The durability of response represents a meaningful treatment benefit in this patient population. However, the FDA notes that the durability of response was primarily observed in patients who achieved a complete response.

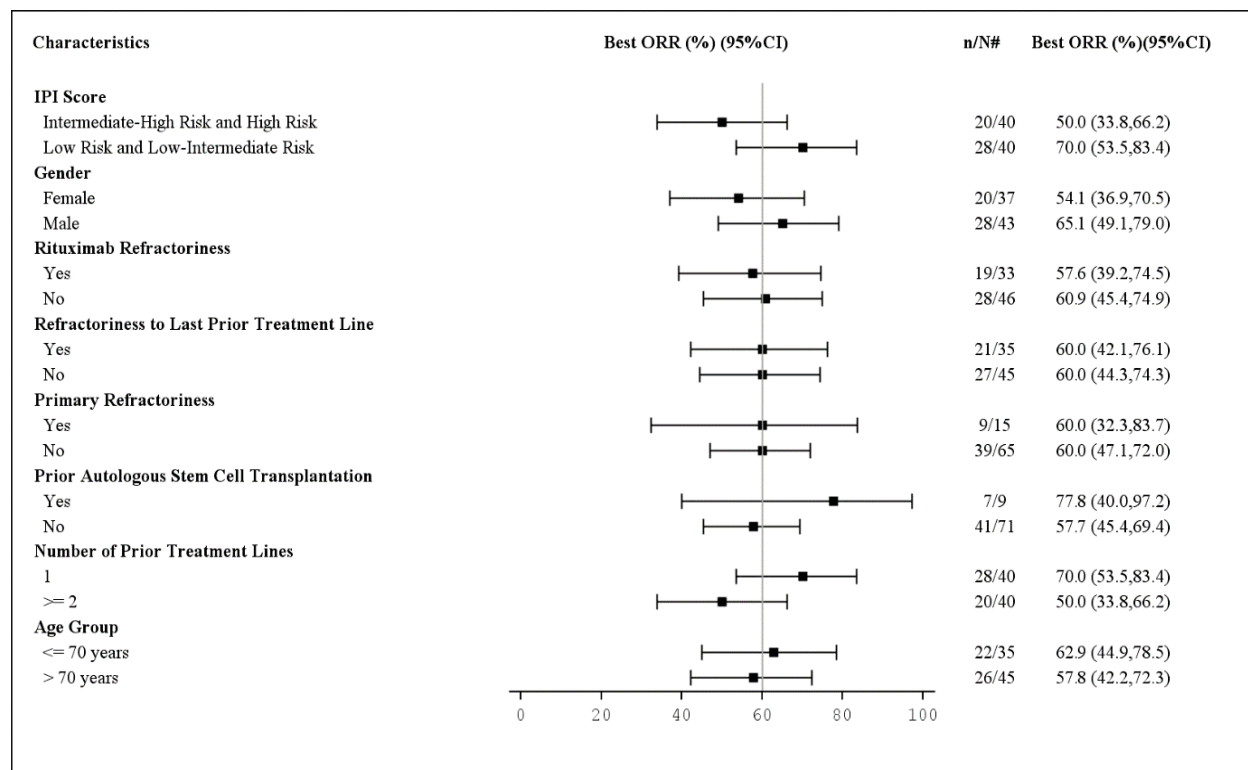
FDA considers time-to-event endpoints such as PFS, OS, TTP, and TTNT in the context of single trials difficult to interpret. As noted in the Efficacy Endpoint section above, FDA evaluates

Subgroup Analysis

Analyses of ORR and other efficacy parameters were performed for several subpopulations, (*i.e.*, IPI score, gender, RTX refractoriness, refractoriness to last prior treatment line, primary refractoriness, prior ASCT, number of prior treatment lines, and age, as well as cell of origin).

The combination treatment with tafasitamab and LEN had consistent activity in patients irrespective of their age, or whether primary refractory, refractory to their last prior therapy, or refractory to RTX.

Figure 14: Forest Plot of Best Objective Response for Subgroups (IRC Evaluation) FAS (MOR208C203)



Abbreviations: CI = confidence interval, CR = complete response, FAS = full analysis set, IPI = International Prognostic Index, N# = number of patients within subgroup category, IRC = Independent Radiology/Clinical Review Committee; n = number of patients with objective response; ORR = objective response rate, PR = partial response.

Applicant’s Position:

For the primary endpoint ORR, consistent results were observed across most patient subgroups of interest, such as those based on age, gender, primary refractory disease, and refractoriness to the last prior therapy.

A trend towards a differential effect with overlapping CIs was observed in the subgroups based on IPI, prior therapy lines, cell of origin. As is typical in DLBCL and many other malignancies, there was a trend for higher response rates in patients who were less heavily pre-treated. However, it is difficult to draw robust conclusions from these results, given the small patient numbers.

The FDA’s Assessment:

FDA agrees with the Applicant that statements about trends in subgroups are difficult to substantiate given that subgroup sample sizes in the L-MIND study are small, and in general lead to estimates that are unstable. The following table restricts ORR subgroup results to the 71 patients who were DLBCL-confirmed. FDA notes that the responses were consistent across the

cell of origin subgroups. However, as previously stated the small sample size precludes a meaningful conclusion regarding efficacy in the subgroups.

Table 19: Summary of L-MIND ORR in DLBCL-Confirmed Patients

Attributes	Frequency (n/N)	ORR (95% CI)
Overall	39/71	55% (42.7%, 66.8%)
Age Group		
<= 70	19/32	59% (40.6%, 76.3%)
> 70	20/39	51% (34.8%, 67.6%)
Gender		
Female	16/32	50% (31.9%, 68.1%)
Male	23/39	59% (42.1%, 74.4%)
Race		
Missing	2/6	33% (4.3%, 77.7%)
White	37/62	60% (46.4%, 71.9%)
ECOG		
0,1	36/64	56% (43.3%, 68.6%)
2	3/7	43% (9.9%, 81.6%)
Refractory to Last Line		
No	22/39	56% (39.6%, 72.2%)
Yes	17/32	53% (34.7%, 70.9%)
Refractory to Rituximab		
Missing	1/1	100% (2.5%, 100.0%)
No	23/40	58% (40.9%, 73.0%)
Yes	15/30	50% (31.3%, 68.7%)
IPI Staging		
Low Risk	9/14	64% (35.1%, 87.2%)
Low Intermediate Risk	12/20	60% (36.1%, 80.9%)
Intermediate Risk	12/21	57% (34.0%, 78.2%)
High Risk	6/16	38% (15.2%, 64.6%)

GCB Status by IH

Missing	7/12	58% (27.7%, 84.8%)
Non-GCB	14/21	67% (43.0%, 85.4%)
GCB	18/38	47% (31.0%, 64.2%)

COO by GEP

Missing	19/39	49% (32.4%, 65.2%)
ABC	13/19	68% (43.4%, 87.4%)
GCB	4/7	57% (18.4%, 90.1%)
Unclassified	3/6	50% (11.8%, 88.2%)

Ann Arbor Staging

I/II	8/16	50% (24.7%, 75.3%)
III/IV	31/55	56% (42.3%, 69.7%)

Number of Prior Lines

< 2	22/35	63% (44.9%, 78.5%)
>=2	17/36	47% (30.4%, 64.5%)

Reasons for ASCT Ineligible

Chemorefractory	10/19	53% (28.9%, 75.6%)
Comorbidities	5/9	56% (21.2%, 86.3%)
High Age	19/33	58% (39.2%, 74.5%)
Refuse HDT/ASCT	5/9	56% (21.2%, 86.3%)

Prior SCT

No	32/62	52% (38.6%, 64.5%)
Yes	7/9	78% (40.0%, 97.2%)

Confirmed DLBCL Status

Missing	1/1	100% (2.5%, 100.0%)
Not DLBCL	1/1	100% (2.5%, 100.0%)
DLBCL	37/69	54% (41.2%, 65.7%)

NK Cell Count

Missing	4/7	57% (18.4%, 90.1%)
< 100	14/32	44% (26.4%, 62.3%)

SOURCE: FDA-analysis.

8.1.3. MOR208C206, RE-MIND

Trial Design

The Applicant's Description:

This observational, retrospective, comparative cohort study MOR208C206 (RE-MIND) was conducted to generate a matched control cohort for MOR208C203 (L-MIND) to isolate the contribution of tafasitamab to the combination. The study was designed and conducted to minimize the potential bias for differences in patient populations, efficacy assessment techniques, definition of endpoints, source selection, and differences in follow-up time.

Site and patient selection criteria were pre-specified in the study protocol. The same eligibility criteria as in the MOR208C203 study were applied to this study with respect to the histological subtypes, number of prior therapy lines, prior therapy types allowed, and ineligibility to receive ASCT.

Eligibility criteria used in MOR208C203 (L-MIND) but not for MOR208C206 (RE-MIND) were justified with the following reasons:

- 1) Inclusion criterion 'ECOG score 0-2': ECOG score was expected to be not frequently documented on patient's medical records in routine clinical care.
- 2) Laboratory parameters, serology and patient's consent to receive anticoagulation therapy: Criteria deemed unnecessary in the context of a retrospective data collection. However, elevated LDH levels, Neutropenia and Anaemia were included as baseline covariates for cohort balancing.
- 3) Exclusion criterion 'patients with primary refractory disease': The definition of primary refractory DLBCL was revised during the L-MIND conduct resulting in enrollment and treatment of 15 patients with primary refractory disease. Consequently, primary refractory disease was not an exclusion criterion for MOR208C206 and included as baseline covariate for cohort balancing. Data were collected retrospectively from health records of patients in either real world, compassionate use and/or clinical trial settings. GCP principles were followed, patient confidentiality was maintained and the data collected underwent medical review.

The statistical analyses were prospectively defined in the SAP. The effectiveness of LEN monotherapy was compared with the efficacy outcomes of tafasitamab+LEN combination therapy in MOR208C203 (L-MIND) after the cohorts were balanced on nine relevant baseline patient and disease characteristics via 1:1 *nearest neighbor* matching based on estimated propensity scores:

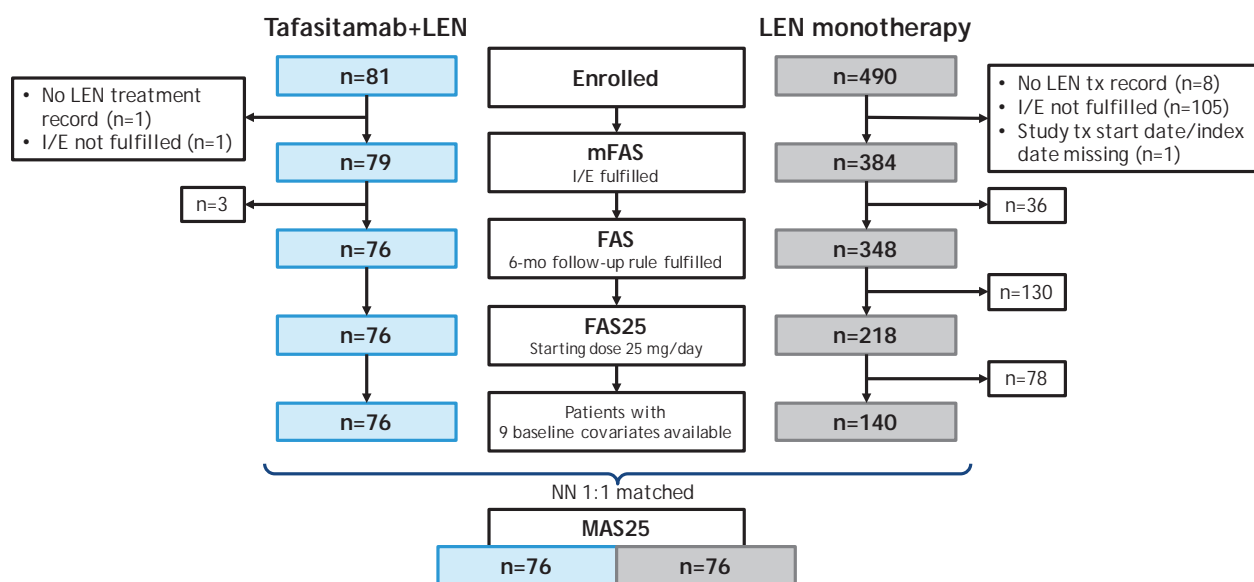
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- Primary refractory (Y/N)
- Refractory to last treatment (Y/N)
- Prior ASCT (autologous stem cell transplant) (Y/N)
- Number of prior therapies (1 vs. 2/3)
- Age (<70 vs >=70)
- Ann Arbor Stage (I/II vs III/IV)
- Increased LDH (Y/N)
- Neutropenia (Y/N)
- Anemia (Y/N)

Of the 490 patients who were enrolled in the observational study, 348 who fulfilled the eligibility criteria and had a sufficient follow-up (6-months) were included in the full analysis set for efficacy (FAS). Of these, 218 patients who had a LEN starting dose of 25 mg/day were included in the FAS25 analysis set. Of those, 140 patients had complete data available on 9 baseline covariates, and hence were used as a patient pool for 1:1 ePS based matching with the L-MIND cohort. For patients in the L-MIND study the same rules were applied. 5 patients out of the 81 enrolled patients were excluded from the comparative analysis (reasons: 1 patient did not fulfill the I/E criteria [had received 4 prior lines of therapy], 1 patient was not treated with lenalidomide and 3 patients discontinued without any post-baseline response assessment or recorded death).

Thus, 76 patients from each cohort were matched 1:1 and included for analysis of the efficacy endpoints in the MAS25, the primary analysis set (Figure 15).

Figure 15: Patient Flow (MOR208C206)



For a subset of patients in the RE-MIND observational cohort, tumor response assessments were validated by independent reviewers (1 radiologist and 1 hemato-oncologist) based on tumor imaging and clinical data in order to evaluate whether response assessments collected in the observational cohort were accurate representations of patient response. Concordance between the independent tumor response assessments and the physician-recorded tumor response assessments in the validation set was measured by percent agreement.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the design of the RE-MIND observational study. However, whether the 9 covariates were "relevant" with respect to ORR heterogeneity and whether they represent a sufficient set in terms of confounder control are still open questions.

The accuracy of the concordance results from the validation study is unclear given that the validation set was small. For example, there were only 22 investigator-assessed responders. Additionally, the concordance results have no direct connection to estimation as the Applicant did not provide a mechanism for translating the concordance results to the estimation of ORR based on IRC assessment.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint of this study was best overall/objective response rate ORR, defined as patients with CR or PR as best response achieved at any time between index date and date of initiation of a new anti-DLBCL medication or death.

Additional efficacy endpoints included;

- DoR, defined as the elapsed time between the date of first documented response (CR or PR) and the date of event defined as the first documented progression or death (from any cause).
- PFS, defined as the time from the index date to the date of tumor progression or death from any cause.
- OS, defined as the time from the index date until death from any cause (documented by the date of death).
- EFS, defined as the time from the index date to the date of disease progression, initiation of a new non-study anti-DLBCL medication, or death from any cause, whatever comes first.
- TTNT, defined as the time from index date to the start of next anti-DLBCL therapy (therapies include- medication, surgery or radiotherapy for any reason including disease progression, treatment toxicity and patient preference) or death due to any cause,

whatever comes first.

- Disease Control Rate (CR+PR+SD)

Subgroups regarding age, Ann Arbor Stage, refractoriness to last therapy line, number of prior therapy lines, primary refractoriness, and prior ASCT were evaluated for best ORR, CR, PFS, and OS.

The FDA's Assessment:

FDA agrees with the Applicant's description. Due to inherent differences in data elicitation between clinical trials and clinical practice with respect to what are being measured, how accurately they are being measured, and when they are measured, FDA considers information from time-to-event endpoints such as OS, PFS, EFS, and TTNT difficult to interpret and not relevant to the consideration of the contribution of effect question.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The first objective of this study was to characterize the effectiveness of LEN monotherapy in the treatment of R/R DLBCL patients. For this purpose, all data of the observational cohort were summarized using appropriate statistics and tabular overviews. The second objective of this study was to compare the effectiveness of LEN monotherapy with the efficacy outcomes from tafasitamab-LEN combination therapy. For this purpose, the following analysis considerations were applied:

- ePS-based *nearest neighbor* (NN) 1:1 matching methodology was utilized to balance cohorts (observational and MOR208C203 cohorts) using the following baseline covariates to estimate the propensity score: age, Ann Arbor Stage, refractoriness to last therapy line, number of previous lines of therapy, history of primary refractoriness, prior ASCT, neutropenia, anemia, and elevated lactate dehydrogenase (LDH).
- Various analysis populations for the comparative analysis were defined based on the patient's follow-up time, LEN starting dose, and cohort balancing approach to address potential selection bias. The primary analysis set was the Nearest Neighbour (NN) 1:1 Matched Analysis Set of patients with a LEN starting dose of 25mg/day (MAS25).
- The primary endpoint, ORR, was estimated using logistic regression. The resulting odds ratio and its associated 95% CI were estimated. The primary analysis was based on Fisher's exact test and was performed on the MAS25.
- A sensitivity analysis was performed to achieve a higher degree of balance in a subgroup of patients by applying a caliper to the 1:1 NN matching algorithm resulting in 2 x 68 patients in the MAS25_Cal analysis population.
- McNemar's conditional test for paired data and conditional logistic regression were conducted as sensitivity analyses for ORR, with p-values reported associated with the

treatment cohort effect. All time-to-event endpoints were analyzed using standard Kaplan-Meier methodology.

- A sensitivity analysis was performed based on a *Balancing Overlap Weights* approach to balance cohorts using only the FAS and FAS with starting dose 25 mg of LEN monotherapy (FAS25).
- Subgroup analyses were performed determining ORR, OS and PFS in the respective subgroups.
- An inclusion of approximately 500 patients in the observational cohort was expected to be necessary to complete a successful NN 1:1 matching for cohort balancing before conducting comparative efficacy outcome analyses. As the MOR208C203 ITT cohort consisted of n=81 patients, the ePS-based 1:1 matching resulted in a sample size of n=162 at maximum for the primary analysis method.

The SAP was amended once, on October 29, 2019. Changes since the original SAP dated September 09, 2019 addressed FDA comments, and included clarifications, and added details for statistical programming. There were no changes to the concept of cohort balancing or primary analysis methodology.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description.

Protocol Amendments

The Applicant's Description:

The initial protocol was amended once, on September 09, 2019 prior to the database lock, which also took place on September 09, 2019. These changes are not expected to have had an impact on the integrity of the trial or interpretation of the results. Key/Critical changes were as follows:

- Definition of best overall/objective response rate (ORR) as primary endpoint (defined as "main endpoint" in previous version)
- Complete response rate added as a secondary endpoint
- New section added for Primary Analysis (defined as "main analysis" in previous version)
- Number of patients expected for validation adjusted
- Identification of Duplicate Records section updated to reflect change in methodology
- Analysis populations updates, including clarifications for the 6-month follow-up rule, clarification of the existing analysis sets and addition of further analysis sets
- Sensitivity Analyses updated to include definition of covariates and new reference added for clarification
- Comparative Efficacy Outcome Analysis section updated to include a description of analysis methods for time-to-event endpoints (log-rank test to be performed and p-values estimated; HR to be estimated using Cox PH model)

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- An additional analysis, considering the matched patients as paired data, Klein and Moeschberger (1997) test, was also added to the Comparative Efficacy Outcome Analysis section, along with two new references
- Validation of Response Assessment section updated to include a broader definition of patient qualification for validation purposes
- In addition, a country-specific protocol amendment (Version 2.0), which included a clarification on the observation period (included in Version 3.0), was generated and submitted in Spain.

The FDA’s Assessment:

In general, FDA agrees with the Applicant’s description.

Study Results

Patient Disposition

In the MAS25, a total of 76 (100%) patients in each cohort (tafasitamab monotherapy and tafasitamab + LEN) received study treatment. A lower number (%) of patients in the tafasitamab+LEN cohort (45 [59.2%]) progressed, relapsed or died compared with the LEN mono cohort (63 [82.9%]). The most common reason for permanent discontinuation of LEN-mono treatment was disease progression or death (30 [39.5%] patients in the tafasitamab+LEN cohort and 48 [63.2%] patients in the LEN mono cohort) (Table 20).

Table 20: Patient Disposition

	Tafasitamab+LEN n (%)	LEN-mono n (%)
MAS25	(N=76)	(N=76)
Patients treated with study treatment in the analysis window	76 (100)	76 (100)
Patients progressed/relapsed/died in the analysis window	45 (59.2)	63 (82.9)
Patients ongoing LEN at the end of the analysis window	0	3 (3.9)
Patients ongoing with tafasitamab at the cut-off ¹	28 (36.8)	-
Patients permanently discontinued LEN	76 (100)	73 (96.1)
Primary reason for permanent discontinuation of LEN		
Adverse event	11 (14.5)	7 (9.2)
As planned	24 (31.6)	7 (9.2)
Disease progression/death	30 (39.5)	48 (63.2)
Others	10 (13.2)	3 (3.9)
Unknown	0	3 (3.9)
Withdrawal by patient	1 (1.3)	5 (6.6)
Patients permanently discontinued tafasitamab	48 (63.2)	
Primary reason for permanent discontinuation of tafasitamab		-
Adverse event	8 (10.5)	-
Death	2 (2.6)	-

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	Tafasitamab+LEN n (%)	LEN-mono n (%)
Disease relapse	35 (46.1)	-
Other	1 (1.3)	-
Withdrawal by patient	2 (2.6)	-

ePS= estimated propensity score; LEN = lenalidomide; MAS = Matched Analysis Set; SD=standard deviation.

1. Cut-off date was 30 November 2018 in the tafasitamab+LEN cohort and 25 August 2019 in the LEN-mono cohort.

The Applicant’s Position:

A lower number of patients receiving tafasitamab + LEN combination treatment progressed, relapsed or died compared with patients receiving LEN monotherapy (59.2% vs. 82.9%).

The FDA’s Assessment:

FDA agrees that the disposition information reflects the data submitted by the Applicant.

Demographic Characteristics for MAS25

The majority of patients in the tafasitamab + LEN and LEN monotherapy cohorts were male (52.6% vs. 56.6%, respectively), white (98.6% vs. 65.8%, respectively) and aged ≥70 years (56.6% vs. 59.2%, respectively). For 23.7% of the patients in the LEN monotherapy cohort, race was unknown. The median age at index date was 71.5 years (min, max: 41, 86) for the tafasitamab + LEN cohort and 71.0 years (min, max: 41, 86) for the LEN monotherapy cohort, respectively. In the LEN monotherapy cohort, 47 and 29 patients originated from data sources in U.S. and Italy, respectively.

Table 21: Demographic Characteristics (MAS25) (MOR208C206)

Variable	Tafasitamab+LEN (N=76)	LEN-mono (N=76)
Age Group, n (%)	Age <70 years old	33 (43.4)
	Age ≥70 years old	43 (56.6)
Sex, n (%)	Female	36 (47.4)
	Male	40 (52.6)
Race, n (%)	Black or African American	0
	American Indian/Alaskan Native	0
	Native Hawaiian or Other Pacific Islander	0
	White	70 (92.1)
	Unknown	0
	Other	1 (1.3)
	Missing	5 (6.8)

The Applicant’s Position:

Overall, the patient demographics at index date were well balanced in terms of age and sex. The majority of patients in both cohorts were white. However, for 23.7% of the patients in the LEN monotherapy cohort race was not documented.

The FDA's Assessment:

FDA agrees with the demographic summary provided in the Applicant's Table 21. Below (Table 22) we restrict patients to those that were DLBCL-confirmed which affects the tafa+LEN cohort.

Table 22: Summary of Baseline Characteristics in MAS25 (DLBCL-Confirmed)

Attributes	LEN (n=76)	tafa+LEN (n=66)
Age Group		
<70	31 (41%)	29 (44%)
>=70	45 (59%)	37 (56%)
Gender		
Female	33 (43%)	31 (47%)
Male	43 (57%)	35 (53%)
Age by Sex		
Age<70, Females	18 (24%)	16 (24%)
Age<70, Males	13 (17%)	13 (20%)
Age>=70, Females	15 (20%)	15 (23%)
Age>=70, Males	30 (39%)	22 (33%)
Race		
Missing	18 (24%)	5 (8%)
Black or African American	4 (5%)	
American Indian or Alaskan Native	1 (1%)	
White	50 (66%)	60 (91%)
Other	3 (4%)	1 (2%)

SOURCE: FDA-analysis

Baseline and Other Characteristics for MAS25

Baseline and other characteristics are summarized for the MAS25 in Table 23.

Table 23: Baseline Characteristics (MAS25) (MOR208C206)

Variable		Tafasitamab+LEN (N=76)	LEN-mono (N=76)
Age at Index Date (years)	n	76	76
	Mean (SD)	69.1 (9.71)	70.0 (8.65)
	Median (Q25, Q75)	71.5 (62.0, 76.0)	71.0 (64.5, 76.0)
	Range (min-max)	41-86	41-86
Ann Arbor Stage (n [%])	I	4 (5.3)	0
	II	15 (19.7)	12 (15.8)
	III	14 (18.4)	12 (15.8)
	IV	43 (56.6)	52 (68.4)
	I/II	19 (25.0)	12 (15.8)
	III/IV	57 (75.0)	64 (84.2)
Prior ASCT (n [%])	Yes	9 (11.8)	6 (7.9)
	No	67 (88.2)	70 (92.1)
Number of prior systemic treatment lines (n [%])	1	39 (51.3)	28 (36.8)
	2	32 (42.1)	42 (55.3)
	3	5 (6.6)	6 (7.9)
	2/3	37 (48.7)	48 (63.2)
Primary refractoriness (n [%])	Yes	14 (18.4)	16 (21.1)
	No	62 (81.6)	60 (78.9)
Refractoriness to last prior therapy (n [%])	Yes	34 (44.7)	34 (44.7)
	No	42 (55.3)	42 (55.3)
Neutropenia (cut-off <1.5x10 ⁹ /L) (n [%])	Yes	2 (2.6)	2 (2.6)
	No	74 (97.4)	74 (97.4)
Anemia (cut-off Hemoglobin <10g/dL) (n [%])	Yes	6 (7.9)	5 (6.6)
	No	70 (92.1)	71 (93.4)
Elevated LDH (>ULN) (n [%])	Yes	41 (53.9)	45 (59.2)
	No	35 (46.1)	31 (40.8)
Time since first DLBCL diagnosis (months)	n	76	75
	Missing	0	1
	Mean (SD)	40.0 (35.96)	38.0 (35.5)
	Median (Q1, Q3)	25.9 (16.8, 54.7)	24.94 (14.5, 45.3)
	Range (min-max)	7.8-189.7	3.0-193.1
IPI Score (n [%])	0-2	40 (52.6)	16 (21.1)
	3-5	36 (47.4)	32 (42.1)
	Missing	0	28 (36.8)
ECOG (0-4) (n [%])	0	29 (38.2)	5 (6.6)
	1	41 (53.9)	36 (47.4)
	2	6 (7.9)	19 (25.0)

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Variable		Tafasitamab+LEN (N=76)	LEN-mono (N=76)
	3	0	6 (7.9)
	≥2	6 (7.9)	25 (32.9)
	Missing	0	10 (13.2)
Rituximab refractoriness (n [%])	Yes	32 (42.1)	33 (43.4)
	No	44 (57.9)	43 (56.6)
Creatinine clearance (ml/min) (n [%])	≥60	69 (90.8)	42 (55.3)
	Missing	7 (9.2)	34 (44.7)
Relapse after first line treatment (n [%])	Relapse ≤12 months	32 (42.1)	32 (42.1)
	Relapse >12 months	41 (53.9)	39 (51.3)
	Missing	3 (3.9)	5 (6.6)
Cell of origin (as determined by immune-histochemistry) (n [%])	GCB	34 (44.7)	14 (18.4)
	Non-GCB	20 (26.3)	16 (21.1)
	Missing	22 (28.9)	46 (60.5)
Cell of origin (as determined by Nanostring/gene expression profiling) (n [%])	GCB	7 (9.2)	0
	ABC	19 (25.0)	0
	Unclassified	4 (5.3)	0
	Missing	46 (60.5)	76 (100)
Time since discontinuation of last prior anti-DLBCL medication or ASCT (months)	n	76	76
	Mean (SD)	17.4 (22.3)	13.6 (19.6)
	Median (Q1, Q3)	9.2 (5.2, 20.7)	6.5 (1.3, 14.78)
	Range (min-max)	0.6-121.9	0.1-103.2

Balance between the 2 treatment cohorts:

The standardized mean difference (SMD) is a measure of balance achieved for the proportions of a certain dichotomized baseline characteristic.

Of the 9 covariates used for NN 1:1 matching (age, Ann Arbor Stage, refractoriness to last therapy line, number of previous lines of therapy, history of primary refractoriness, prior ASCT, neutropenia, anemia, and elevated LDH), 5 achieved a SMD <0.1, 2 achieved a SMD <0.2, and 2 achieved a SMD of ≤0.29 (Ann Arbor and Number of Prior Lines) in the MAS25. For each of the 9 baseline covariates, an SMD of ≤0.18 was achieved for MAS25_Cal.

The Applicant's Position:

The comparative cohorts are representative for patients with R/R DLBCL and have baseline characteristics representative of the target population. The two cohorts were well matched with a SMD <0.20 for 7 of the 9 covariates in the MAS25, which allows for a robust estimation of the additional treatment effect attributable to tafasitamab when added to LEN as in the MOR208C203 trial. Sensitivity analysis achieved a higher degree of balance with an SMD of ≤0.18 for all 9 baseline covariates in the MAS25_Cal analysis population.

The FDA's Assessment:

In general, FDA agrees with the Applicant's summary of baseline disease characteristics in

Table 23. Below (Table 24) we restrict patients to those that were DLBCL-confirmed, which affects the tafa+LEN cohort. **NOTE:** Statements about two cohorts being balanced in the setting of the RE-MIND study is difficult to substantiate. From a marginal distribution point of view, the data show that LEN patients exhibit poorer Ann Arbor, ECOG, and number of prior lines. Additionally, even if the marginal distributions of these characteristics look similar, whether visually or by the SMD metric, it does not in any way guarantee that the joint distributions of multiple risk factors are similar. Unlike randomization which theoretically induces similar marginal and joint distributions of patient characteristics, the RE-MIND observational study cannot guarantee this. An assessment of the joint distribution cannot be rigorously performed as the sample size is too small to identify the joint distributions in a robust manner. As shown in Table 24, an estimate of the joint distribution of relapse to last line and number of prior lines suggest that jointly the baseline disease characteristics between the two cohorts may be imbalanced.

Table 24: Summary of Baseline Characteristics in MAS25 (DLBCL-Confirmed)

Attributes	LEN (n=76)	tafa + LEN (n=66)
Ann Arbor Staging		
I/II	12 (16%)	15 (23%)
III/IV	64 (84%)	51 (77%)
ECOG		
Missing	10 (13%)	
0/1	41 (54%)	60 (91%)
2	19 (25%)	6 (9%)
>2	6 (8%)	
Refractory to Last Line		
No	42 (55%)	36 (55%)
Yes	34 (45%)	30 (45%)
Number of Prior Lines		
1	28 (37%)	34 (52%)
2	42 (55%)	28 (42%)
>2	6 (8%)	4 (6%)
Refractory to Last Line by Num Prior Lines		
Not R2LL, 1 PL	19 (25%)	29 (44%)

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Not R2LL, 2 PLs	22 (29%)	5 (8%)
Not R2LL, 3 PLs	1 (1%)	2 (3%)
R2LL, 1 PLs	9 (12%)	5 (8%)
R2LL, 2 PLs	20 (26%)	23 (35%)
R2LL, 3 PLs	5 (7%)	2 (3%)
IPI Score		
Missing	28 (37%)	
0/1	5 (7%)	14 (21%)
2/3	27 (36%)	39 (59%)
4/5	16 (21%)	13 (20%)
Prior ASCT		
No	70 (92%)	57 (86%)
Yes	6 (8%)	9 (14%)
Elevated LDH		
No	31 (41%)	30 (45%)
Yes	45 (59%)	36 (55%)
Neutropenia		
Missing	5 (7%)	
No	70 (92%)	65 (98%)
Yes	1 (1%)	1 (2%)
Anemic		
No	71 (93%)	60 (91%)
Yes	5 (7%)	6 (9%)

*R2LL = Refractory to last line, PL = Number of prior lines.

SOURCE: FDA-analysis

With respect to the studied cohorts being representative of RR DLBCL patients in the target population, FDA does not agree that this statement is defensible, as it would require a precise definition of the DLBCL target population followed by a random sample of patients from a listing of DLBCL patients from the target population. This is not the case.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

In the MAS25, the numbers (%) of patients with CR and PR were higher in the tafasitamab + LEN cohort (CR: 39.5% and PR: 27.6%) compared with the LEN monotherapy cohort (CR: 13.2% and PR: 21.1%). The primary endpoint was met comparing ORR of the matched cohorts: best ORR was 67.1% (95% CI: 55.4, 77.5) in the tafasitamab+LEN cohort and 34.2% (95% CI: 23.7, 46.0) in the LEN monotherapy cohort (Odds Ratio=3.885 [95% CI: 1.900, 8.142]). This difference was statistically significant (Fisher’s exact test $p < 0.0001$); the magnitude of the difference was clinically meaningful.

Table 25: Best Overall Response Rate Summary (Investigator Evaluation) (MAS25) (MOR208C206)

Category/Statistic	Tafasitamab+LEN (N=76)	LEN-mono (N=76)
ORR, n (%)	51 (67.1)	26 (34.2)
95% CI of Best ORR ¹	(55.4, 77.5)	(23.7, 46.0)
Complete responses (CR), n (%)	30 (39.5)	10 (13.2)
95% CI of CR ¹	(28.4, 51.4)	(6.5, 22.9)
Partial responses (PR), n (%)	21 (27.6)	16 (21.1)
95% CI of PR ¹	(18.0, 39.1)	(12.5, 31.9)

1 - Clopper-Pearson exact method.

Sensitivity analysis performed with the MAS25_Cal set achieved a standardized difference of ≤ 0.18 for all 9 baseline covariates and led to highly consistent results with the primary analysis.

Additional sensitivity analyses were performed and confirmed the primary analysis. These included using the assumption of correlated data for matched datasets and performing Mc Nemar’s instead of Fisher’s exact test, analysis of PFS and EFS with different censoring rules, analyses of ORR, PFS and OS with cohorts balanced using overlap weights constructed from the ePS (i.e., instead of 1:1 NN matching), multiple imputation on missing baseline covariates and modified analysis sets including patients not satisfying the 6-month follow up rule.

The Applicant’s Position:

Combination tafasitamab and LEN demonstrated substantial evidence of efficacy over LEN monotherapy cohort in R/R DLBCL for the MAS25 set, with ORR of 67.1% vs 34.2% in the tafasitamab + LEN cohort vs LEN monotherapy cohorts, respectively. The difference of almost doubling the ORR and tripling the CR rate between the two cohorts is clinically meaningful. These results were confirmed by all sensitivity analyses. The addition of tafasitamab to LEN results in increased activity in R/R DLBCL, demonstrating the contribution of tafasitamab to the combination regimen. Notably, outcomes from the observational cohort of LEN monotherapy

were similar to the published literature with LEN monotherapy in R/R DLBCL with best ORR ranging from 21-29% (Wiernik et al., 2008; Witzig et al., 2011; Czuczman et al., 2017).

The FDA’s Assessment:

In general, FDA agrees with the Applicant’s presentation in Table 25. However, due to the nature of the observational study, statements about evidence of substantial advantage of tafa+LEN over LEN monotherapy cannot be rigorously substantiated. Table 26 following provides additional FDA-generated results restricted to centrally-confirmed DLBCL, per IRC. **NOTE:** In the LEN arm, only patients in the validation study had IRC response. For those not in the validation study, they did not have IRC response; thus, the response for these patients are INV-assessed.

Table 26: IRC Response (INV if IRC Not Available) in MAS25 (DLBCL-Confirmed)

Endpoint	tafa + LEN		LEN	
	Freq (n/N)	Rate	Freq (n/N)	Rate
ORR	39/66	59% (46.3%, 71.0%)	24/76	32% (21.4%, 43.3%)
CR	27/66	41% (29.0%, 53.7%)	6/76	8% (3.0%, 16.4%)
PR	12/66	18% (9.8%, 29.6%)	18/76	24% (14.7%, 34.8%)

SOURCE FDA-analysis

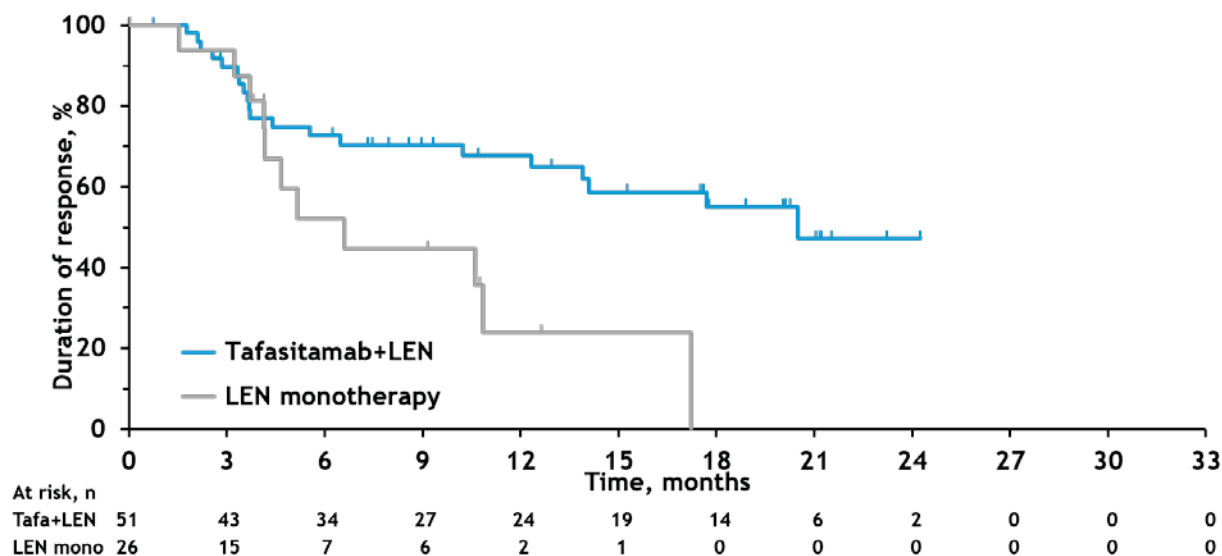
FDA’s results are similar to the Applicant’s results. However, the interpretation remains ambiguous. The primary reasons stem from these sources. First, as noted previously, the distribution (marginal and joint) of the observable covariates, are not well-balanced. Second, the role of unmeasured confounders are unknown. Thus, how much of the observed difference in the results is due in part or in whole to factors favorable to the tafa+LEN arm is still unclear. Third, since not all patients in the LEN cohort had IRC-assessed response, the potential for outcome misclassification exists.

Efficacy Results – Secondary and other relevant endpoints

In the MAS25, the effect size of all secondary endpoints was consistent with the primary endpoint. Median DoR (Kaplan-Meier estimate) was 20.5 (95% CI: 12.3, NR) months in the tafasitamab + LEN cohort and 6.6 (95% CI: 4.1, 17.2) months in the LEN monotherapy cohort (Figure 16). Median PFS (Kaplan-Meier estimate) in the MAS25 was 12.1 (95% CI: 5.9, NR) months in the tafasitamab + LEN cohort and 4.0 (95% CI: 3.1, 7.4) months in the LEN monotherapy cohort. The HR for PFS was 0.463 (0.307, 0.698) in favor of the tafasitamab + LEN

cohort (Cox proportional hazard model $p=0.0002$). The median follow up time for PFS was 19.7 months in the tafasitamab + LEN cohort and 12.6 months in the LEN monotherapy cohort.

Figure 16: Duration of Response (Excluding Non-Responders) (MOR208C206)



Median OS (Kaplan-Meier estimate) was NR (95% CI: 15.5, NR) in the tafasitamab + LEN cohort and 9.4 (95% CI: 5.1, 20.0) months in the LEN monotherapy cohort. The HR for OS was 0.499 (95% CI: 0.317, 0.785) in favor of the tafasitamab + LEN cohort (Cox proportional hazard model $p=0.0026$). The median follow up time for OS was 21.5 months in the tafasitamab + LEN cohort and 21.8 months in the LEN monotherapy cohort.

Results for the secondary efficacy endpoints DoR, PFS, OS, EFS, and DCR in the MAS25_Cal were consistent with those in the MAS25.

The Applicant’s Position:

Median DoR was extended by approximately 14 months in the combination tafasitamab+LEN compared with LEN monotherapy, a clinically meaningful prolongation of response duration. All time-to-event endpoints supported the primary analysis results, with clinically meaningful and statistically significant differences between tafasitamab + LEN combination and LEN monotherapy.

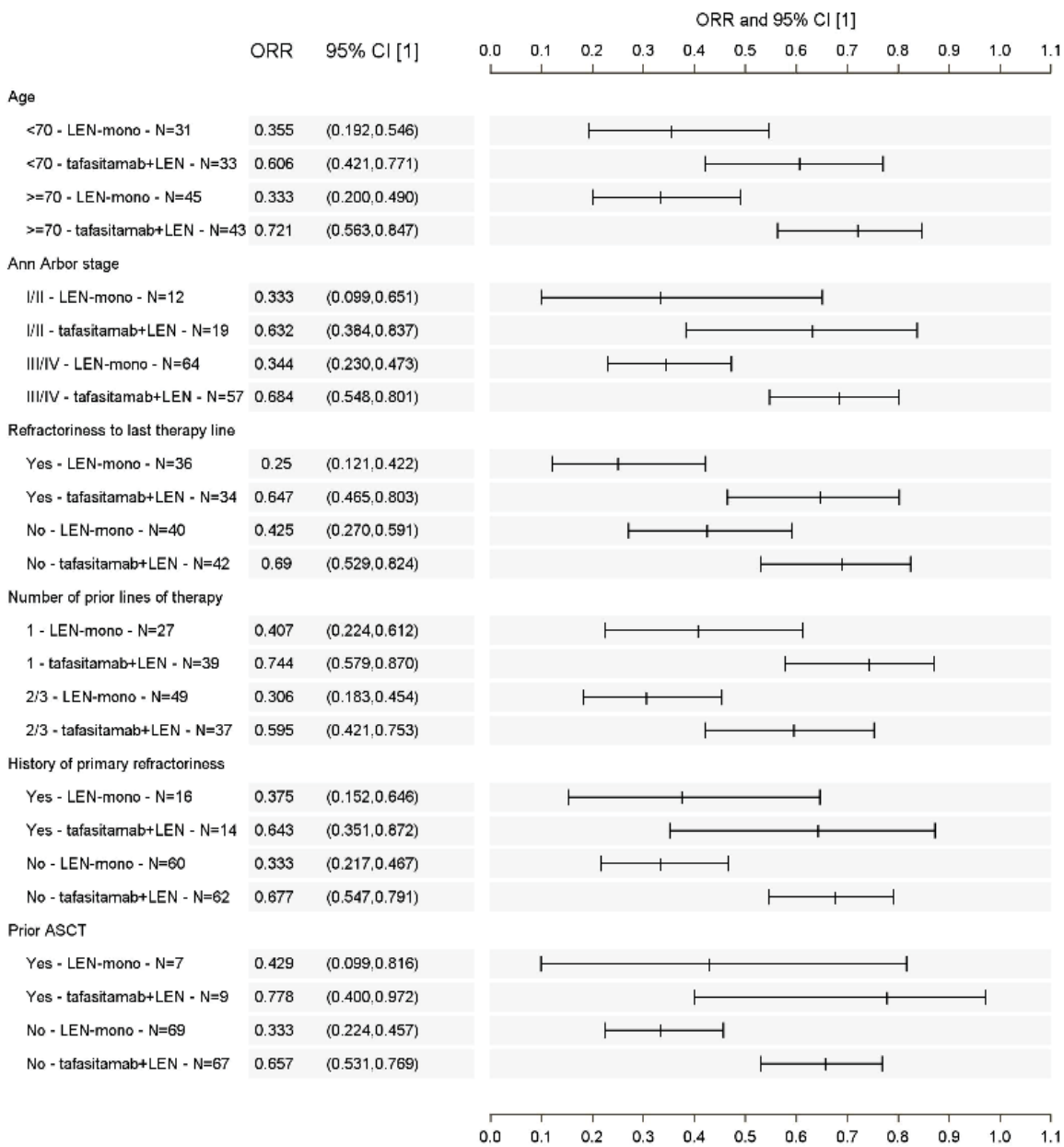
The FDA’s Assessment:

Due to the limitations of the observational study, the secondary endpoints described by the Applicant are not utilized.

Subgroup Analysis

Best ORRs by subgroups for the MAS25 are summarized in Figure 17.

Figure 17: Forest Plot of Best Objective Response Rate by Subgroups (MAS25) (MOR208C206)



1 - Clopper-Pearson exact method.

The Applicant's Position:

Best ORR in subgroups were consistent with the best ORR in the overall population (MAS25), although the numbers are too small to draw definitive conclusions.

OS and PFS subgroup analyses were consistent in the main matched analysis population across all presented subgroups.

The FDA's Assessment:

FDA agrees with the Applicant that subgroup sample sizes are small, precluding meaningful statements about subgroup heterogeneity with respect to ORR.

Additional Analyses Conducted on the Individual Trial

Physician-reported, real-world tumor response assessments were validated in a subset of patients via independent radiology and clinical review assessments in the retrospective, observational cohort of R/R DLBCL patients treated with LEN monotherapy in the RE-MIND study. The combined concordance for the responders (CR+PR) + non-responders (SD+PD) was 79.8% in a subset of 79 patients assessed.

The Applicant's Position:

The validation assessment demonstrated that response assessment by an independent panel of experts was generally concordant with the response assessment by the treating physicians.

The FDA's Assessment:

Based on the Applicant's definition of concordance, FDA agrees with the Applicant's statement. However, as noted earlier, there were only 22 patients who were responders per INV. As such, it is not clear how reliable the concordance estimates are. In addition, it is not clear what the concordance threshold should be for the purpose of deciding whether the results are robust to misclassification.

8.1.4. MOR208C201

Trial Design

The Applicant's Description:

This trial was a phase 2a, 2-stage, open-label, single-arm, multicenter, study to evaluate the efficacy and safety of tafasitamab monotherapy in adult patients with R/R NHL who had received at least 1 prior therapy containing RTX.

A two-stage design was used to minimize exposure of patients with NHL subtypes not adequately responding to MOR208. In stage 1, ten patients were to be enrolled into each of four NHL subtype-specific cohorts; DLBCL, FL, other iNHL and MCL. If ≥ 2 patients (20%) in a cohort had a partial or complete response after 8–12 weeks of treatment, then ≥ 20 additional patients with that NHL subtype were to be enrolled. Based on the data from stage 1, the DLBCL and FL subtype-specific cohorts were expanded in Stage 2. At the completion of enrolment (n=92), the subtype-specific cohorts included following number of patients: DLBCL n=35; FL n=34; other iNHL n=11; MCL n=12.

Treatment consisted of tafasitamab monotherapy which was to be administered until 8 weeks (2 cycles) for all patients. Patients who had a response of at least SD or better, could receive on additional treatment cycle. At the end of cycle 3, patients who had a PR or CR, (regardless of Stage 1 or 2 or the histological subtype) were eligible to receive further study drug until progression (either every two or every four weeks, as decided by the investigator).

The FDA's Assessment:

As mentioned by the Applicant the primary objective of this trial was to assess the antitumor activity of single-agent tafasitamab in patients with relapsed or refractory NHL. The dose used was the same as the pivotal trial, 12 mg/kg. Patients were treated for an initial 2 cycles, each 28 days with tafasitamab administered on day 1, 8, 15 and 22. Premedication was given for the first 3 infusions. Patients with stable disease would then qualify for cycle 3, again tafasitamab administered on day 1, 8, 15 and 22. For patients with an ongoing response of at least a PR at the end of cycle 3, may then progression to receive maintenance treatment which was further treatment every 2 weeks or monthly until disease progression.

Premedication consisted of antipyretics, histamine H1 receptor blockers, and glucocorticosteroids, which were given for the first 3 infusions.

The secondary objectives for this trial included evaluation of the duration of response, safety and tolerability, evaluation of potential immunogenicity and evaluation of the pharmacokinetics and pharmacodynamics in patients with relapsed or refractory NHL.

Design

The trial enrolled in two stages. Stage 1 consisted of at least 10 patients per NHL subtype:

- FL
- DLBCL
- MCL
- Other indolent NHL

For those NHL subtypes with 2 or more responders, an additional 20 patients will be enrolled for a total of 30 patients per subtype for stage 2. The cohorts may have been stopped for

futility after stage 1.

Inclusion criteria (summarized)

- Age ≥ 18 years of age
- Histologically confirmed diagnosis according to the Revised European American lymphoma/World Health Organization classification:
 - Follicular lymphoma
 - Other indolent NHL
 - DLBCL
 - MCL
- Progression of lymphoma after at least 1 prior rituximab containing regimen. This could be 1 completed cycle of combination therapy with rituximab and chemotherapy or at least 4 weekly administration of rituximab as monotherapy.
- If previous ASCT, patients must be at least 4 weeks following transplantation and have full hematologic recovery
- Life expectancy of >3 months
- ECOG performance status of < 3
- The following laboratory criteria at screening:
 - ANC ≥ 1.0 ($1000/\text{mm}^3$)
 - Platelet count $\geq 75 \times 10^9/\text{L}$
 - Hemoglobin ≥ 8.0 g/dL
 - Serum creatinine $< 2.0 \times \text{ULN}$
 - Total bilirubin $\leq 2.0 \times \text{ULN}$
 - ALT and AST $\leq 2.5 \times \text{ULN}$
- Females of childbearing potential, a negative pregnancy test and use of a double-barrier contraception during and for 3 months after the last dose or documented total hysterectomy and/or oophorectomy, tubal ligation.
- If male, an effective barrier method must be used during the trial and for 3 months after the last dose if sexually active with a female of childbearing potential.

Exclusion Criteria (summarized)

- Previous treatment with an anti-CD19 antibody
- Previous allogeneic stem cell transplantation
- Clinically significant cardiovascular disease or cardiac insufficiency
- Positive hepatitis serology
- History of HIV infection
- Any active systemic infection requiring active parenteral antibiotic therapy within 4 weeks
- Current treatment with immunosuppressive agents other than corticosteroids, not more than 10 mg prednisone or equivalent.

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- History or clinical evidence of CNS meningeal or epidural disease including brain metastasis.
- Pregnancy or breastfeeding in women and women of childbearing potential not using acceptable birth control

Management of Toxicities

If a patient developed a study drug related grade 3 or 4 toxicity and the toxicity had not resolved to grade 1, or baseline if pre-existing, at the day of the next scheduled dose, treatment was to be postponed. If treatment was postponed for more than 15 days for the same toxicity, the patients treatment was to be discontinued.

Patients were to begin the next treatment cycle of criteria were met. These criteria are below:

- ANC $\geq 1.0 \times 10^9/L$
- Platelet count $\geq 75 \times 10^9/L$
- Hemoglobin ≥ 8.0 g/dL (may be transfused)
- Serum creatinine $< 2.0 \times$ ULN
- Total bilirubin $\leq 2.0 \times$ ULN
- ALT and ASLT $\leq 2.5 \times$ ULN
- No treatment related grade 3 or 4 toxicity in CNS, cardiovascular, infections or gastrointestinal system organ class.

Prophylactic antibiotics/antifungals were allowed at the discretion of the investigator. Medications for treatment of symptoms of NHL or other diseases were allowed at the discretion of the investigator.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was best ORR (CR + PR), assessed by Investigators. Additional efficacy endpoints included;

- TTP, the time from study entry (first dosing) until documented lymphoma progression or death as a result of lymphoma. Deaths from other causes were censored at the time of death.
- DoR, defined as the time from first meeting of criteria for response (i.e., CR or PR) to first documentation of relapse or progression.
- PFS, defined as the time from study entry (first dosing) until lymphoma progression or death as a result of any cause.
- SD rate, defined as failure to attain CR/PR or PD.

The FDA's Assessment:

FDA agrees with the Applicant's description of the endpoints. Response was determined using the revised IWG response criteria for malignant lymphoma (Cheson response criteria), standard criteria for response assessment in DLBCL. TTP is considered to be exploratory. Stable disease is not considered clinically meaningful from a regulatory perspective. Since this is a single arm study, time-to event endpoints such as PFS and OS have limited interpretability.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The initial SAP was amended three times prior to the data cut-off of the interim analysis used for this BLA. The changes do not have any impact on the interpretation of previous trial results since modifications were restricted to rephrasing and the addition of analyses. SAP changes are summarized as follows:

- SAP Version 2.0 (July 7, 2015): Few paragraphs were rephrased. No analyses were added or amended.
- SAP Version 3.0 (November 30, 2018):
 - The analysis on patient disposition was modified to report a more granular patient flow.
 - A tabulation of protocol non-compliances was added.
 - Efficacy analyses were added.
- SAP Version 4.0 (April 03, 2019):
 - Deletion of analyses on composite PK parameters since these had not been conducted before, and are not going to be performed in the future.
 - Further refinement of disposition tables, addition of Listings.

All analyses were performed using the ITT population, comprising all patients who received at least one dose of tafasitamab. The ITT and safety populations in this study were the same.

Best ORR, overall and per NHL subtype, was summarized alongside with exact (Clopper-Pearson) 95% CIs. In addition, the tumor response categories were evaluated by visit. The corresponding numbers of patients in each of the response categories were summarized in a frequency table by visit.

All secondary efficacy analyses were provided based on the response assessment of the investigator as well as based on the central radiology review assessment. For time-to-event endpoints DoR, TTP, and PFS, data were summarized using standard Kaplan Meier methodology.

The DCO for this study occurred on September 28, 2018.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description.

Protocol Amendments

The Applicant's Description:

The initial protocol was amended four times prior to the completion of the study. These changes had no impact on the integrity of the trial or interpretation of the results. Key changes were as follows:

- Amendment 1 (Date: January 07, 2013), submitted prior to patient enrollment, included changes to various safety assessments and reporting, as well as eliminated minimal disease assessment, removed a longitudinal assessment of CD19 expression on tumor cells, and introduced formal study termination rules.
- Amendment 2 (Date: October 02, 2013) was done after patient enrollment began. It allowed for patients who had an ongoing response of at least PR after Cycle 3 eligible to receive 12 mg/kg tafasitamab as extended therapy until disease progression; CT/PET examinations performed up to 3 weeks before Cycle 1 Day 1 could be used as a patient's baseline assessment; the futility decision if a further 20 patients in a subtype would be enrolled to continue enrollment after the first 10 patients in each subtype could now be based on response at both 8 and 12 weeks (since therapy with monoclonal antibodies is expected to have a slower effect than cytotoxic drugs); and radiographic investigations could now be performed 4 working days before or after the actual visit. Clarifications to CT/PET procedures, dosing/body weight calculations, lymphomas that could be included in the subtype of indolent lymphoma, concomitant medication entry into the eCRF were added.
- Amendment 3 (Date: April 15, 2014) introduced minor changes to various safety assessments; added a definition for having received at least 1 prior therapy containing RTX; updated eligibility and management of patients with positive HBV screens; excluded allergic reactions and infusion-related reactions grade 2 and less from the definition of AEs of special interest; widened the visit window (due to practical reasons) for radiographic assessment by 3 days in treatment period; added an inclusion criteria for transformed lymphomas that the subtype at screening for the MOR208C201 study was relevant for the assignment to the respective subtype (this ensured a correct classification of patients who had their DLBCL transformed from a prior indolent lymphoma to the DLBCL subtype cohort in the study); widened the window for postponements of visits; detailed the use of MRI; clarified that early termination of patients was defined as patients who terminated the study before the end of Cycle 2; and clarified that patients who terminated before the end of Cycle 2 would undergo an EOS visit, whereas patients who had at least SD at the end of Cycle 2 and had not progressed would continue with the first follow up visit.

- Amendment 4 (Date: September 19, 2017) prolonged the extended treatment beyond Follow-up Visit 12 until progression, limited the amount of data collected beyond follow-up visit 12, and removed the ADA assessment from the end of study visit.

The FDA's Assessment:

The FDA did not independently confirm the protocol amendments above, but notes the above protocol amendments stated by the Applicant.

Study Results

Patient Disposition

A total of 92 patients were treated with tafasitamab (ITT population) in this study. Of these, 75 (81.5%) patients completed the first 2 cycles, 44 (47.8 %) patients continued treatment in Cycle 3, and 16 (17.4%) patients entered the extended treatment (also referred to as maintenance therapy) phase. Six (6.5%) patients were still on treatment at data cut-off, and 1 patient had completed study participation with 46 months of treatment.

Patients were considered to have completed the study if they finished the first 2 cycles of treatment plus the end of Cycle 2 assessments. A total of 15 of the 92 treated patients (16.3%, ITT population) discontinued from the study prior to completion of the first 2 cycles, the majority of these due to progressive disease (46.7%). Fifty-two patients discontinued the study in Cycle 1 to Cycle 3. Reasons for study discontinuation at any time during Cycle 1 to 3 were progressive disease (61.5%), Investigator decision (13.5%), new cancer therapy (3.8%), death (9.6%), other (13.5%), AE (3.3%), patient withdrawal of consent (3.3%) and protocol violation (1.9%).

DLBCL Subset

Thirty-five DLBCL patients were treated with tafasitamab in the ITT/safety population. Of these, 25 (71.4%) DLBCL patients completed the first 2 cycles, 12 (34.3%) DLBCL patients continued treatment in Cycle 3, and 6 (17.1%) DLBCL patients entered the extended treatment phase (maintenance treatment per protocol). One (2.9%) DLBCL patient was still on treatment at the DCO (September 28, 2018).

A total of 10 out of 35 treated DLBCL patients (28.6%) discontinued from the study prior to completion of the first 2 cycles, the majority of these due to PD (50.0%). Reasons for discontinuation for the DLBCL patients were progressive disease (50.0%), death (30.0%), protocol violation (10.0%), and physician decision (10.0%). 25 DLBCL patients discontinued from the study during Cycle 1 to Cycle 3. Reasons for discontinuation at any time during Cycle 1 to Cycle 3 were progressive disease (68.0%), death (16.0%), Investigator decision (12.0%), and protocol violation (4.0%), Twenty-eight of the 35 patients (80.0%) in the DLBCL subgroup discontinued treatment during the first 3 cycles.

The Applicant's Position:

The most common cause of discontinuation of study drug was disease progression. A subset of patients benefitted from the tafasitamab monotherapy and remained in treatment for an extended period of time.

The FDA's Assessment:

The subtype relevant to FDA's evaluation of tafasitamab monotherapy activity is DLBCL. Per the data submitted to FDA, 13 (37%) patients completed cycle 3.

Protocol Violations/Deviations

In the ITT population, 1 patient (1.1%) had a critical protocol non-compliance (i.e., did not satisfy the study entry criteria). Major protocol non-compliance was reported for 42 patients (45.7%). This included 25.0% patients who had major protocol deviations belonging to the "Other critical or major protocol noncompliance" category (bone marrow aspiration/biopsy not done, site missed timely re-consent with revised informed consent forms, IRR reported with delay, ECG not performed, local laboratory parameters not collected, End of Study Visit not performed, SAE not reported within timeframe, CT images not performed with contrast as required, vital signs collected out of allowed timeframes, radiological evaluation not reported within timeframe, or biopsy at Screening not performed correctly). A further 21.7% patients had protocol deviations due to procedural errors during the study drug administration (e.g. incorrect infusion rates or infusion materials [lines and filters] than as specified per protocol were used).

The Applicant's Position:

After a critical review of these protocol deviations, the applicant concluded that the analysis and the overall interpretation of efficacy and safety results were not impacted. A Per Protocol analysis Set (PPS) was not prespecified in the study protocol.

The FDA's Assessment:

While it is not clear what is meant by the phrase "efficacy and safety results were not impacted", FDA considers the efficacy and safety results of tafasitamab monotherapy to be interpretable within the context of protocol deviations.

Table of Demographic Characteristics

Most patients were male (60.9%) and white (94.6%). The median age of the 92 patients was 66.5 (min, max: 35.0, 90.0); the majority (53.3%) were ≥65 years of age. Similarly, most patients in the DLBCL subset were male (68.6%) and white (94.3%). The median age of the 35 DLBCL patients was 71.0 (min, max: 35.0, 90.0); the majority (54.3%) were ≥65 years of age.

Table 27: Demographics at Baseline (Safety Population) (MOR208C201)

Characteristic	Statistic	DLBCL Subtype (N=35)	Total (N=92)
Age (years)	N	35	92
	Mean (StD)	66.7 (14.4)	65.6 (12.2)
	Med	71.0	66.5
	Min, Max	35.0, 90.0	35.0, 90.0
Gender, n (%)	Male	24 (68.6)	56 (60.9)
	Female	11 (31.4)	36 (39.1)
Race, n (%)	Asian	1 (2.9)	1 (1.1)
	Black or African American	0	1 (1.1)
	White	33 (94.3)	87 (94.6)
	Other	1 (2.9)	3 (3.3)
Age category (years)	<65	16 (45.7)	43 (46.7)
	≥65	19 (54.3)	49 (53.3)

Abbreviations: DLBCL = diffuse large B-cell lymphoma; Max = maximum; Med = median; Min = minimum; N = total number of patients; n = number of patients in category; StD = standard deviation

Note: Percentages are based on N.

The Applicant’s Position:

Overall, the demographic characteristics were similar in the entire ITT population and the DLBCL subset. The DLBCL subset in particular is representative of the proposed indication, i.e. a population of adult patients with R/R DLBCL, who are not eligible for (b) (4) ASCT.

The FDA’s Assessment:

The clinical reviewer agrees with the data and demographic table. Similar to the L-MIND trial, there was severe underrepresentation of racial subgroups other than Whites in the single arm MOR208C201 trial similar to the L-MIND trial.

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

Of the DLBCL subset, 34.3% of DLBCL patients had 1 prior treatment line, and 22.9% and 25.7% DLBCL patients had 2 or 3 prior treatment lines, respectively. The majority (88.6%) of DLBCL patients did not have previous ASCT. Nineteen (54.3%) DLBCL patients had an ECOG score of 0; all other DLBCL patients had an ECOG score of 1 (42.9%) or 2 (2.9%), respectively. Twenty (57.1%) DLBCL patients had an Ann Arbor Stage of IV, and 28.6% of DLBCL patients had an Ann Arbor Stage of III. Most (68.6%) DLBCL patients were RTX-refractory. Patients were considered RTX refractory if they had no response or a response lasting <6 months to any RTX-containing therapy.

The Applicant's Position:

The DLBCL patients enrolled in this study were representative of the intended population in the BLA (R/R DLBCL, not eligible for ASCT). Their baseline characteristics were similar to the patients enrolled in the pivotal L-MIND study. Thus, this study provides an appropriate population to characterize the efficacy of tafasitamab monotherapy in R/R DLBCL patients.

The FDA's Assessment:

The size of the DLBCL cohort is small such that a characterization of its representativeness of the "intended population" is difficult to substantiate.

Regarding the 35 DLBCL patients, 20 patients (57.1%) had a ECOG category of 0 at baseline, ECOG of 1 at baseline was 12 patients (34.3%) and 3 patients (8.6%) had a ECOG category of 2 at baseline. The FDA agrees with the remaining data presented.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

One patient in the FL subgroup received concomitant therapy excluded per protocol.

The Applicant's Position:

Treatment compliance for tafasitamab was ensured as it was infused under the direct supervision of study personnel. No statistical analysis for measurement of treatment compliance was planned for this study. The patient who received the excluded concomitant therapy did not change the interpretation of study outcomes.

The FDA's Assessment: The FDA did not independently confirm the Applicant position above, but note the position stated above stated by the Applicant.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

For the DLBCL patients in the ITT population (N=35), the best ORR for patients based on Investigator evaluation was CR for 2 (5.7%) patients and PR for 7 (20.0%) patients. Based on these data, the ORR was 25.7% (95% CI: 12.5, 43.3). Five (14.3%) patients had SD as their best response. Eleven (31.4%) patients had PD (progressive disease) as their best response. No patients were not evaluable. The ORR based on the IRC was 17.1% (95% CI: 6.6, 33.6).

The concordance analysis (responder vs non-responder) for the Investigator's assessment vs. IRC revealed 91.4% concordance for DLBCL patients.

The Applicant's Position:

Tafasitamab monotherapy showed encouraging clinical activity (ORR) in patients with R/R DLBCL based on the Investigator's assessment.

The FDA's Assessment:

Numerically, FDA agrees with the INV and IRC ORR results presented by the Applicant. Whether it is encouraging is an open question. With respect to concordance between IRC and INV assessments:

- Out of 9 responders per INV, 6 (67%) were classified as responders by IRC.
- Out of 26 non-responders per INV, 26 (100%) were classified as responders by IRC.

Concordance is more salient in non-responders.

Efficacy Results – Secondary and other relevant endpoints

Based on the Investigator evaluation, the median DoR was 20.1 months for the DLBCL subgroup. Of the 9 responders, five patients were in remission for ≥ 12 months and 2 were in remission for >4 years. The 12-month PFS rate was 34.3% for DLBCL, and the median TTP was 3.1. The DCR was 40.0% for DLBCL patients. Similar results were seen across all endpoints for the IRC reads as well.

The Applicant's Position:

The data from the DLBCL subgroup demonstrate a long duration of response with tafasitamab monotherapy. All time-to-event endpoints supported the primary analysis results. No statistical inference for the time-to-event endpoints can be made from this single-arm study, and results presented are descriptive only.

The FDA's Assessment:

FDA agrees with the Sponsor's general assessment. The phrase "demonstrate a long duration of response" is not statistically defensible as there were only 9 patients in the denominator.

Subgroup Analysis

Based on the investigator assessment, 5 out of 12 DLBCL patients with 1 prior treatment line showed a response resulting in an ORR of 41.7% (95% CI: 15.2 to 72.3%). For patients with 2, 3, or more than 3, prior treatment lines the ORR was 12.5% (1/8 patients; 95% CI: 0.3% to 52.7%), 33.3% (3/9 patients; 95% CI: 7.5% to 70.1%), and 0% (0/6 patients; 95% CI: 0% to 45.9%), respectively. The median PFS was 3.4 months (95% CI: 1.7 to 15.4 months) for DLBCL patients who had 1 prior treatment line. For patients with 2, 3, or more than 3, prior treatment lines the median PFS was 2.1 months (95% CI: 0.7 to 2.1 months), 23 months (95% CI: 1.6 months – not reached), and 2.6 months (95% CI: 2.5 to 2.7 months), respectively.

DLBCL patients with low or low/intermediate IPI score exhibited an ORR of 26.7% (4/15 patients), which was comparable to the ORR of patients with intermediate/high or high IPI score who showed an ORR of 21.1% (4/19 patients). The median PFS for DLBCL patients with low/intermediate IPI score was 13.2 months (95% CI: 1.6 months to not reached), compared

with those with intermediate/intermediate-high IPI score who had a median PFS of 2.1 months (95% CI: 1.7 months to 3.4 months).

Selected subgroups were only analyzed in terms of PFS: DLBCL patients who were younger than 65 years of age demonstrated a median PFS of 23 months (95% CI: 1.8 months to not reached; n=16 patients), compared with patients who were 65 years or older who had a median PFS of 2.1 months (95% CI: 1.6 to 3.1 months; n=19 patients).

The subgroup of DLBCL patients refractory to any prior rituximab-containing treatment regimen had a median PFS of 2.7 months (95% CI: 1.6 to 23 months; n=24 patients), while patients without rituximab-refractory disease had a median PFS of 3.1 months (95% CI: 0.7 months to not reached; n=11 patients).

The Applicant's Position:

The analysis of subgroups based on number of prior treatment lines, IPI, age, or refractoriness to anti-CD20 regimens, irrespective of whether ORR or PFS were analyzed did not reveal any clear patterns, based on the small number of DLBCL patients contained in the various subgroups.

The FDA's Assessment:

Results from subgroup analysis are difficult to substantiate given that subgroup sample sizes are small, and in general lead to estimates that are unstable.

Assessment of Efficacy Across Trials

Primary Endpoints

The primary efficacy endpoint for the 3 studies was best ORR (CR + PR), for which each study used standardized response criteria based on the International Working Group Response Criteria ([Cheson, 2007](#)). Table 28 presents a summary of ORR for Studies MOR208C203, MOR208C206, and MOR208C201, as well as for 3 published prospective LEN monotherapy trials ([Czuczman et al, 2007](#); [Wiernik et al, 2008](#); [Witzig et al, 2011](#)).

With tafasitamab + LEN combination therapy, ORR was 60.0% (34 [42.5%] patients with CR and 14 [17.5%] patients with PR) in the MOR208C203 study.

With LEN monotherapy, ORR was 34.2% for the observational cohort in the MOR208C206 study (10 [13.2%] patients with CR and 16 [21.1%] patients with PR), and ORR ranged from 19% to 28% across the published LEN studies ([Czuczman et al, 2007](#); [Wiernik et al, 2008](#); [Witzig et al, 2011](#)).

Tafasitamab monotherapy results showed an ORR of 25.7% (2 [5.7%] DLBCL patients with CR and 7 [20.0%] DLBCL patients with PR) in study MOR208C201.

Table 28: Best Overall/Objective Response Rate (MOR208C203, MOR208C206, MOR208C201, and LEN Monotherapy Literature)

	MOR208C203 (L-MIND) (IRC) Tafa + LEN N=80 (FAS)	MOR208C206 (RE-MIND) (INV)		MOR208C201 (INV) Tafa Mono DLBCL N=35 (ITT Population)	LEN Mono (Literature) N=total across the 3 Prospective Trials Wiernik, Witzig, Czuczman (N=185)
		Tafa + LEN N=76 (MAS25)	LEN Mono N=76 (MAS25)		
	n (%)	n (%)	n (%)	n (%)	Range: n (%) - n (%)
ORR (CR + PR)	48 (60.0)	51 (67.1)	26 (34.2)	9 (25.7)	5 (19)-30 (28)
95% CI	(48.4, 70.8)	(55.4, 77.5)	(23.7, 46.0)	(12.5, 43.3)	-
Complete response	34 (42.5)	30 (39.5)	10 (13.2)	2 (5.7)	3 (11.5)-5 (9.8)
Partial response	14 (17.5)	21 (27.6)	16 (21.1)	7 (20.0)	2 (7.7)-22 (20)
Stable disease	11 (13.8)	8 (10.5)	11 (14.5)	5 (14.3)	23 (21.3)-7 (26.9)
Progressive disease	13 (16.3)	12 (15.8)	34 (44.7)	11 (31.4)	40 (37.0)-14 (53.8)
Not evaluable	8 (10.0)	-	-	0	-
No response assessment	8 (10.0)	-	-	10 (28.6)	-

Confidence intervals for rates are calculated using the 2-sided 95% Clopper-Pearson exact method.

The Applicant's Position:

In study MOR208C201, tafasitamab monotherapy showed activity in DLBCL patients. Study MOR208C203 demonstrated a strongly increased signal of efficacy with the combination regimen of tafasitamab + LEN combination therapy. The study was single armed, and the superiority of the tafasitamab + LEN combination over LEN monotherapy could not be statistically tested. Cross-study comparisons with published LEN monotherapy results are difficult to interpret given potential differences in the patient population for key baseline characteristics. Therefore, MOR208C206 was conducted to generate a control cohort of LEN monotherapy for comparison to the combination regimen. The prospectively designed ePS-based 1:1 matching in this study allowed for a robust estimation of the additional treatment effect attributable to tafasitamab when added to LEN, as in Study MOR208C203.

Compared with LEN monotherapy, the tafasitamab + LEN combination resulted in a ORR that was higher by 33%, nearly two-fold the ORR observed for LEN monotherapy. Further, the CR rate was three-fold higher in the combination arm versus LEN monotherapy, suggesting

substantial additional activity for the novel combination of tafasitamab + LEN versus LEN monotherapy in transplant ineligible R/R DLBCL patients.

The FDA’s Assessment:

FDA’s results for the L-MIND study are as described earlier and do not numerically agree with those in Table 28 above. As noted previously, FDA’s analyses were restricted to patients who were DLBCL-confirmed. For the RE-MIND study, this reduces the denominator to 66 patients and the numerator to 39, resulting in ORR of 59% (95% CI: 46%, 71%). While the data suggest that tafa+LEN provides for a substantial improvement over LEN with respect to ORR, it is unknown how much of that improvement is due to confounding factors. While the RE-MIND study attempts to provide clarity, whether the study is robust in the sense of adequately controlling for confounding remains an open question.

Secondary and Other Endpoints

Table 29 presents a summary of DoR and other secondary endpoints for Studies MOR208C203, MOR208C206, and MOR208C201, as well as for 2 published prospective LEN monotherapy trials (Czuczman et al, 2007; Witzig et al, 2011).

Table 29: Summary of Secondary Endpoints across studies (MOR208C203, MOR208C206, MOR208C201, and LEN Monotherapy Literature)

		MOR208C203 (L-MIND) (IRC) Tafa + LEN N=80 (FAS)	MOR208C206 (RE-MIND) (INV)		MOR208C201 (INV) Tafa Mono DLBCL N=35 (ITT)	LEN Mono (Literature ^e) N=159 Range: median DoR – median DoR
			Tafa + LEN N=76 (MAS25)	LEN Mono N=76 (MAS25)		
DoR	Patients with Response	48	51 (67.1)	26 (34.2)	9	44 (27.7)
	Progression/death n (%)	13 (27.1)	-	-	11 (31.4)	40 (37) - 24 (47.1) ^a
	Progression	12 (25.0)	12 (15.8)	34 (44.7)	-	-
	Death	1 (2.1)	5 (6.6)	5 (6.6)	-	-
	Censored n (%)	35 (72.9)	-	-	-	-
	Median, (95% CI)	21.7 months (21.7, NR)	20.5 months (12.3, NR)	6.6 months (4.1, 17.2)	20.1 months (1.1, NR)	4.6 months - 73.9 weeks (16.4, NR)
PFS	Progression/death n(%)	39 (48.8)	42 (55.3)	58 (76.3)	11 (31.4)	24 (47.1) ^a
	Progression	32 (40.0)	35 (46.1)	48 (63.2)	-	-
	Death	7 (8.8)	7 (9.2)	10 (13.2)	-	-
	Censored n(%)	41 (51.3)	34 (44.7)	18 (23.7)	-	-
	Median, (95% CI) or HR (95% CI)	12.1 months (5.7, NR) ^b	12.1 months (5.9, NR) ^b	4.0 months (3.1, 7.4) ^b	2.7 months (2.1, 13.2) ^b	2.7 months (NP) ^b – 13.6 weeks 0.64 (0.41, 0.99) ^c

		MOR208C203 (L-MIND) (IRC) Tafa + LEN N=80 (FAS)	MOR208C206 (RE-MIND) (INV)		MOR208C201 (INV) Tafa Mono DLBCL N=35 (ITT)	LEN Mono (Literature ^e) N=159 Range: median DoR – median DoR
			Tafa + LEN N=76 (MAS25)	LEN Mono N=76 (MAS25)		
OS	Death	29 (36.3)	7 (9.2)	10 (13.2)		-
	Censored n (%)	51 (63.8)	-	-		-
	Median, (95% CI) or HR (95% CI)	NR months (18.3, NR)	NR months (15.5, NR)	9.4 months (5.1, 20.0)		31.0 weeks 0.91 (0.59, 1.41) ^d
TTP	Progression/death n(%)	35 (43.8)			11 (31.4)	
	Progression	32 (40.0)			-	
	Death	3 (3.8)			-	
	Censored n(%)	45 (56.3)			-	
	Median, (95% CI)	16.2 months (7.4, NR)			3.1 months (2.1, 15.4)	
DCR	CR or PR or SD	59 (73.8)	59 (77.6)	37 (48.7)	14 (40.0)	
	95% CI	(62.7-83.0)	(66.6, 86.4)	(37.0, 60.4)	(23.9-57.9)	

95% CIs for the median and the 25th and 75th percentiles were calculated using the method of Brookmeyer and Crowley, 1982.

Percentages are based on N.

^an (%) with Progression/death not available for Witzig.

^b Median months (95% CI)

^c Median weeks and HR (95% CI)

^d HR (95% CI)

The Applicant's Position:

Deeper, more durable responses were observed for the combination arm of tafasitamab + LEN versus LEN monotherapy. DoR results above show that patients who achieve a CR with tafasitamab + LEN combination therapy have a high probability to remain in remission for an extended period of time. Patients achieving a PR as best response tend to progress within the next 6 months. Median DoR was extended by approximately 14 months in the combination tafasitamab+LEN as compared to LEN monotherapy, suggesting substantial additional activity for the combination therapy as opposed to LEN alone.

The observed DoR, PFS, OS, TTP, and DCR, with tafasitamab supported the meaningful clinical benefit of treatment with tafasitamab 12 mg/kg alone or in combination with LEN and represent a substantial improvement in a population of patients with a high unmet medical need.

The FDA's Assessment:

As noted earlier, FDA does not consider time-to-event endpoints relevant to the determination of efficacy outside of the randomized setting. However, FDA notes that the durability of

response in the responders is approximately 2 years.

Subpopulations

Data for exploratory subgroup analyses is presented in each of the individual trial sections.

The Applicant's Position:

The primary endpoint ORR was consistent across all presented subgroups (*i.e.*, age group, IPI score, number of prior treatment lines, primary refractoriness, refractoriness to last prior treatment line, prior ASCT, and NK cell count at baseline).

Subgroups analyses did not identify any major demographic factor or baseline disease characteristic predictive of lack of response to the tafasitamab + LEN combination or tafasitamab monotherapy in any of the trials.

The FDA's Assessment:

Results from subgroup analysis are difficult to substantiate given that subgroup sample sizes are small, and in general lead to estimates that are unstable.

Additional Efficacy Considerations

The FDA's Assessment:

As noted in previous sections, the RE-MIND observational study was designed to learn about the activity of tafa+LEN relative to LEN alone. However, there were a number of issues that limited the interpretability of results. The Statistical Issues subsection in SUMMARY AND CONCLUSIONS provides additional details.

Compliance with Good Clinical Practices

The Applicant's Position:

All studies included in the development program for tafasitamab in DLBCL have been conducted in compliance with Good Clinical Practice and with the approvals of the relevant Ethics Committees or Institutional Review Boards. Informed consent was obtained for all patients, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

The FDA's Assessment:

FDA agrees with the Applicant's description.

Financial Disclosure

The Applicant disclosed all financial interests/arrangements with clinical investigators as per 21 CFR Part 54. None of the investigators or sub-investigators involved in the clinical trials had

financial interests to disclose or arrangements that required disclosure. Limited instances of missing financial disclosure information for each study is summarized below;

- For MOR208C203, information was missing from 3 sub-investigators at 3 distinct locations, none of whom have made a significant contribution to the data due to no patients being treated at the site during the time the concerned sub-investigator was assigned to the study (2 cases), or a limited amount of time spent as a sub-investigator for that site (1 case; 1 month).
- For MOR208C201, information was missing from 1 sub-investigator who was assigned to the study 2 months after the last patient completed the study at the concerned site. Thus, the sub-investigator could not have made a significant contribution to the data.
- For Xmab5574-01, information was missing from 2 sub-investigators at 1 study center due to unresponsiveness or lack of contact information.

The Applicant's Position:

The lack of disclosures across investigators in the clinical trials does not raise concerns about the overall integrity of study data. The 3 studies which formed the basis for the demonstration of efficacy (MOR28C203, MOR208C201 and MOR208C206) were conducted over multiple sites and in multiple countries, thus limiting the potential for a single investigator or sub-investigator to make a significant contribution to the data.

The FDA's Assessment:

FDA agrees with the Applicant's description of the financial disclosures on for the L-MIND trial.

Data Quality and Integrity

For applicable studies, study monitoring was performed in accordance with ICH E6 GCP guidelines, the sponsor's and CRO's standard operating procedures, the sponsor's and CRO's written instructions, the protocol, and all applicable laws and regulations. The handling of data, including data quality control, complied with all applicable regulatory guidelines.

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets; these were sufficiently complete to allow for a thorough review of efficacy. Furthermore, no data integrity concerns were reported following completion of site inspections by the Applicant.

The FDA's Assessment:

The datasets, Clinical Study Reports, narratives and responses to information requests were considered adequate to allow for review of the submission.

8.1.5. Integrated Assessment of Effectiveness

This Summary of Clinical Efficacy presents results from 1 tafasitamab + LEN combination study (MOR208C203 [L-MIND]) demonstrating a clinically relevant effect size, consistent with the mechanism-of-action-based rationale for combining the 2 agents. In this difficult-to-treat population of R/R DLBCL patients ineligible for ASCT, combination treatment with tafasitamab + LEN resulted in a high overall response in 60% (95% CI: 48.4, 70.8) of patients and a CR in 42.5% of patients. Responses were durable, with DoR of 71.6% (95% CI: 55.1, 82.9), 71.6% (95% CI: 55.1, 82.9), and 47.7% (95% CI: 10.5, 78.4) at 12, 18 and 24 months, respectively. PFS rates were 50% (95% CI: 37.9, 61.2) and 45.8% (95% CI: 33.4, 57.4) at 12 and 18 months, respectively, and OS of 73.7% (95% CI: 62.2, 82.2), 63.6% (95% CI: 50.9, 73.7), and 56.6 (95% CI: 43.0, 68.0) at 12, 18, and 24 months, respectively. Secondary endpoint analyses were generally consistent with the primary analysis, and consistent results were observed across patient subgroups of interest.

The contribution of each of the single agents (tafasitamab and LEN) in the combination was determined via 1) the MOR208C201 clinical trial for tafasitamab, which demonstrated the activity of tafasitamab monotherapy in DLBCL patients, and 2) the MOR208C206 (RE-MIND) study, in which the efficacy of LEN monotherapy was assessed in a matching observational cohort to the MOR208C203 (L-MIND) study. The MOR208C206 (RE-MIND) study provides a statistical comparison of LEN monotherapy vs. tafasitamab + LEN.

In summary, the effect of the tafasitamab and LEN combination therapy can be considered to lead to substantial additional activity versus each agent alone, since for physician-assessed best ORR, CR and median PFS, the effect of the combination is greater than the sum of the respective monotherapies when considering the results in the MOR208C206 (RE-MIND) trial for LEN and the results in study MOR208C201 for tafasitamab.

Further, in the MOR208C206 (RE-MIND study), the results reached statistical significance and all time to event endpoints supported the primary analysis results, with clinically meaningful and statistically significant differences between tafasitamab + LEN combination and LEN monotherapy.

The aggregate patient population was similar for demographic and baseline characteristics. Patients were elderly and had DLBCL, an orphan indication. Thus, it is reasonable and valid to draw conclusions about the efficacy of the tafasitamab + LEN combination from this patient population.

The Applicant's Position:

Patient outcomes with available treatments for R/R DLBCL remain largely unsatisfactory, in particular for patients unable to receive high-dose chemotherapy followed by ASCT or treatment with chimeric antigen receptor T cell therapies. Efficacy in this application is based on IRC-assessed ORR for the combination of tafasitamab and LEN, for which a clinically meaningful ORR of 60% and CR of 42.5% were observed. The responses observed with the

tafasitamab and LEN were durable, in particular in patients who achieved a CR. The contribution of tafasitamab to the combination was put into context by the matched observational cohort of LEN-treated patients, as the combination demonstrated a nearly two-fold increase in ORR and three-fold increase in CR over LEN monotherapy.

Similar, statistically significant benefit was observed in terms of duration of response and overall survival for patients who received tafasitamab + LEN vs LEN alone.

Overall, the data presented in this application demonstrates substantial evidence of effectiveness for tafasitamab in combination with LEN to treat patients with R/R DLBCL who are not suitable for HDC and ASCT. Furthermore, the effectiveness of this regimen compares favorably with that of LEN alone in the MOR208C206 (RE-MIND) study and also compares favorably in the context of many other salvage regimens evaluated in this setting.

The FDA's Assessment:

FDA agrees with the Applicant that patients with relapsed or refractory DLBCL who are unable to receive high-dose chemotherapy followed by ASCT have limited treatment options. The efficacy data from the L-MIND study with supportive evidence of the response rate of single agent tafasitamab from the relapsed or refractory DLBCL population from the single arm MOR208C201 Study represents a clinically meaningful treatment benefit of tafasitamab in this patient population. FDA's analysis of efficacy from the L-MIND trial was based on 71 patients with central pathology confirmed diagnosis of DLBCL and are different from that stated by the Applicant. FDA disagrees with the Applicant's assertions regarding the statistical significance of the results from the RE-MIND study. FDA notes several limitations with the RE-MIND study and does not agree that the data can be used to confirm statistically significant improvement of response of tafa+LEN compared to lenalidomide. The response data from this study was used to provide context to the results from the L-MIND trial. FDA notes that the response rate of single agent lenalidomide from the RE-MIND study is consistent with the data from the literature.

The time-to-event endpoints (PFS and OS) are difficult to interpret in single-arm studies. The time-to-event endpoints are not likely to constitute supportive evidence because their measurements in isolation are out of context and comparing them to historical controls is prone to bias. FDA also notes that the eligibility criteria for L-MIND trial did not specify a requirement for ineligibility for CAR-T therapy.

See also the SUMMARY AND CONCLUSIONS section.

8.2. Review of Safety

Assessment of the safety of tafasitamab is based on data from 569 patients in seven studies, analyzed as follows:

The primary safety analysis comprising two major components:

1. The pivotal study MOR208C203 in patients with DLBCL, treated with a combination of tafasitamab plus lenalidomide, followed by tafasitamab alone (N=81)
2. Three (3) studies with tafasitamab monotherapy (N=141), which were analyzed individually and pooled:
 - 2.1. XmAb5574-01 in patients with CLL/SLL (N=27)
 - 2.2. MOR208C201 in patients with NHL (N=92, of whom 35 were of the DLBCL sub-type)
 - 2.3. MOR208C202 in patients with ALL (N=22)

This analysis comprises safety data from 222 patients, treated with at least one (1) dose of tafasitamab in different indications. Two-hundred eleven (211) of these 222 patients (95%) were dosed with 12 mg/kg of tafasitamab.

The primary analysis was complemented by safety data (deaths and SAEs) from three (3) studies with tafasitamab in combination with other therapies:

1. MOR208C204 (B-MIND) in patients with R/R DLBCL, treated with bendamustine and tafasitamab, or bendamustine and rituximab (N=283, blinded, with 1:1 randomization therefore estimated 141 patients on tafasitamab combination arm); ongoing
2. MOR208C205 (COSMOS) in patients with R/R CLL/SLL, treated with tafasitamab with idelalisib or venetoclax (N=24); completed
3. OSU 13031 – Investigator Initiated Trial in patients with CLL/SLL, treated with tafasitamab with lenalidomide or ibrutinib (N=40); ongoing

The Applicant's Position:

The total safety data available allow for a comprehensive assessment of the safety profile of tafasitamab, at a dose of 12mg/kg, in combination with lenalidomide followed by tafasitamab monotherapy and an evaluation of the overall benefit-risk, in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from low grade lymphoma, who are not eligible for, or refuse autologous stem cell transplant (ASCT). This safety population is considered adequate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The FDA's Assessment:

The safety review primarily focused on the pivotal trial, MOR208C203 in patients with DLBCL. In addition to the pivotal trial, the safety of the three monotherapy trials, XmAb5574-01, MOR208C201 and MOR208C202 was evaluated.

8.2.1. Safety Review Approach

To demonstrate the safety of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy, the primary analysis included detailed summaries of the clinical safety data from the pivotal trial MOR208C203 in 81 patients with DLBCL, of whom 80 received at least one dose each of tafasitamab and lenalidomide, which were evaluated to characterize common AEs and to provide guidance on toxicity management. In order to understand the relative contributions of each component to the safety profile of the combination, in addition to the analysis of safety data from the tafasitamab monotherapy phase of MOR208C203, a pooled analysis of data from a total of 141 patients in three tafasitamab monotherapy trials (XmAb5574-01, MOR208C201, and MOR208C202) was performed. Of these, MOR208C201, in NHL, included 35 patients with the DLBCL sub-type.

A comparison of the safety data from the combination phase of MOR208C203 with safety data for lenalidomide monotherapy in the lenalidomide USPI was also performed.

This primary analysis was supported by a review of deaths and SAEs from the patients in the three trials of tafasitamab in combination with other therapies: MOR208C205 (COSMOS), MOR208C204 (B-MIND), and OSU-13031 trials (see Table 10).

The Applicant's Position:

The pooling strategy was agreed with FDA as part of a Type B pre-BLA meeting (July 01, 2019). This approach enables characterization of the risk profile for tafasitamab in combination with lenalidomide followed by monotherapy in the target population.

The FDA's Assessment:

The FDA safety evaluation focused primarily on the pivotal trial MOR208C203. The safety of the pooled analysis of data from the three monotherapy trials was also evaluated.

8.2.2. Review of the Safety Database

Overall Exposure

The Safety Analysis Set was defined as all patients who received at least one dose of study drug. For studies (XmAb5574-01, MOR208C201, and MOR208C202), tafasitamab was the only study drug. For the L-MIND study, tafasitamab and lenalidomide were the study drugs. Patients were analyzed as treated. The primary safety analysis for this submission includes 81 patients (80 of whom received both tafasitamab and lenalidomide, and all of whom received tafasitamab) in study MOR208C203 and 141 patients from the tafasitamab monotherapy studies.

In MOR208C203, the median time on tafasitamab in combination with lenalidomide was 190.0 days (range: 3 to 436 days) (Table 30).

The median time on tafasitamab monotherapy was 375.5 days in MOR208C203 (Table 30) and 51.0 days in the pooled monotherapy trials (Table 31).

The proportion of patients who received ≥ 12 cycles of tafasitamab monotherapy (Table 30) in MOR208C203 was 28.4% and 7.8% in the pooled monotherapy trials (Table 31). The proportion of patients in MOR208C203 who received > 20 doses of tafasitamab was 53.1% and 9.9% in the pooled monotherapy trials (Table 31). The differences between studies are expected due to differing numbers of treatment cycles to be applied by study design.

In addition, data on deaths and SAEs are available from three studies of tafasitamab in combination with other therapies, 64 patients from MOR208C205 (COSMOS) and OSU-13031, and 283 patients in MOR208C204 where treatment allocation is still blinded and exposure to tafasitamab is estimated as 141 patients (see Table 37).

Table 30: MOR208C203 (L-MIND): Summary of Duration of Exposure to Tafasitamab and Lenalidomide (Safety Analysis Set)

	N (%) (N=81)
All Study Treatment	
Total Number of Study Treatment Cycles n (%)	
1 Cycle	9 (11.1)
2 - 5 Cycles	26 (32.1)
6 - 12 Cycles	45 (55.6)
Duration of Exposure to Study Treatment (days)	
N	80
Mean (SD)	210.6 (136.01)
Median	190.0
Min, Max	3, 436
Duration of Exposure to Tafasitamab Monotherapy n (%)	
1 Cycle	4 (4.9)
2 - 5 Cycles	6 (7.4)
6 - 11 Cycles	7 (8.6)
12 - 24 Cycles	15 (18.5)
> 24 Cycles	8 (9.9)
Duration of Exposure to Tafasitamab Monotherapy	
N	40
Mean (SD)	394.9 (264.35)
Median	375.5
Min, Max	1, 827
Exposure to Tafasitamab	
Duration of Exposure to Tafasitamab (days)	
N	81
Mean (SD)	397.9 (372.62)

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	N (%) (N=81)
Median	232.0
Min, Max	1, 1170
Exposure to Lenalidomide	
Duration of Exposure to Lenalidomide (days)	
N	80
Mean (SD)	201.2 (130.19)
Median	189.0
Min, Max	3, 380

Percentages were based on the number of patients in the Safety Analysis Set.
Abbreviations: Max = maximum; Min = minimum; SD = standard deviation

Table 31: Monotherapy Trials: Summary of Duration of Exposure to Tafasitamab Monotherapy (Safety Analysis Set)

	Monotherapy Trials			
	XmAb5574-01 N=27	MOR208C201 N=92	MOR208C202 N=22	Pooled N=141
Time on Tafasitamab Treatment (days)				
n	27	92	22	141
Mean (SD)	82.9 (60.48)	234.5 (480.78)	36.1 (29.10)	174.5 (397.54)
Median	50.0	83.0	23.0	51.0
Min, Max	7, 190	1, 1998	3, 134	1, 1998
Time on Tafasitamab Monotherapy (days)				
n	27	92	22	141
Mean (SD)	82.9 (60.48)	234.5 (480.78)	36.1 (29.10)	174.5 (397.54)
Median	50.0	83.0	23.0	51.0
Min, Max	7, 190	1, 1998	3, 134	1, 1998
Tafasitamab Cumulative Dose (mg)				
n	27	92	22	141
Mean (SD)	7061.35 (3986.216)	15716.39 (22844.274)	6433.67 (4086.493)	12610.68 (19050.952)
Median	8100.00	8936.00	5084.70	8160.00
Min, Max	205.2, 14757.6	576.0, 157848.0	1323.7, 19081.7	205.2, 157848.0
Tafasitamab Total Number of Doses n (%)				
1 - 5 Doses	1 (3.7)	11 (12.0)	13 (59.1)	25 (17.7)
6 - 10 Doses	18 (66.7)	32 (34.8)	8 (36.4)	58 (41.1)
11 - 15 Doses	8 (29.6)	35 (38.0)	0	43 (30.5)
16 - 20 Doses	0	0	1 (4.5)	1 (0.7)
> 20 Doses	0	14 (15.2)	0	14 (9.9)

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	Monotherapy Trials			
	XmAb5574-01 N=27	MOR208C201 N=92	MOR208C202 N=22	Pooled N=141
Tafasitamab Total Number of Cycles n (%)				
1 Cycle	1 (3.7)	9 (9.8)	13 (59.1)	23 (16.3)
2 - 5 Cycles	19 (70.4)	68 (73.9)	9 (40.9)	96 (68.1)
6 - 11 Cycles	7 (25.9)	4 (4.3)	0	11 (7.8)
12 - 24 Cycles	0	2 (2.2)	0	2 (1.4)
> 24 Cycles	0	9 (9.8)	0	9 (6.4)
Tafasitamab Monotherapy Total Number of Cycles n (%)				
1 Cycle	1 (3.7)	9 (9.8)	13 (59.1)	23 (16.3)
2 - 5 Cycles	19 (70.4)	68 (73.9)	9 (40.9)	96 (68.1)
6 - 11 Cycles	7 (25.9)	4 (4.3)	0	11 (7.8)
12 - 24 Cycles	0	2 (2.2)	0	2 (1.4)
> 24 Cycles	0	9 (9.8)	0	9 (6.4)

Percentages were based on the number of patients in the Safety Analysis Set.

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation

The Applicant's Position:

The exposure to study drug was considered adequate to allow for a comprehensive assessment of safety in patients who were representative of the intended target population.

The FDA's Assessment:

In the Applicant's table, Table 30, Total Number of Study Treatment Cycles and Duration of Exposure to Study Treatment (days) is referring to exposure to the combination of tafasitamab and lenalidomide. The data provided by the Applicant in Table 30 and Table 31 was verified by the reviewer. For duration of exposure in the pivotal trial MOR208C203, the exposure obtained by the clinical reviewer is displayed in Table 32. The table displays the total number of cycles as long as at least 1 drug was administered and the total number of cycles of tafasitamab regardless of lenalidomide administration.

As shown in Table 32, a total of 35 patients (43.2%) received ≥ 12 cycles of treatment. For the pooled monotherapy trials, 11 patients (7.8%) received ≥ 12 cycles of treatment. A total of 116 patients (82.2%) of the pooled monotherapy patients received between 1-3 total treatment cycles. In general, the duration of exposure for the pooled monotherapy patients is lower compared to trial MOR208C203, the pivotal trial.

For trial MOR208C203, a total of 46 patients (56.8%) were exposed to tafasitamab for > 6 months, a total of 34 patients (42.0%) were exposed for greater than 1 year and a total of 19 patients (23.5%) were exposed for > 2 years.

Table 32: Total Number of Cycles Treated on Trial MOR208C203

Number of cycles	Total number of cycles as long at least 1 drug was administered N=81 n (%)	Total number of cycles of tafasitamab N=81 n (%)
1	10 (12.3)	10 (12.3)
2-5	20 (24.7)	21 (25.9)
6-11	16 (19.8)	16 (19.8)
12-24	14 (17.3)	13 (16.0)
>24	21 (25.9)	21 (25.9)

Source: FDA analysis

Relevant characteristics of the safety population:

The patients' baseline characteristics, demographics and disease characteristics are summarized in Table 33 and Table 34.

In MOR208C203, 56/81 (69.1%) patients were >65 years of age, with a median age of 72.0 years. In the pooled monotherapy trials, 64/141 (45.4%) patients were >65 years of age, with a median age of 63.0 years.

In MOR208C203, 52/81 (64.2%) patients had a baseline ECOG performance status graded ≥ 1 , and 7/81 (8.6%) of Grade 2. In the pooled monotherapy trials these proportions were 63/141 (44.7%) and 11/141 (7.8%) patients respectively.

The proportion of patients with an elevated baseline LDH level (>190 U/L) was 52/81 (64.2%) in MOR208C203, and 106/141 (75.2%) in the pooled monotherapy trials.

In MOR208C203, 61/81 (75.3%) patients had an Ann Arbor Stage of III or IV and 41/81 (50.6%) patients had a high and intermediate-high International Prognostic Index (IPI) category risk.

Overall the patient population in MOR208C203 had a poor prognosis, as indicated by a median age of 72 years (range: 41 to 86 years), high and intermediate-high IPI category in 41 (50.6%) patients, advanced Ann Arbor disease staging (61 patients (75.3%) Stage III and IV) and elevated baseline LDH levels (52 patients (64.2%) >190 U/L) (see also Table 33).

Table 33: Monotherapy Trials: Summary of Demographics and Disease Characteristics (Safety Analysis Set)

	Monotherapy Trials				MOR208C203
	XmAb5574-01 N=27	MOR208C201 N=92	MOR208C202 N=22	Pooled N=141	L-MIND N = 81
Age (years)					
n	27	92	22	141	81
Median	66.0	66.5	52.0	63.0	72.0
Min, Max	40, 84	35, 90	16, 79	16, 90	41, 86
Age Groups, n (%)					
≤65 years	12 (44.4)	44 (47.8)	21 (95.5)	77 (54.6)	25 (30.9)
>65 years	15 (55.6)	48 (52.2)	1 (4.5)	64 (45.4)	56 (69.1)
≤75 years	25 (92.6)	75 (81.5)	21 (95.5)	121 (85.8)	58 (71.6)
>75 years	2 (7.4)	17 (18.5)	1 (4.5)	20 (14.2)	23 (28.4)
Sex, n (%)					
Male	18 (66.7)	56 (60.9)	12 (54.5)	86 (61.0)	44 (54.3)
Female	9 (33.3)	36 (39.1)	10 (45.5)	55 (39.0)	37 (45.7)
Race, n (%)					
White	26 (96.3)	87 (94.6)	18 (81.8)	131 (92.9)	72 (88.9)
Asian	0	1 (1.1)	0	1 (0.7)	2 (2.5)
Black/African American	1 (3.7)	1 (1.1)	3 (13.6)	5 (3.5)	0
Other	0	3 (3.3)	1 (4.5)	4 (2.8)	1 (1.2)
Missing/Not available	0	0	0	0	6 (7.4)
Baseline BMI (kg/m²)					
n	26	90	22	138	79
Median	27.02	26.35	26.35	26.50	27.10
Min, Max	17.6, 45.3	12.6, 41.1	20.2, 51.3	12.6, 51.3	16.7, 44.8
ECOG Status, n (%)					
0	11 (40.7)	60 (65.2)	7 (31.8)	78 (55.3)	29 (35.8)
1	15 (55.6)	27 (29.3)	10 (45.5)	52 (36.9)	45 (55.6)
2	1 (3.7)	5 (5.4)	5 (22.7)	11 (7.8)	7 (8.6)

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Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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	Monotherapy Trials				MOR208C203
	XmAb5574-01 N=27	MOR208C201 N=92	MOR208C202 N=22	Pooled N=141	L-MIND N = 81
Time Since Diagnosis (months)					
n	27	92	22	141	81
Median	97.05	42.69	13.16	45.96	26.87
Min, Max	10.7, 287.0	0.7, 231.5	1.9, 322.8	0.7, 322.8	7.8, 189.3
Baseline LDH Level, n (%)					
≤190 U/L	11 (40.7)	20 (21.7)	3 (13.6)	34 (24.1)	29 (35.8)
>190 U/L	16 (59.3)	71 (77.2)	19 (86.4)	106 (75.2)	52 (64.2)
Missing/Not available	0	1 (1.1)	0	1 (0.7)	0

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

Abbreviations: BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; Max=maximum; Min=minimum.

Table 34: MOR208C203 (L-MIND): Summary of Disease Characteristics (Safety Analysis Set)

Characteristic	Tafasitamab + Lenalidomide (N=81)
Ann Arbor Disease Staging Dichotomized, n (%)	
Stage I and II	20 (24.7)
Stage III and IV	61 (75.3)
Disease Risk (IPI) at Screening	
N	81
Median	3.0
Time Between First DLBCL Diagnosis and First Documented Relapse or Progression, n (%)	
≤ 12 months	19 (23.5)
> 12 months	61 (75.3)
Unknown	1 (1.2)

Percentages were based on the number of patients in the Safety Analysis Set.

Abbreviations: DLBCL = diffuse large B-cell lymphoma; IPI = International Prognostic Index; SD = standard deviation

The Applicant's Position:

The characteristics of the patients in the pivotal study MOR208C203 were representative of the target population. The characteristics of the patients in the three studies with tafasitamab monotherapy are sufficiently consistent to enable an assessment of the contribution of tafasitamab to the safety profile of tafasitamab/lenalidomide combination therapy in this population.

The FDA's Assessment:

The clinical reviewer verified the data discussed in the above section. A few minor differences were seen. The majority of the patients were white. The race of trial MOR208C203 was 99.9% white, 2.5% Asian, 0% Black/African American 7.4%, 1.2% other and 7.4% missing. The race of the pooled monotherapy patient population was 92.9% white, 0.7% Asian, 3.5% Black/African American, and 2.8% other.

8.2.3. Adequacy of the safety database

An integrated safety database was created to support the integrated safety analyses described in this application. Integrated Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) datasets were created from individual study ADaM or SDTM datasets and followed the CDISC Analysis Data Model Implementation Guide version 1.1. A process of data reconciliation ensured that data on the safety database were consistent with those on the clinical trials database. The datalock date for the safety analyses was 30th June 2019.

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The evaluation of safety is based on the primary safety analysis comprising data from the 81 patients in the pivotal MOR208C203 study, and the 141 patients in the three tafasitamab monotherapy studies as described in Section 8.2.4

The Applicant's Position:

The safety database is sufficient to evaluate the safety of the combination of tafasitamab with lenalidomide followed by tafasitamab monotherapy in the target population.

The FDA's Assessment:

The clinical reviewer agrees the safety database was adequate.

Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

All individual case safety reports were followed up as necessary to obtain complete information on the case. A process of source data verification during study monitoring ensured the accuracy of these data. A thorough QC check was performed on all data entered to the safety database, and data were reconciled with the clinical trials database. No data integrity concerns were reported from site audits.

The Applicant's Position:

No meaningful concerns were detected in the quality and integrity of the submitted datasets or individual case narratives; these are sufficiently complete to allow for a thorough review of safety.

The FDA's Assessment:

Based on the datasets, narratives, Clinical Study Reports, and other submitted reports a sufficient review of the safety was able to be conducted.

Data:

Categorization of Adverse Event

The safety of treatment with tafasitamab in combination with lenalidomide and as monotherapy was evaluated on the basis of the following:

- Frequency, type, severity, and causal relationship of AEs to study treatment
- Frequency of deaths, serious AEs, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction)
- Frequency and type of AEs related to key intrinsic and extrinsic factors (e.g. age and geography)
- Changes in laboratory variables, with particular attention to Grade 3/4 abnormalities

Adverse events and medical history terms were re-coded in the integrated ADaM datasets using the MedDRA dictionary version 21.0. Laboratory and AE toxicities were graded according to CTCAE, version 4.03.

Treatment-emergent adverse events (TEAEs) were defined as those adverse events that either started or worsened in severity on or after the First Treatment Date/Time and on or before the End of On-Treatment Phase Date/Time (i.e., during the On-Treatment Phase). Any AE that occurred more than 30 days after the date/time of last dose of study treatment was considered treatment emergent (TEAE). If the End of Treatment Date was missing, any AE occurring after the treatment start date was considered treatment-emergent. As disease progression was collected as an adverse event in trials MOR208C201 and MOR208C202, but not in trials XmAb5574-01 and MOR208C03 (L-MIND), AEs of disease progression (identified as events with preferred term = 'Disease Progression') were not included in the adverse event summaries.

The Applicant's Position:

The approach to categorization of AEs was consistent with regulatory guidance and appropriate for evaluation of the safety data.

The FDA's Assessment:

A TEAE was defined as any AE reported from the first date of administration of study drug to the last date of administration of study drug + 30 days. The FDA agrees with above.

Routine Clinical Tests

Adverse events could be directly observed, reported spontaneously by the patient or elicited by questioning the patient at each study visit. Per protocol, patients were to be questioned in a general way, without asking about the occurrence of any specific symptoms. In addition, AEs could also be detected when reported by the subjects during or between visits or through physical examination, laboratory test results, or other assessments. Adverse events of Special Interest (AESIs) were selected based on the mechanism of action of tafasitamab and lenalidomide as well as nonclinical and early clinical observations. Laboratory data from all sources (central and local laboratories) were combined as described in the ISS Statistical Analysis Plan.

The hematological parameters in relation to Grade 3 or more anemia, leukopenia, neutropenia, and thrombocytopenia were summarized as the number and percent of patients demonstrating any such value at least once during the On-Treatment Phase in the pivotal MOR208C203 (L-MIND) trial, and for the tafasitamab monotherapy studies.

Evidence of drug-induced liver injury was sought by review of ALT, AST, bilirubin and alkaline phosphatase data and by respective MedDRA PTs.

The Applicant's Position:

The clinical monitoring and summarization of patient safety (methods and time points) described in the protocols and in the ISS Statistical Analysis Plan followed a standard approach and were appropriate for a comprehensive assessment of the safety of tafasitamab in combination with lenalidomide and as monotherapy for the target population and indication.

The FDA's Assessment:

For the pivotal trial, MOR208C203, central laboratory values were collected at screening and on day 1 of each treatment cycle. Local laboratory values were done at other times up to 24 hours before administration of study drugs. These local laboratory values were not collected in the clinical database. Investigators were asked to report clinically significant laboratory abnormalities based on central and local laboratory test results as adverse events which resulted in higher reporting rates of laboratory AEs in the AE dataset as compared to the lab dataset.

8.2.4. Safety Results

Deaths

As of the submission cutoff date of June 30, 2019, a total of 50 (22.5%) deaths was reported in the 222 patients in the primary safety analysis (a summary overview of all fatalities is provided in Table 35).

- 10 (10.9%) deaths out of 92 patients in MOR208C201,
- 6 (27.3%) deaths out of 22 patients in MOR208C202, and
- 34 (42.0%) deaths out of 81 patients in MOR208C203
- No deaths were reported in XmAb5574-01 (27 patients).

Of the 50 deaths,

- 38/222 (17.1%) these resulted from disease progression
- 8/222 (3.6%) were due to TEAEs. These 8 patients had 10 TEAEs with a fatal outcome assessed as not related to disease progression (For patient (b) (6) in MOR208C201 three TEAE with fatal outcome were reported, for all other patients 1 TEAE with fatal outcome each was reported). All 10 TEAEs with fatal outcome except one event 'sclerosing cholangitis' (see short narrative for MOR208C202, patient (b) (6)) were considered not related to study medication by both the investigator and applicant.
- 4 fatalities not related to disease progression and not caused by TEAE occurred later than 30 days post last study drug administration.

Below are brief summaries for the eight patients with a fatal outcome due to TEAE which were considered unrelated to study medication by the investigators:

- Patient (b) (6) (MOR208C201) experienced 3 TEAE with fatal outcome, namely (i) sudden and severe pneumonia accompanied by (ii) respiratory failure and (iii) cardiac failure in Cycle 1 (Study Day 23). The patient died on the same day.
- Patient (b) (6) (MOR208C202) developed sclerosing cholangitis on Study Day 97 and died one month later on Study Day 124 due to fulminant liver failure. A causal relationship of the event to tafasitamab could not be excluded; however, the patient suffered from intercurrent acute hepatitis A, which was diagnosed 10 days prior to death, and had suspected acute Graft versus Host Disease (GvHD) after bone marrow transplant starting approximately 3 months prior to initiating study medication. The GvHD involved the gastrointestinal tract and liver, either of which could lead to liver failure. However, a causal relationship between death and study medication cannot be ruled out.
- Patient (b) (6) (MOR208C202) experienced sepsis with symptoms of hypotension, respiratory distress and acute kidney injury, secondary to sepsis on Study Day 33. The event was likely to have been caused by *Stenotrophomonas maltophilia* infection. The patient died two days after event onset (Study Day 35).
- Patient (b) (6) (MOR208C202) developed sepsis with hypotension on Study Day 20. Multi-organ system failure progressed, and patient died 23 days after event onset (Study Day 43). The event was considered rather to have been caused by progression of disease.
- Patient (b) (6) (MOR208C203, L-MIND, Combination Therapy phase) experienced cerebrovascular accident with left-sided hemiplegia secondary to stroke on Study Day 109 and concurrently developed Grade 4 pulmonary embolism and Grade 4 deep vein thrombosis two days prior to stroke. Although the investigator stated biological evidence for disease progression, the stroke with fatal outcome (Study Day 111) was not just a consequence of disease progression, but rather potentially due to multiple reasons, including prolongation in bed, underlying comorbidities and the inability to administer preventive treatment with low molecular weight heparin.
- Patient (b) (6) (MOR208C203, L-MIND, Combination therapy phase) experienced sudden death at home on Study Day 17 of Cycle 1. The event was likely to have resulted from cardiovascular comorbidities, to which the patient was predisposed due to treatment with R-CHOP twice, as frontline therapy for DLBCL as well as for the first relapse. No additional relevant details were available.
- Patient (b) (6) (MOR208C203, L-MIND, Combination therapy phase) experienced multifactorial respiratory failure on Study Day 43 in the context of a respiratory superinfection (adenovirus infection), neutropenic fever, pleural effusion of neoplastic nature and mixed acidosis. The event was likely to have resulted from suspected lymphoma progression (pleural fluid was of neoplastic nature). The patient died 8 days after event onset (Study Day 51).
- Patient (b) (6) (MOR208C203, L-MIND, Combination therapy phase) experienced a worsening of progressive multifocal leukoencephalopathy. The patient had first

experienced non-specific neurological symptoms 10 days prior to initiation of study treatment, which then worsened on-treatment (Study Day 9). The patient received in total four infusions of tafasitamab and lenalidomide daily for 15 days, and died 68 days after end of treatment. The event was likely to have resulted from the patient's prolonged immunocompromised state due to multiple prior lymphoma treatments (immuno-chemotherapies) during the preceding two years.

Table 35: Summary of Deaths as of 30 June 2019 (Safety Analysis Set)

	Monotherapy Trials[a]				MOR208C203	
	XmAb5574-01	MOR208C201	MOR208C202	Pooled	L-MIND Overall	All Deaths
	N=27 n (%)	N=92 n (%)	N=22 n (%)	N=141 n (%)	N=81 n (%)	N=222 n (%)
Deaths	0	10 (10.9)	6 (27.3)	16 (11.3)	34 (42.0)	50 (22.5)
On-Treatment Phase ^[a] Cause of Death	0	8 (8.7)	3 (13.6)	11 (7.8)	8 (9.9)	19 (8.6)
Disease Progression	0	7 (7.6)	2 (9.1)	9 (6.4)	5 (6.2)	14 (6.3)
Not Related to Disease Progression (TEAE)	0	1 (1.1)	1 (4.5)	2 (1.4)	3 (3.7)	5 (2.3)
Within 30 Days of First Study Treatment	0	3 (3.3)	0	3 (2.1)	3 (3.7)	6 (2.7)
Within 60 Days of First Study Treatment	0	5 (5.4)	4 (18.2)	9 (6.4)	7 (8.6)	16 (7.2)
Post-Treatment Phase ^[b] Cause of Death	0	2 (2.2)	3 (13.6)	5 (3.5)	26 (32.1)	31 (14.0)
Disease Progression	0	2 (2.2)	1 (4.5)	3 (2.1)	21 (25.9)	24 (10.8)
Not Related to Disease Progression	0	0	2 (9.1)	2 (1.4)	5 (6.2)	7 (3.2)

N=total number of patients in category of interest; n=number of patients with event of interest (death).

[a] On-treatment phase is between the time of first study treatment until the earliest of 30 days after the last study treatment, the data cut date or death date.

[b] Post-treatment phase includes any events occurring after on-treatment phase.

The Applicant's Position:

A review of the deaths across the pivotal MOR208C203 trial and the 3 tafasitamab monotherapy trials (MOR208C201, MOR208C202, and XmAb5574-01) indicated that most deaths (38/50, 76%) were due to disease progression. Of the remaining 8 fatalities caused by TEAEs, 6 were related to infections, a pattern seen similarly with other B cell depleting antibodies, although none of these were considered to be related to study medication by the investigators. The only death for which a causal relationship to tafasitamab could not be excluded was a case of sclerosing cholangitis confounded by acute hepatitis A and Graft versus Host Disease after bone marrow transplant that started approximately 3 months prior to start of study medication in study MOR208C202.

The FDA's Assessment:

The data presented in Table 35 was verified by the clinical reviewer. Two minor differences were noted for deaths within 60 days of first study treatment.

For trial MOR208C203, 8 patients (9.9%) died within 30 days of the last dose. For trials MOR208C201 this was 8 patients (8.7%) and 3 patients (13.6%) for trial MOR208C202. For trial MOR208C203, the 8 patients that died within 30 days of last dose 5 patients were due to disease progression and 3 patients were due to adverse events. One patient, (b) (6), (described above), died from PML 68 days after the last dose of treatment, however, the PML was diagnosed prior to this date. Thus, a total of 4 patients died as a result of adverse events on trial MOR208C203.

The clinical reviewer reviewed the 8 narratives regarding deaths within 30 days of last dose for trial MOR208C203. Below is a summary of these narratives.

Patient (b) (6) was a 81-year-old woman with DLBCL with ECOG score of 2 at screening. The patient had a PMH of TIA, hyperthyroidism, renal failure, PE, epilepsy, PRES, and hypokalemia. At the time of enrollment she had hypertension, atrial fibrillation, vertigo, AV block, hypogammaglobulinemia, anemia, thrombocytopenia, urinary tract infection and hypomagnesemia, Adverse events and SAEs during the trial included diarrhea, (SAE), neutropenia, muscular weakness (SAE), CMV infection (SAE), febrile neutropenia (SAE), and urinary tract infection. The patient was hospitalized on day 93 due to febrile neutropenia which was prolonged due to a grade 4 DVT and pulmonary embolism on day 107, the following day the patient had acute renal failure. Anticoagulation was not possible due to thrombocytopenia. Two days later the patient had a CVA. The last dose of tafasitamab was day 99 and the last dose of lenalidomide was day 93. A CT on day 109 did not confirm evolution of lymphoma, however, the investigator felt lymphoma lesions in the leg were evolving. The patient received palliative care on day 109. The patient died on day 111. The probable cause of death was reported as CVA, an autopsy was not done.

Patient (b) (6) was a 59-year-old woman with DLBCL, stage 3 prior treatment included two

lines of therapy, R-CHOP and R-DHAP. Concurrent conditions including polyneuropathy, hypothyroidism, anemia, ankle fracture, abdominal pain, decreased white blood cell count, hepatitis B core antigen positive and sinus tachycardia. On day 4 the patient had segmental resection of small intestine invagination due to progression of lymphoma. She was withdrawn on day 3 due to disease progression. On day 14 she had a surgery for burst abdomen. On day 24 the patient died from disease progression.

Patient (b) (6) was a 76-year-old man with DLBCL with prior treatment including R-CHOP. Past medical history included hypoacusis, gastric ulcer, peripheral arterial occlusive disease, peripheral edema and cardiac failure. Medications at the time of sudden death included lansoprazole, acetylsalicylic acid, allopurinol and enoxaparin sodium. On study day 17 during cycle 1 the patient had sudden death at home. According to the investigator probable cause of death was cardiac arrhythmia or ischemic heart disease. An autopsy was not performed. There was no medical data of his death.

Patient (b) (6) was a 75-year-old woman with DLBCL, stage IV with prior treatment of 1 line of therapy including R-COMP (combined rituximab, cyclophosphamide, doxorubicin, prednisone and rituximab). The patient had an ECOG score of 0 at screening. Past medical history included thrombocytopenia. Concurrent medical conditions included hypertension and anemia. TEAEs during the trial included deep vein thrombosis, neutropenia, dyspnea and congestive heart failure which led to treatment discontinuation during cycle 7. The patient was diagnosed with non-serious obstructive hypertrophic cardiomyopathy on day 190 with prior pneumonia and pleural effusion. Six days later, the patient was diagnosed with grade 3 congestive heart failure thought to be due to progressive disease. On day 211 treatment with both study drugs was discontinued and the patient died on day 214 with a cause of death reported as diffuse large B cell lymphoma.

Patient (b) (6) was a 55-year-old man with DLBCL, stage IV with prior treatment including R-CHOP as first line and R-ESHAP as second line. ECOG at screening was 1. Past medical history included tonsillectomy, vasectomy, prior tobacco use, dyspnea, hypomagnesemia and pyrexia. Concurrent conditions included glomerulonephritis, sleep apnea, pleural effusion and anemia. On study day 43 the patient had two TEAEs of grade 3 febrile neutropenia and grade 5 respiratory failure. The last dose of tafasitamab was on day 36 and the last dose of lenalidomide was day 42. The patient had dyspnea, temperature of 37.8°C, oxygen saturation of 88%, general malaise and a non-tender, nonpruritic maculopapular rash on both flanks. The PleurX catheter was noted to be leaking a small amount of fluid. On day 44 the patient was hospitalized due to multifactorial respiratory failure with a respiratory superinfection and pleural effusion of neoplastic nature. The patient was diagnosed with adenovirus infection. Despite treatment, the patient's condition progressed and the patient died on day 51 after being placed on palliative measures.

Patient (b) (6) was a 76-year-old man with DLBCL with prior therapy including RCHOP, DHAP

(cisplatin, cytarabine, dexamethasone) rituximab/pixantrone, cyclophosphamide/doxorubicin, radiation and right lower leg amputation. Prior medical history included prostatectomy, sleep apnea, atrial fibrillation, hiatal hernia, mitral valve incompetence, obesity, drug hypersensitivity, back pain, peripheral and localized edema and anemia. During cycle 1 day 8 the patient developed the SAE of soft tissue infection. The soft tissue infection was due to lymphoma necrosis, the infection was caused by several bacteria. The soft tissue infection prolonged an existing hospitalization. As a result of the soft tissue infection his study treatment was held for 10 days. The soft tissue infection resolved and the patient remained hospitalized for ongoing treatment with study medication. The patient died 12 days after resolution of the soft tissue infection due to progressive disease.

Patient ^{(b) (6)} was a 75-year-old woman with DLBCL with prior therapy including RCHOP, and R-GEMOX (rituximab, gemcitabine, oxaliplatin). The patient had a medical history of hypertension, sleep apnea, arthralgia, diabetes mellitus, breast neoplasm, atrial fibrillation, depression dyslipidemia, pulmonary hypertension and urinary tract infection. On day 19 of cycle 1 the patient developed cognitive disorder grade 2 associated with a urinary tract infection and was hospitalized. During the hospitalization the patient developed a deep vein thrombosis due to disease progression. The enlargement of the inguinal adenopathy produced compression. The patient died from disease progression 38 days after the start of treatment and 21 days after the last dose of study medication.

Patient ^{(b) (6)} was 68-year-old man with DLBCL with prior treatment including R-CHOP, and rituximab ifosfamide, gemcitabine, and vinorelbine for his second line of treatment. Medical history included nosocomial infection and nausea. Concurrent conditions included tuberculosis, myocardial ischemia, myelodysplastic syndrome, anemia and thrombocytopenia, hydronephrosis, fatigue and axillary mass. On cycle 1 day 1, the patient had an AE of acute kidney injury grade 2. On study day 2 cycle 1 that patient had an AE of loss of consciousness grade 1. The patient was put on palliative treatment after 2 infusions of tafasitamab, cycle 1 day 1 and day 4. The patient did not receive lenalidomide due to the kidney injury. He died on day 13 due to disease progression.

Serious Adverse Events

As of the data cutoff date of June 30, 2019, there were 59 serious TEAEs experienced by 37/141 (26.2%) patients in the three tafasitamab monotherapy trials (MOR208C201, MOR208C202, and XmAb5574-01) and 76 serious TEAEs experienced by 42/81 (51.9%) patients in MOR208C203 (Table 37).

Of these serious TEAE, a causal relationship to tafasitamab alone was suspected for a total of 16 TEAEs in 14 patients (see Table 36).

Table 36: Serious Treatment-Emergent Adverse Events For Which a Causal Relationship to Tafasitamab Alone was Suspected

	Total No. of patients	TEAE	Patients	% Patients
XmAb5574-01	27	2	2	7.4%
	(Febrile neutropenia, tumor lysis syndrome)			
MOR208C201	92	4	4	4.3%
	(Genital herpes zoster, febrile neutropenia, myelodysplastic syndrome, infusion-related reaction)			
MOR208C202	22	6	4	18.2%
	(Fungal infection, pneumonia viral, febrile neutropenia, cholangitis sclerosing, tumor lysis syndrome (2))			
MOR208C203	81	4	4	4.9%
	(pneumonia, Streptococcal sepsis, pyrexia, CMV infection)			

Specific details of AEs related to infusion-related reactions, myelosuppression, and infections that were identified as part of the comprehensive safety review during the development of tafasitamab in combination with lenalidomide are provided in Section 8.2.5.

Table 37: Serious Treatment-Emergent Adverse Events Reported for ≥2% of Patients in L-MIND or in the Pooled Monotherapy Trials (Safety Analysis Set)

MedDRA Preferred term	MOR208C203 (L-MIND)							
	Pooled Monotherapy[a] N=141		Overall N=81		Combination Therapy N=80		Extended Monotherapy N=40	
	n (%)	# of Events	n (%)	# of Events	n (%)	# of Events	n (%)	# of Events
Any Serious TEAE	37 (26.2)	59	42 (51.9)	76	35 (43.8)	59	9 (22.5)	14
Pneumonia	4 (2.8)	6	6 (7.4)	6	5 (6.3)	5	1 (2.5)	1
Pulmonary embolism	0	0	3 (3.7)	3	3 (3.8)	3	0	0
Atrial fibrillation	0	0	2 (2.5)	2	2 (2.5)	2	0	0
Bronchitis	0	0	2 (2.5)	2	2 (2.5)	2	0	0
Cardiac failure congestive	0	0	2 (2.5)	2	2 (2.5)	2	0	0
Lower respiratory tract infection	0	0	2 (2.5)	4	1 (1.3)	1	2 (5.0)	3
Sepsis	3 (2.1)	3	1 (1.2)	2	1 (1.3)	2	0	0
Febrile neutropenia	6 (4.3)	10	5 (6.2)	5	4 (5.0)	4	0	0
Pyrexia	4 (2.8)	4	1 (1.2)	1	1 (1.3)	1	0	0
Tumor lysis syndrome	3 (2.1)	3	0	0	0	0	0	0

Any AE that occurs more than 30 days after the date/time of last dose of study treatment with a causality of related will also be considered treatment emergent.

Patients are counted once per system organ class and preferred term.

[a] Total reports of serious AEs from monotherapy trials XmAb5574-01, MOR208C201, and MOR208C202.

The Applicant's Position:

These results indicate risks which are consistent with the target population of patients with R/R-DLBCL receiving B-cell depleting therapy.

The cases of tumor lysis syndrome seen in the monotherapy trials are indicative of tumor types treated. There were no cases of tumor lysis syndrome in MOR208C203 in target population.

The FDA's Assessment:

Regarding the above analysis, for Table 36 a causal relationship to tafasitamab was suspected. In a single arm trial, attribution of causality is difficult and all AEs regardless of attribution should be considered for evaluation of safety. For trial MOR208C203 for an SAE to be included in this analysis the TEAE had to be considered not related to lenalidomide. The serious adverse events, limited to 1 per patient at the TEAE and at the System Organ Class level, obtained by

the reviewer is displayed in Table 38. As shown in the table, the majority of SAEs were in the System Organ Class of infections and infestations, with the most common SAE of pneumonia at 7.4% in this System Organ Class.

Table 38: Serious Adverse Events

	L-MIND (N=81)	Monotherapy (N=141)	Total (N=222)
Table Section 1			
Blood and lymphatic system disorders	6 (7.4)	8 (5.7)	14 (6.3)
Febrile neutropenia	5 (6.2)	6 (4.3)	11 (5.0)
Cardiac disorders	6 (7.4)	2 (1.4)	8 (3.6)
Atrial fibrillation	2 (2.5)	0	2 (0.9)
Cardiac failure congestive	2 (2.5)	0	2 (0.9)
General disorders and administration site conditions	3 (3.7)	21 (14.9)	24 (10.8)
Pyrexia	1 (1.2)	4 (2.8)	5 (2.3)
Infections and infestations	21 (25.9)	16 (11.3)	37 (16.7)
Bronchitis	2 (2.5)	0	2 (0.9)
Lower respiratory tract infection	2 (2.5)	0	2 (0.9)
Pneumonia	6 (7.4)	4 (2.8)	10 (4.5)
Sepsis	1 (1.2)	3 (2.1)	4 (1.8)
Metabolism and nutrition disorders	0	4 (2.8)	4 (1.8)
Tumor lysis syndrome	0	3 (2.1)	3 (1.4)
Respiratory, thoracic and mediastinal disorders	6 (7.4)	1 (0.7)	7 (3.2)
Pulmonary embolism	3 (3.7)	0	3 (1.4)

Source: OCS Analysis Studio, Custom Table Tool.
 Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
 Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y'; Percent Threshold: >= 2%.

Dropouts and/or Discontinuations Due to Adverse Effects

In MOR208C203 a total of 20 (24.7%) patients discontinued study medication due to a TEAE. Of these, 8 patients discontinued lenalidomide alone, 10 discontinued both tafasitamab and lenalidomide, and 2 patients discontinued only tafasitamab.

After the cessation of lenalidomide in the combination therapy phase in MOR208C203, one (1/40 [2.5%]) patient on extended tafasitamab monotherapy discontinued study treatment in response to a TEAE (marginal zone lymphoma recurrent).

For the pooled monotherapy trials (XmAb5574-01, MOR208C201, and MOR208C202), the majority of the 10 patients who discontinued tafasitamab for a TEAE did so as a result of myelosuppression or infection.

The Applicant's Position:

A low number of patients discontinued tafasitamab due to a TEAE. The pattern of TEAEs leading to discontinuation is consistent with a heavily pretreated population receiving B-cell depleting therapy.

The FDA's Assessment:

The clinical reviewer obtained similar data to that presented above. A total of 20 patients in trial MOR208C203 discontinued study treatment, either both drugs or either drug alone. In reviewing the TEAE that lead to withdrawal of study medication for either drug or both, on trial MOR208C203 neutropenia was the most frequent TEAE reported for 3 patients; thrombocytopenia lead to discontinuation for 1 patient in this trial. At the system organ class level, 5 patients (6.2%) had a TEAE in infections and infestations that led to withdrawal of either tafasitamab or lenalidomide, 4 patients (4.9%) the TEAE was in blood and lymphatic system disorders, and 2 patients (2.5%) for each of the following system organ classes, cardiac disorders, neoplasms benign malignant and unspecified, nervous system disorders, respiratory, thoracic and mediastinal disorders and skin and subcutaneous tissue disorders.

Dose Modification Due to Adverse Effects

In the pivotal trial MOR208C203 (L-MIND), 55/81 (68.8%) patients experienced 184 TEAEs that resulted in study drug modification (i.e., study drug interruption or dose reduction) during the combination therapy phase. The most frequent TEAE resulting in study drug modification of either tafasitamab or lenalidomide was neutropenia (28 [35.0%]).

In the monotherapy trials, a total of 59 (41.8%) patients experienced in TEAE resulting in study drug modification, the most frequent of these being infusion related reactions, neutropenia and thrombocytopenia, in total 59 patients.

The Applicant's Position:

The pattern of TEAEs leading to dose modification (reduction or interruption) is consistent with a heavily pretreated population receiving B-cell depleting therapy.

The FDA's Assessment:

For the L-MIND trial, a total of 57 patients (70.4%) had 222 TEAE that resulted in dose reduction, interruption of both drugs or either drug alone regardless of the phase of the trial. TEAE which resulted in a dose interruption or dose reduction is shown in Table 39. As shown in the table, the majority of these TEAE were in the SOC of Blood and lymphatic system disorders and the SOC of infections and infestations.

Table 39: TEAE Which Led to Dose Interruption or Dose Reduction

	L-MIND (N=81)	Monotherapy (N=141)	Total (N=222)
Table Section 1			
Blood and lymphatic system disorders	36 (44.4)	10 (7.1)	46 (20.7)
Febrile neutropenia	5 (6.2)	1 (0.7)	6 (2.7)
Leukopenia	5 (6.2)	0	5 (2.3)
Neutropenia	30 (37.0)	4 (2.8)	34 (15.3)
Thrombocytopenia	7 (8.6)	7 (5.0)	14 (6.3)
General disorders and administration site conditions	10 (12.3)	1 (0.7)	11 (5.0)
Pyrexia	7 (8.6)	1 (0.7)	8 (3.6)
Infections and infestations	24 (29.6)	7 (5.0)	31 (14.0)
Bronchitis	7 (8.6)	1 (0.7)	8 (3.6)
Pneumonia	5 (6.2)	0	5 (2.3)
Injury, poisoning and procedural complications	5 (6.2)	42 (29.8)	47 (21.2)
Infusion related reaction	3 (3.7)	41 (29.1)	44 (19.8)

Source: FDA analysis

Significant Adverse Events

Three specific risks were identified which are explained in in detail in Section 8.2.5.

Other significant adverse events leading to modification and/or discontinuation of study medication are described in detail under **Dropouts and/or Discontinuations Due to Adverse Effects** in this section.

The Applicant’s Position:

The most common and significant AEs were linked to myelosuppression and infections; infusion related reactions were seen in R/R DLBCL patients treated with tafasitamab/lenalidomide. The proposed USPI recommends pre-medication including antipyretics, histamine H1 receptor blockers, and glucocorticosteroids.

Overall, the adverse events seen in the clinical development program of tafasitamab are consistent with the mode of action of a B-cell depleting drug in the target population.

The FDA’s Assessment:

The FDA agrees that myelosuppression, infections, and infusion related reactions are significant adverse events and these will be Warnings and Precautions in the U.S. Prescribing Information.

Treatment Emergent Adverse Events and Adverse Reactions:

Most Frequent Adverse Events by Preferred Term

TEAEs in the safety analysis are listed in Table 44.

When patients completed the tafasitamab/lenalidomide therapy phase and continued on tafasitamab monotherapy the frequency of hematological and non-hematological TEAEs decreased.

Hematologic TEAEs

The following differences in the incidences of the most frequently reported hematological TEAEs in the Combination Therapy phase in MOR208C203 compared with the pooled monotherapy trials were noted (see also Table 40).

- Neutropenia (48.8% versus 12.8%,).
- Anemia (33.8% versus 10.6%,).
- Thrombocytopenia (31.3% versus 10.6%,).

The frequencies of hematologic events in the combination phase of MOR208C203 were similar to those described the lenalidomide monotherapy trials in the lenalidomide USPI (REVLIMID USPI, Revised: 10/2019).

Non-hematologic TEAEs

In the MOR208C203 combination therapy phase, 4/80 (5.0%) patients experienced an infusion-related reaction, compared with 43/141 (30.5%) patients in the tafasitamab monotherapy trials (XmAb5574-01, MOR208C201, MOR208C202).

The following differences (i.e., at least +10%) in the incidences of the most frequently reported non-hematological TEAEs in the Combination Therapy phase in MOR208C203 compared with the pooled monotherapy trials were noted (see also Table 40)

- Diarrhea (28.8% versus 14.2%,).
- Asthenia (23.8% versus 5.7%,).
- Decreased appetite (20.0% versus 5.0%,).
- Edema peripheral (21.3% versus 7.8%,).

The frequencies of non-hematologic events in the combination phase of MOR208C203 were similar to those described the lenalidomide monotherapy trials in the lenalidomide USPI (REVLIMID USPI, Revised: 10/2019).

Table 40: Treatment-Emergent Adverse Events in 10% or Greater of Patients Either in MOR208C203 Overall or in the Pooled Monotherapy by Descending Order of Frequency in MOR208C203 Overall (Safety Analysis Set)

MedDRA Preferred Term	Tafasitamab Monotherapy Trials				MOR208C203[a]			Lenalidomide Monotherapy Trials[b]		
	XmAb5574-01 N=27 n (%)	MOR208C201 N=92 n (%)	MOR208C202 N=22 n (%)	Pooled N=141 n (%)	Overall N=81 n (%)	Combination Therapy N=80[c] n (%)	Extended Tafasitamab Monotherapy N=40[c] n (%)	Mantle Cell Lymphoma N=134 n (%)	Multiple Myeloma[d] N=224 (%)	del 5q MDS N=148 n (%)
Neutropenia	8 (29.6)	9 (9.8)	1 (4.5)	18 (12.8)	41 (50.6)	39 (48.8)	11 (27.5)	65 (48.5)	177 (79.0)	87 (58.8)
Anemia	6 (22.2)	5 (5.4)	4 (18.2)	15 (10.6)	29 (35.8)	27 (33.8)	5 (12.5)	41 (30.6)	47 (21.0)	17 (11.5)
Diarrhea	8 (29.6)	8 (8.7)	4 (18.2)	20 (14.2)	29 (35.8)	23 (28.8)	9 (22.5)	42 (31.3)	122 (54.5)	72 (48.7)
Thrombocytopenia	8 (29.6)	5 (5.4)	2 (9.1)	15 (10.6)	25 (30.9)	25 (31.3)	1 (2.5)	48 (35.8)	162 (72.3)	91 (61.5)
Upper respiratory tract infection	5 (18.5)	11 (12.0)	0	16 (11.3)	8 (9.9)	7 (8.8)	2 (5.0)	17 (12.7)	60 (26.8)	22 (14.9)
Cough	4 (14.8)	8 (8.7)	4 (18.2)	16 (11.3)	21 (25.9)	15 (18.8)	9 (22.5)	38 (28.4)	23 (10.3)	29 (19.6)
Asthenia	0	7 (7.6)	1 (4.5)	8 (5.7)	19 (23.5)	19 (23.8)	2 (5.0)	19 (14.2)	0	22 (14.9)
Edema peripheral	1 (3.7)	7 (7.6)	3 (13.6)	11 (7.8)	19 (23.5)	17 (21.3)	5 (12.5)	21 (15.7)	NS	30 (20.3)
Pyrexia	5 (18.5)	5 (5.4)	6 (27.3)	16 (11.3)	19 (23.5)	17 (21.3)	6 (15.0)	31 (23.1)	17 (7.6)	31 (21.0)
Decreased appetite	3 (11.1)	3 (3.3)	1 (4.5)	7 (5.0)	18 (22.2)	16 (20.0)	2 (5.0)	19 (14.2)	NS	NS
Hypokalemia	3 (11.1)	4 (4.3)	6 (27.3)	13 (9.2)	15 (18.5)	15 (18.8)	0	17 (12.7)	24 (10.7)	16 (10.8)
Fatigue	3 (11.1)	8 (8.7)	9 (40.9)	20 (14.2)	14 (17.3)	12 (15.0)	4 (10.0)	45 (33.6)	51 (22.8)	46 (31.1)
Back pain	4 (14.8)	8 (8.7)	0	12 (8.5)	15 (18.5)	12 (15.0)	4 (10.0)	18 (13.4)	NS	31 (21.0)
Constipation	4 (14.8)	6 (6.5)	6 (27.3)	16 (11.3)	14 (17.3)	12 (15.0)	2 (5.0)	21 (15.7)	12 (5.4)	35 (23.7)
Leukopenia	0	1 (1.1)	0	1 (0.7)	12 (14.8)	12 (15.0)	5 (12.5)	20 (14.9)	51 (22.8)	12 (8.1)
Nausea	1 (3.7)	9 (9.8)	6 (27.3)	16 (11.3)	12 (14.8)	12 (15.0)	2 (5.0)	40 (29.9)	33 (14.7)	35 (23.7)
Muscle spasms (cramps)	6 (22.2)	1 (1.1)	0	7 (5.0)	12 (14.8)	11 (13.8)	1 (2.5)	17 (12.7)	0	27 (18.2)
Bronchitis	1 (3.7)	6 (6.5)	0	7 (5.0)	13 (16.0)	9 (11.3)	5 (12.5)	NS	10 (4.5)	9 (6.1)
Vomiting	1 (3.7)	3 (3.3)	2 (9.1)	6 (4.3)	12 (14.8)	10 (12.5)	2 (5.0)	16 (11.9)	17 (7.6)	15 (10.1)
Febrile neutropenia	1 (3.7)	1 (1.1)	5 (22.7)	7 (5.0)	10 (12.3)	9 (11.3)	0	8 (6.0)	39 (17.4)	8 (5.4)
Dyspnea	2 (7.4)	7 (7.6)	5 (22.7)	14 (9.9)	10 (12.3)	10 (12.5)	1 (2.5)	24 (17.9)	15 (6.7)	25 (16.9)
Headache	5 (18.5)	10 (10.9)	3 (13.6)	18 (12.8)	7 (8.6)	7 (8.8)	2 (5.0)	1-10	11 (4.9)	29 (19.6)
Infusion related reaction	18 (66.7)	12 (13.0)	13 (59.1)	43 (30.5)	5 (6.2)	4 (5.0)	1 (2.5)	NA	NA	NA
Insomnia	6 (22.2)	7 (7.6)	2 (9.1)	15 (10.6)	4 (4.9)	3 (3.8)	2 (5.0)	1-10	NS	15 (10.1)

[a] Overall includes AEs starting during the entire on-treatment phase; the Combination Therapy phase includes AEs starting between the start of the on-treatment phase and the last date of treatment with lenalidomide + 30 days; and the Extended Tafasitamab Monotherapy phase includes AEs starting after the last date of treatment with lenalidomide + 30 days through the end of the on-treatment phase. Planned treatment for L-MIND is twelve 28-day cycles of Combination Therapy followed by Extended Tafasitamab Monotherapy until progressive disease or unacceptable toxicity or trial discontinuation for any reason.

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[b] REVLIMID USPI, Revised: 10/2019

[c] One patient ^{(b) (6)} received infusions of tafasitamab on Days 1 and 4 of Cycle 1, but lenalidomide was not administered due to acute kidney injury at the time of treatment, and the patient discontinued the study treatment after Cycle 1 Day 4.

[d] The Cancer and Leukemia Group B (CALGB)/Alliance 100104 assessed lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma.

The Applicant's Position:

Overall, the addition of tafasitamab to lenalidomide does not meaningfully add toxicity to the known safety profile of lenalidomide alone.

The FDA's Assessment:

The TEAE obtained by the clinical review are shown in Table 41. Each TEAE was limited to 1 per patient and recoding was done. The table lists the TEAE from most common to least in the L-MIND trial. As shown the TEAE that occurred in more than 20% of patients on the L-MIND trial include neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, peripheral edema, pyrexia, respiratory tract infection, and decreased appetite.

Table 41: TEAE

Treatment Emergent Adverse Events			
	L-MIND (N=81)	Monotherapy (N=141)	Total (N=222)
Table Section 1			
Neutropenia ¹	41 (50.6)	25 (17.7)	66 (29.7)
Fatigue ²	31 (38.3)	27 (19.1)	58 (26.1)
Anemia	29 (35.8)	15 (10.6)	44 (19.8)
Diarrhea	29 (35.8)	20 (14.2)	49 (22.1)
Thrombocytopenia ³	25 (30.9)	22 (15.6)	47 (21.2)
Cough	21 (25.9)	16 (11.3)	37 (16.7)
Edema peripheral ⁴	21 (25.9)	18 (12.8)	39 (17.6)
Pyrexia	19 (23.5)	16 (11.3)	35 (15.8)
Respiratory tract infection ⁵	19 (23.5)	18 (12.8)	37 (16.7)
Decreased appetite	18 (22.2)	7 (5.0)	25 (11.3)
Back pain	15 (18.5)	12 (8.5)	27 (12.2)
Hypokalemia	15 (18.5)	13 (9.2)	28 (12.6)
Constipation	14 (17.3)	16 (11.3)	30 (13.5)
Urinary tract infection ⁶	14 (17.3)	3 (2.1)	17 (7.7)
Bronchitis	13 (16.0)	7 (5.0)	20 (9.0)
Rash ⁷	13 (16.0)	13 (9.2)	26 (11.7)
Abdominal pain ⁸	12 (14.8)	14 (9.9)	26 (11.7)
Leukopenia	12 (14.8)	1 (0.7)	13 (5.9)
Muscle spasms	12 (14.8)	7 (5.0)	19 (8.6)
Nausea	12 (14.8)	16 (11.3)	28 (12.6)
Vomiting	12 (14.8)	6 (4.3)	18 (8.1)
Dyspnoea ⁹	11 (13.6)	15 (10.6)	26 (11.7)
Nasopharyngitis ¹⁰	11 (13.6)	4 (2.8)	15 (6.8)
Febrile neutropenia	10 (12.3)	7 (5.0)	17 (7.7)
Headache	7 (8.6)	18 (12.8)	25 (11.3)
Infusion related reaction	5 (6.2)	43 (30.5)	48 (21.6)
Insomnia	4 (4.9)	15 (10.6)	19 (8.6)

Treatment Emergent Adverse Events		L-MIND (N=81)	Monotherapy (N=141)	Total (N=222)
1.	Neutropenia includes neutropenia and neutrophil count decrease			
2.	Fatigue includes fatigue and asthenia			
3.	Thrombocytopenia includes thrombocytopenia and platelet count decreased			
4.	Edema peripheral includes edema, oedemic peripheral and peripheral swelling			
5.	Respiratory tract infection includes lower respiratory tract infection, respiratory tract infection, upper respiratory tract infection, viral upper respiratory tract infection, respiratory syncytial virus infection, and upper respiratory tract infection bacterial			
6.	Urinary tract infection includes Escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial and urinary tract infection enterococcal			
7.	Rash includes rash rash erythematous rash maculo-papular rash pruritic rash pustular			
8.	Abdominal pain includes abdominal pain, abdominal pain lower, and abdominal pain upper			
9.	Dyspnea includes dyspnea and dyspnoea exertional			
10.	Nasopharyngitis includes nasopharyngitis and nasal congestion			

Source: OCS Analysis Studio, Custom Table Tool.
 Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
 Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >= 10%.

Severity of Treatment Emergent Adverse Events

The Grade 3 and 4 TEAEs in the safety analysis are presented in Table 42. The most frequently occurring Grade 3/4 TEAEs are hematological (neutropenia, thrombocytopenia, leukopenia, anemia, febrile neutropenia).

When patients completed the tafasitamab/lenalidomide therapy phase and continued on tafasitamab monotherapy the frequency of Grade 3/4 TEAEs decreased.

Grade 3/4 Hematologic TEAEs

Compared to the pooled monotherapy trials, the following differences in the incidence (i.e., at least +10%) of the most frequently Grade 3/4 TEAEs reported in the Combination Therapy phase in MOR208C203 were noted for the following hematologic TEAEs Table 42:

- Grade 3/4 neutropenia (38/80 [47.5%] versus 14/141 [9.9%] patients, respectively).
- Grade 3/4 thrombocytopenia (14/80 [17.5%] versus 7/141 [5.0%] patients, respectively).

The frequencies of Grade 3/4 neutropenia and thrombocytopenia in the combination phase of MOR208C203 were similar to those described for the lenalidomide monotherapy trials in the lenalidomide USPI (REVLIMID USPI, Revised: 10/2019).

Grade 3/4 Non-hematologic TEAEs

None of the most frequent Grade 3/4 TEAEs in MOR208C203 Combination Therapy phase differed in frequency by $\geq 10\%$ compared with the pooled monotherapy trials (Table 42).

Overall, the incidence of Grade 3/4 non-hematologic TEAEs reported in the MOR208C203 Combination Therapy phase did not differ from the incidence described for the lenalidomide monotherapy trials in the lenalidomide USPI (REVLIMID USPI, Revised: 10/2019).

Table 42: Grades 3/4 Treatment-Emergent Adverse Events Reported in ≥2% of Patients in Overall by Descending Order of Frequency in MOR208203 Overall (Safety Analysis Set)

MedDRA Preferred Term	Monotherapy Trials				MOR208C203_a			Lenalidomide Monotherapy Trials[b]		
	XmAb5574-01 N=27 n (%)	MOR208C201 N=92 n (%)	MOR208C201 N=22 n (%)	Pooled N=141 n (%)	Overall N=81 n (%)	Combination Therapy N=80[c] n (%)	Extended Tafasitamab Monotherapy N=40[c] n (%)	Mantle Cell Lymphoma N=134 n (%)	Multiple Myeloma [d]/ N=224 n (%)	del 5q MDS N=148 n (%)
Neutropenia	6 (22.2)	7 (7.6)	1 (4.5)	14 (9.9)	40 (49.4)	38 (47.5)	7 (17.5)	58 (43.3)	133 (59.4)	79 (53.4)
Thrombocytopenia	3 (11.1)	2 (2.2)	2 (9.1)	7 (5.0)	14 (17.3)	14 (17.5)	0	37 (27.6)	84 (37.5)	74 (50.0)
Leukopenia	0	1 (1.1)	0	1 (0.7)	9 (11.1)	6 (7.5)	3 (7.5)	9 (6.7)	45 (20.1)	8 (5.4)
Febrile neutropenia	1 (3.7)	1 (1.1)	5 (22.7)	7 (4.9)	10 (12.3)	9 (11.3)	0	8 (6.0)	39 (17.4)	6 (4.1)
Anemia	1 (3.7)	3 (3.3)	2 (9.1)	6 (4.3)	6 (7.4)	6 (7.5)	0	15 (11.2)	23 (10.3)	9 (6.1)
Pneumonia	0	2 (2.2)	1 (4.5)	3 (2.1)	6 (7.4)	5 (6.3)	1 (2.5)	12 (9.0)	23 (10.3)	11 (7.4)
Hypokalemia	0	2 (2.2)	2 (9.1)	4 (2.8)	5 (6.2)	5 (6.3)	0	3 (2.2)	16 (7.1)	NS
Pulmonary embolism	0	0	0	0	4 (4.9)	4 (5.0)	0	2 (1.5)	0	3 (2.0)
Atrial fibrillation	0	0	0	0	3 (3.7)	3 (3.8)	0	NS	NS	NS
Dermatitis allergic	0	0	0	0	3 (3.7)	3 (3.8)	0	NS	NS	NS
Hypertension	0	1 (1.1)	3 (13.6)	4 (2.8)	3 (3.7)	2 (2.5)	1 (2.5)	NS	NS	NS
Lymphopenia	0	0	0	0	3 (3.7)	3 (3.8)	0	5 (3.7)	37 (16.5)	NS
Asthenia	0	1 (1.1)	0	1 (0.7)	2 (2.5)	1 (1.3)	1 (2.5)	4 (3.0)	0	2 (1.4)
Back pain	0	2 (2.2)	0	2 (1.4)	2 (2.5)	2 (2.5)	0	2 (1.5)	NS	7 (4.7)
Cardiac failure congestive	0	0	0	0	2 (2.5)	2 (2.5)	0	NS	NS	NS
Fatigue	0	2 (2.2)	2 (9.1)	4 (2.8)	2 (2.5)	1 (1.3)	1 (2.5)	9 (6.7)	21 (9.4)	7 (4.7)
Lower respiratory tract infection	0	0	0	0	2 (2.5)	1 (1.3)	2 (5.0)	NS	6 (2.7)	NS
Renal failure	0	0	0	0	2 (2.5)	2 (2.5)	0	2 (1.5)	NS	NS
Transaminases increased	0	0	0	0	2 (2.5)	2 (2.5)	1 (2.5)	NS	NS	NS
Upper respiratory tract infection	0	0	0	0	2 (2.5)	2 (2.5)	0	0	7 (3.1)	2 (1.4)

[a] Overall includes AEs starting during the entire on-treatment phase, the Combination Therapy phase includes AEs starting between the start of the on-treatment phase and the last date of treatment with lenalidomide + 30 days, and the Extended Tafasitamab Monotherapy phase includes AEs starting after the last date of treatment with lenalidomide + 30 days through the end of the on-treatment phase. Planned treatment for MOR208C203 (L-MIND) is twelve 28-day cycles of Combination Therapy followed by Extended Tafasitamab Monotherapy until progressive disease or unacceptable toxicity or trial discontinuation for any reason.

[b] REVLIMID USPI, Revised: 10/2019

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- [c] One patient (b) (6) received infusions of tafasitamab on Days 1 and 4 of Cycle 1, but lenalidomide was not administered due to acute kidney injury at the time of treatment, and the patient discontinued the study treatment after Cycle 1 Day 4.
- [d] The Cancer and Leukemia Group B (CALGB)/Alliance 100104 assessed lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma.

The Applicant’s Position:

These results indicate risks which are consistent with the target population of patients with R/R-DLBCL receiving B-cell depleting therapy. The addition of tafasitamab to lenalidomide does not meaningfully add toxicity to the known safety profile of lenalidomide alone.

The FDA’s Assessment:

The clinical reviewer verified the data presented above from the clinical trials. The grade 3, 4, or 5 TEAE that occurred in >5% of patients are presented in Table 43. This analysis was limited maximum grade per patient per TEAE and adjudication was done. As shown the more common grade 3, 4, or 5 TEAE which occurred in more than 10% of patients on the L-MIND trial are neutropenia, thrombocytopenia and febrile neutropenia.

Table 43: TEAE Grade 3, 4 or 5

	L-MIND (N=81)	Monotherapy (N=141)	Total (N=222)
Grade 3/4/5 TEAE			
Neutropenia ¹	40 (49.4)	20 (14.2)	60 (27.0)
Thrombocytopenia ²	14 (17.3)	12 (8.5)	26 (11.7)
Febrile neutropenia	10 (12.3)	7 (5.0)	17 (7.7)
Anemia	6 (7.4)	6 (4.3)	12 (5.4)
Pneumonia ³	6 (7.4)	6 (4.3)	12 (5.4)
Leukopenia	9 (11.1)	1 (0.7)	10 (4.5)
Hypokalemia	5 (6.2)	4 (2.8)	9 (4.1)

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	L-MIND (N=81)	Monotherapy (N=141)	Total (N=222)
1.	Neutropenia includes neutropenia and neutrophil count decreased		
2.	Thrombocytopenia includes thrombocytopenia and platelet count decreased		
3.	Pneumonia includes pneumonia, pneumonia haemophilus, pneumonia klebsiella, pneumonia pneumococcal, and pneumonia viral		

Source: OCS Analysis Studio Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Grade 3/4/5 TEAE - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AETOXGR = '3' or '4' or '5'; Percent Threshold: >= 5%.

Adverse Drug Reactions

To define ADRs, the treatment-emergent adverse events were reviewed taking into consideration temporal association, biological plausibility, evidence of positive de-challenge and re-challenge where available, consistency, causality assessment by investigators and alternative explanations for adverse events. Study MOR208C203 was used to determine the frequency of ADRs.

For TEAEs reported during the combination therapy phase in MOR208C203 (L-MIND) both lenalidomide and tafasitamab had to be considered as suspect drugs for a causality assessment.

Table 44 summarizes commonly reported adverse reactions in MOR208C203 (L-MIND) overall, in the combination therapy and tafasitamab monotherapy phases separately, and in the tafasitamab monotherapy trials individually and pooled.

Table 44: Summary of Treatment Emergent Adverse Reactions for Overall Tafasitamab and Lenalidomide Treatment, Combination Therapy, and Tafasitamab Monotherapy Treatment Period (L-MIND Study) in $\geq 10\%$ of Subjects

Preferred Terms	Overall (N=81) [a]	Tafasitamab plus Lenalidomide Combination Therapy (N=80) [b]			Tafasitamab Extended Monotherapy (N=40) [c]		
	All Grades n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
<i>Hematological adverse reactions</i>							
Neutropenia	41 (50.6)	39 (48.8)	23 (28.8)	15 (18.8)	11 (27.5)	1 (2.5)	6 (15.0)
Anemia	29 (35.8)	27 (33.8)	6 (7.5)	0	5 (12.5)	0	0
Thrombocytopenia	25 (30.9)	25 (31.3)	10 (12.5)	4 (5.0)	1 (2.5)	0	0
Leukopenia	12 (14.8)	12 (15.0)	5 (6.3)	1 (1.3)	5 (12.5)	2 (5.0)	1 (2.5)
Febrile neutropenia	10 (12.3)	9 (11.3)	7 (8.8)	2 (2.5)	0	0	0
<i>Non hematological adverse reactions</i>							
Diarrhea	29 (35.8)	23 (28.8)	1 (1.3)	0	9 (22.5)	1 (2.5)	0
Cough	21 (25.9)	15 (18.8)	1 (1.3)	0	9 (22.5)	0	0
Asthenia	19 (23.5)	19 (23.8)	1 (1.3)	0	2 (5.0)	1 (2.5)	0
oedemic peripheral	19 (23.5)	17 (21.3)	0	0	5 (12.5)	0	0
Pyrexia	19 (23.5)	17 (21.3)	1 (1.3)	0	6 (15.0)	0	0
Decreased appetite	18 (22.2)	16 (20.0)	0	0	2 (5.0)	0	0
Hypokalemia	15 (18.5)	15 (18.8)	4 (5.0)	1 (1.3)	0	0	0
Back pain	15 (18.5)	12 (15.0)	2 (2.5)	0	4 (10.0)	0	0
Constipation	14 (17.3)	12 (15.0)	0	0	2 (5.0)	0	0
Fatigue	14 (17.3)	12 (15.0)	1 (1.3)	0	4 (10.0)	1 (2.5)	0
Bronchitis	13 (16.0)	9 (11.3)	0	1 (1.3)	5 (12.5)	0	0
Nausea	12 (14.8)	12 (15.0)	0	0	2 (5.0)	0	0
Vomiting	12 (14.8)	10 (12.5)	0	0	2 (5.0)	0	0
Muscle spasms	12 (14.8)	11 (13.8)	0	0	1 (2.5)	0	0
Dyspnea	10 (12.3)	10 (12.5)	1 (1.3)	0	1 (2.5)	0	0
Nasopharyngitis	8 (9.9)	4 (5.0)	0	0	6 (15.0)	0	0
Pruritus	8 (9.9)	8 (10.0)	1 (1.3)	0	0	0	0

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Preferred Terms	Overall (N=81) [a]	Tafasitamab plus Lenalidomide Combination Therapy (N=80) [b]			Tafasitamab Extended Monotherapy (N=40) [c]		
	All Grades n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
C-reactive protein decreased	8 (9.9)	8 (10.0)	0	0	0	0	0

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[a] Overall includes both treatment phases (tafasitamab plus lenalidomide combination phase and tafasitamab extended monotherapy phase) and includes adverse events that started during these treatment phases. One patient received tafasitamab and no Lenalidomide,

[b] Tafasitamab plus Lenalidomide includes adverse events that started during the tafasitamab plus lenalidomide combination phase.

[c] Tafasitamab extended monotherapy phase includes adverse events that started after the last date of treatment with lenalidomide + 30 days through the end of tafasitamab treatment

Events were graded using NCI CTCAE version 4

In MOR208C203 (L-MIND) the most commonly reported adverse reactions occurring in more than 20% of patients included neutropenia, anemia, thrombocytopenia, diarrhea, asthenia, peripheral edema, pyrexia, decreased appetite, and cough.

The medically most important risks identified in the clinical development program of tafasitamab comprise infusion related reactions, myelosuppression and infections. These are described in detail in Section 8.2.5.

The Applicant’s Position:

Overall, the adverse drug reactions are consistent with the mode of action of a B-cell depleting drug in the target population.

The FDA’s Assessment:

The clinical reviewer verified the data presented in Table 44. A few differences were found.

Laboratory Findings

Hematology parameters to be summarized included platelets, hemoglobin, WBC count, absolute neutrophil count, and lymphocytes; blood chemistry parameters included sodium, magnesium, potassium, calcium, AST, ALT, serum creatinine, BILI, and ALP. Shift tables using CTCAE grades to compare baseline to the worst post-baseline CTCAE grade were produced for applicable hematology and biochemistry laboratory parameters. The grades for laboratory parameters are based on the numeric component of the CTCAE grading scale v4.0. Per protocol, abnormal laboratory values considered clinically significant by the investigator were to be reported as AEs.

Changes in hematological parameters were analyzed for patients with both baseline and post baseline values. Overall, the observed changes in MOR208C203 were consistent with the reported hematologic TEAEs:

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- Hemoglobin: 4/81 (4.9%) patients had a shift of 2-3 grades toward worsening CTCAE grade.
- Neutrophil Count: 14 (17.3%) patients of 2-3 grades toward worsening CTCAE grade.
- Platelet Count: 1/81 (1.2%) patients had a shift of 2-3 grades toward worsening CTCAE grade.

The hematological parameters $\geq$ Grade 3 anemia, leukopenia, neutropenia, and thrombocytopenia are of special interest. The number and percent of patients demonstrating any of the following values at least once during the On-Treatment Phase are shown below for the pooled monotherapy trials and for MOR208C203:

- Hemoglobin $<$ 8 g/dL (16 [11.3%] versus 1 [1.3%])
- Leukocytes $<$ $2 \times 10^3/\mu\text{L}$ (29 [20.6%] versus 10 [12.5%])
- Neutrophils $<$ $1 \times 10^3/\mu\text{L}$ (41 [29.1%] versus 16 [20.0%])
- Platelets $<$ $50 \times 10^3/\mu\text{L}$ (28 [19.9%] versus 3 [3.8%])

Mean baseline and end-of-treatment values and change from baseline values for serum chemistries were analyzed. No clinically relevant changes were observed in any parameter. There were no cases with laboratory values that fulfilled the criteria for potential Hy’s Law.

The Applicant’s Position:

The observed laboratory abnormalities were as expected in this population. Laboratory abnormalities were consistent with the observation of TEAEs.

The FDA’s Assessment:

The clinical reviewer verified the data above and some differences where seen. One significantly different calculation obtained was for patients with a neutrophil count that had a shift of 2-3 grades toward worsening CTCAE. The clinical reviewer obtained that 41/81 (50.6%) patients had a worsening neutrophil count of 2-3 grades. Other differences seen were not as significant.

The laboratory analysis obtained by the clinical reviewer is shown in Table 45. For Table 45 the safety population was used. In the USPI for tafasitamab the population used to calculate laboratory values was patients with a baseline value and at least 1 post-treatment value.

Table 45: Laboratory Analysis Trial MOR208C203

	All Grades n (%)	Grades 3/4 n (%)

Chemistry		
Alanine aminotransferase	9 (11.1)	0 (0.0)
Hypoalbuminemia	20 (24.7)	0 (0.0)
Alkaline phosphatase	10 (12.3)	0 (0.0)
Amylase	1 (1.2)	0 (0.0)
Aspartate aminotransferase	16 (19.8)	0 (0.0)
Bilirubin	9 (11.1)	0 (0.0)
Calcium low	39 (48.1)	1 (1.2)
Creatine kinase	11 (13.6)	1 (1.2)
Creatinine	15 (18.5)	1 (1.2)
Gamma Glutamyl transferase	25 (30.9)	4 (4.9)
Glucose high	39 (48.1)	3 (3.7)
Lipase, pancreatic	4 (4.9)	1 (1.2)
Magnesium low	16 (19.8)	0 (0.0)
Potassium low	15 (18.5)	1 (1.2)
Potassium high	5 (6.2)	1 (1.2)
Sodium low	8 (9.9)	1 (1.2)
Urate	15 (18.5)	5 (6.2)
Coagulation		
Activated partial thromboplastin time	32 (2.5)	3 (3.7)
Prothrombin international normalized ratio	30 (37.0)	1 (1.2)
Hematology		
Hemoglobin	45 (55.6)	2 (2.5)
Leukocytes	42 (51.9)	11 (13.6)
Lymphocyte	35 (43.2)	10 (12.3)
Neutrophils	48 (59.3)	16 (19.8)
Platelets	26 (32.1)	3 (3.7)

Source: FDA Analysis

Vital Signs

Vital sign parameters included heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP), respiratory rate, temperature, and weight. The data collected in different units were converted into standard international (SI) units for summary. The number and percentage of patients meeting the abnormal vital sign criteria by visit and at any time during the On-Treatment Phase were summarized.

The number and percent of patients with notable abnormalities (i.e., individual outlier values based on prespecified criteria) were similar between the pooled monotherapy trials and MOR208C203.

The Applicant's Position:

No clinically relevant changes in vital signs or trends over time were observed.

The FDA's Assessment:

The clinical reviewer reviewed the Applicant's analysis.

Electrocardiograms (ECGs) and QT

An analysis of recordings from patients enrolled in L-MIND did not reveal any abnormal QTc prolongation or any other electrocardiographic abnormality potentially associated with the study drug.

Immunogenicity

The clinical assessment of immunogenicity for tafasitamab was evaluated in 245 patients, of whom 81 (33.1%) of the 245 patients were part of MOR208C203. The other 164 (66.9%) patients were derived from the four other clinical trials (XmAb5574-01, MOR208C201, MOR208C202, and MOR208C205 (COSMOS), in which tafasitamab was tested in different indications and/or different treatment settings compared with MOR208C203. In MOR208C203, mean exposure time to tafasitamab was 49.3 weeks, and anti-drug antibody (ADA) samples were collected for up to two years.

A low number of patients (17 [6.9%] of the 245 patients overall) tested ADA-positive before start of tafasitamab treatment, suggesting the presence of pre-existing antibodies. Only six of these patients with pre-existing ADAs were ADA-positive on an intermittent basis after start of tafasitamab treatment (i.e., ADA positive at one to seven sampling time points). The other 11 of these patients with pre-existing ADAs did not show any positive ADA assessment during treatment. No patients testing negative before the start of tafasitamab treatment subsequently tested positive. Thus, in all five clinical trials, no treatment-emergent or treatment-boostered ADAs could be detected. The ADA titers were low, and there was no apparent clinical impact of ADAs on PK, safety, or efficacy.

The Applicant's Position:

No clinically significant immunogenicity was detected for tafasitamab.

The FDA's Assessment:

Refer to section 6.2.1 immunogenicity.

8.2.5. Analysis of Submission-Specific Safety Issues

Specific AEs related to infusion-related reactions, myelosuppression, and infections were identified as part of the comprehensive safety review during the development of tafasitamab in combination with lenalidomide.

Myelosuppression

Treatment with tafasitamab can cause serious or severe myelosuppression including neutropenia, thrombocytopenia, and anemia. In patients treated with tafasitamab and lenalidomide (n = 81), Grade 3 hematologic adverse reactions occurring in $\geq 5\%$ of patients included neutropenia (25%), thrombocytopenia (12%), febrile neutropenia (10%), leukopenia (9%), and anemia (7%). Grade 4 hematologic adverse reactions occurring in $\geq 5\%$ of recipients included neutropenia (25%) and thrombocytopenia (5%). Cytopenia's were the most common reason for treatment discontinuation (1% of patients due to tafasitamab; 5% of patients due to lenalidomide).

Neutropenia, Grade 3 or Higher: Neutropenia is a known adverse effect associated with lenalidomide treatment. Events of neutropenia occurred more frequently in patients receiving tafasitamab-lenalidomide combination therapy in MOR208C203 compared with patients receiving tafasitamab monotherapy in the monotherapy trials, and the number declined in the tafasitamab monotherapy extension phase of MOR208C203. There were no fatal neutropenic events.

In the pooled monotherapy trials, 14/141 (9.9%) patients experienced neutropenia Grade ≥ 3 compared with 40/81 (49.4%) patients in MOR208C203. In the pooled monotherapy trials, 7/141 (5.0%) patients experienced febrile neutropenia Grade ≥ 3 compared with 10/81 (12.3%) patients in MOR208C203. One patient in MOR208C203 experienced Grade 3 neutropenic sepsis while receiving combination therapy.

Most Grade ≥ 3 neutropenia events (preferred terms of neutropenia, febrile neutropenia, neutropenic sepsis, neutrophil count decreased) were non-serious (140 events in 64 patients). Onset of Grade ≥ 3 neutropenia events occurred earlier in the pooled monotherapy trials compared with MOR208C203 which may be explained by the different tumor types. The median duration of events was similar in pooled monotherapy trials and MOR208C203 (7 to 8 days) (Table 46).

Table 46: Time to Onset and Duration of Neutropenia Events, Grade 3 or Higher (Safety Analysis Set)

Neutropenia Events[a]	Pooled Monotherapy[b]	MOR208203 Overall
n (%), Events	22 (15.6%), 34	45 (55.6%), 121
Time to onset (days)[c]		
Median	20.5	113
Minimum-Maximum	2-1359	1-994
Duration of adverse event (days)[d]		
Mean	22.6	11.3
Median	7	8
Minimum-Maximum	1-387	1-222

[a] Neutropenia events include preferred terms of neutropenia, febrile neutropenia, neutropenic sepsis, neutrophil count decreased

[b] Pooled monotherapy trials: MOR208C201, MOR208C202, and Xmab5574-01.

[c] Time to onset from 1st tafasitamab treatment initiation. If a patient had multiple occurrence of same adverse event (AE), all the events were considered for the calculation.

[d] Duration of AE is defined as start of AE to end of AE. For multiple AEs from same patient, all the events were considered.

There were 15 serious neutropenia events in 11 patients (6/141 [4.3%] patients in monotherapy trials; 5/81 [6.2%] patients in MOR208C203). Of the 15 SAEs, 14 were events of febrile neutropenia and one event of neutropenic sepsis. All patients recovered except for one. The remaining patient recovered with sequelae of disease progression, assessed as unrelated to tafasitamab (Patient ^{(b) (6)} in MOR208C202). For the five patients with six serious neutropenia events in MOR208C203, tafasitamab-lenalidomide combination therapy was temporarily interrupted for three events, was not stopped for two events, and action taken with drug was ‘not applicable’ for the remaining event. For the six patients in the monotherapy studies with nine serious neutropenia events, tafasitamab therapy was withdrawn for one event, interrupted for one event, continued unchanged for four events, and action taken with drug was ‘not applicable’ for the remaining three events. All 11 patients required treatment, typically with antibiotics, G-CSF, or other supportive treatment, as appropriate.

The neutropenia profile for the tafasitamab-lenalidomide combination therapy is consistent with that documented for lenalidomide therapy in multiple myeloma patients as described in the lenalidomide USPI (REVLIMID USPI, Revised: 10/2019).

Infections

Bacterial, fungal, and new or reactivated viral infections can occur during and following tafasitamab therapy. Grade 3 or higher infections occurred in 30% of patients treated with tafasitamab and lenalidomide (n=81). Infection-related deaths were reported in 1% (1/81) of patients within 30 days of last treatment. Pneumonia was the most frequently reported serious infection occurring in 7% (6/81) patients. Infections occurring in ≥5% of patients included

bronchitis (16%), nasopharyngitis (10%), pneumonia (10%), respiratory tract infection (10%), upper respiratory tract infection (10%), urinary tract infections (10%), gastroenteritis (6%), escherichia urinary tract infection (5%), rhinitis (5%), sinusitis (5%), and lower respiratory tract infection (5%).

Infections, Grade 3 or Higher: For the analysis of infections, all serious AEs were considered. In addition, to capture non-serious infections of interest (Grade 3 or higher), a Customized MedDRA Query (CMQ) with categories of infectious pneumonia, sepsis and urogenital tract infections was used.

As of the data cutoff date of June 30, 2019, a total of 16/141 (11.3%) patients experienced 22 serious TEAEs of infection in the pooled monotherapy trials. In MOR208C203 overall, a total of 21/81 (25.9%) patients experienced 32 serious such TEAEs. More infections were observed in the MOR208C203 Combination Therapy phase of (18/80 [22.5%] patients) than in the Tafasitamab Monotherapy phase (4/40 [10.0%] patients).

Grade 3 or higher infections were reported for 43 patients in total with 19/141 (13.5%) patients with 27 events in the pooled monotherapy trials and 24/81 (29.6%) patients with 36 events in MOR208C203 overall. The majority of these events of infections were pneumonia events (20/63) in 17 of 222 (7.7%) patients including the preferred terms of pneumonia, pneumonia viral, pneumonia pneumococcal, pneumonia Klebsiella, pneumonia Hemophilus. Pneumonia events led to sepsis events in nine of 222 (4.0%) patients (PTs: sepsis, bacterial sepsis, Klebsiella sepsis, Streptococcal sepsis, neutropenic sepsis reported).

In MOR208C203, 5/81 (6.2%) patients had infections of Grade 3 or higher assessed as related to both tafasitamab and lenalidomide; 2/81 (2.5%) patients had infection events of Grade 3 or higher assessed as suspected to tafasitamab alone; and 1/81 (1.2%) patients had infection events of Grade 3 or higher assessed as suspected to lenalidomide alone.

In the pooled monotherapy trials, one infection > Grade 3 was assessed as related to tafasitamab alone.

Serious herpes virus or CMV infections of Grade 3 or higher

Three patients developed serious infections with a herpes virus or CMV:

- One 90-year-old male patient in MOR208C201 suffered genital herpes zoster which was of Grade 3, assessed as suspected to tafasitamab treatment; the patient recovered.
- One 70-year-old female patient in MOR208C203 developed disseminated varicella zoster in blood, gut, lungs and liver of Grade 4, which was assessed as not related to any study drug. Confounding factor was reported as decreased immunity due to the underlying leukemia. The patient recovered.
- Also in MOR208C203, one 83-year-old female developed a Grade 3 CMV infection suspected to be associated with colitis. The investigator assessed as related to tafasitamab, not related to lenalidomide; the patient recovered.

Infection events with a fatal outcome

In the pooled monotherapy trials, three patients had infection events with a fatal outcome, all in Cycle 1; all three deaths were not considered related to tafasitamab (Table 35):

- One patient died from *Stenotrophomonas maltophilia* sepsis.
- One patient died from *Enterococcus faecium* sepsis in multi-organ failure.
- One patient died from pneumonia in respiratory and cardiac failure.

Patient (b) (6) (MOR208C203) experienced multifactorial respiratory failure on study day 43 in the context of a respiratory superinfection (adenovirus), neutropenic fever, pleural effusion of neoplastic nature and mixed acidosis. The event was likely to have resulted from suspected lymphoma progression (pleural fluid was of neoplastic nature). The patient died 8 days after event onset (Study Day 51).

In the MOR208C203 study, one patient experienced a worsening of progressive multifocal leukoencephalopathy with a fatal outcome. The patient first developed unspecific neurological symptoms ten days prior to initiation of study treatment, which worsened while on study drug. The case was assessed as not related to any study drug. The patient died more than 30 days after cessation of study therapy.

Infections are considered an identified risk of treatment with tafasitamab. Most patients recovered after receiving standard antibiotic treatment. The five patients who died were severely debilitated with underlying comorbidities that predisposed them to risk of infection with poor outcome.

Infusion-Related Reactions

In the tafasitamab monotherapy trials (XmAb5574-01, MOR208C201, MOR208C202) which were performed in the indications CSL/CLL, NHL and B-ALL) approximately 30% of the patient enrolled in the studies experienced an infusion related reaction. In the L-MIND Study in R/R DLBCL, 5 (6%) patients experienced an infusion reaction; all were Grade 1 and resolved on the same day of occurrence. The majority of these reactions occurred during the first infusion. Symptoms included chills, flushing, dyspnea, and hypertension. Tafasitamab infusion was interrupted then resumed for 3 patients and supportive treatment was required for 3 of these 5 patients. Premedication including antipyretics, histamine H1 receptor blockers, and glucocorticosteroids in the first cycle is recommended in the USPI.

Infusion-Related Reactions, Grade 3 or Higher: A Customized MedDRA Query 'Infusion-related reaction' was used to identify cases of possible interest for all toxicity grades. In the pooled monotherapy trials, a total of 43/141 (30.5%) patients experienced 49 events of infusion-related reaction (CMQ), of which two patients had an IRR of Grade 3 or greater. In MOR208C203, 5/81 (6.2%) patients experienced five events of infusion-related reaction (CMQ) during the first infusion, all of which were Grade 1 in severity.

Per protocol, patients in the monotherapy trials and in MOR208C203 received pre-medication including antipyretics, histamine H1 receptor blockers, and glucocorticosteroids in the first cycle, at the discretion of the Investigators.

In the monotherapy studies and in MOR208C203, the majority of infusion-related reactions occurred during the first infusion (86%). One case of infusion-related reaction (dyspnea) was considered to be serious and required discontinuation of tafasitamab treatment. The two Grade 3/4 cases are summarized in Table 47.

Table 47: Analysis of Infusion-Related Reactions, Grade 3 or Higher (Safety Analysis Set)

Trial Patient ID	Age/Sex/Race	MedDRA Preferred Term	Toxicity [Serious]	Onset [Duration, D]	Causality Tafasitamab Lenalidomide	Outcome
MOR208C201 (b) (6)	59/M/White	Infusion related reaction VT=DYSPNEA	Grade 4 [Yes]	D1/C1 [6]	Suspected NA	Resolved
MOR208C202 (b) (6)	18/F/White	Infusion related reaction VT=INFUSION REACTION WITH SYMPTOMS OF THROAT CLOSING UP AND VOMITING	Grade 3 [No]	D1/C1 [1]	Suspected NA	Resolved

Abbreviations: C=cycle; D=day; F=female; ID=identification; M=male; MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable; VT=verbatim term.

The majority of infusion-related reactions were accompanied by symptoms of flushing (22/141 [15.6%]) and nausea (18/141 [12.8%] patients) in the pooled monotherapy trials. In MOR208C203, infusion-related reactions were characterized by chills (2/81 [2.5%] patients) and hypertension, increased systolic blood pressure, and pain in the renal lodge (1/81 [1.2%] patient each).

The Applicant’s Position:

Specific safety issues of tafasitamab concern adverse events which are consistent with the targeted patient population and the pharmacological mode of action of a B-cell depleting drug.:

Adverse events linked to myelosuppression, in particular neutropenia, anemia and thrombocytopenia are the primarily expected events with the combination therapy with tafasitamab and lenalidomide due to its B-cell depleting properties.

Infections are expected events with the combination therapy with tafasitamab and lenalidomide due to its B-cell depleting properties. The most common infections are respiratory tract and urinary tract infections. High Grade infections and poor outcomes are also considered to be due to the underlying conditions of the patients.

Infusion related reactions events were observed, all of which resolved without serious sequelae. Infusion related reactions typically occurred during the first infusion and tended to be mild in severity. All patients in the clinical trials received standard prophylactic treatment which appears to be sufficient to manage these reactions.

The FDA's Assessment:

The FDA agrees that infusion related reactions, myelosuppression, and infections are important safety risks with tafasitamab. The FDA analysis of the data from the L-MIND trial will be included in the USPI.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Patient-reported outcomes were not included in the trials of tafasitamab with or without lenalidomide.

The FDA's Assessment:

The clinical reviewer is in agreement.

8.2.7. Safety Analyses by Demographic Subgroups

Subgroup evaluations of TEAEs were conducted for patients in MOR208C203 to identify potential safety issues in particular subpopulations defined by intrinsic/extrinsic factors: age, sex, race, geography, and manufacturing process. Findings are as follows:

Age

Among 80 patients treated with tafasitamab in combination with lenalidomide in MOR208C203, 56 (69%) patients were > 65 years of age, 45 (56%) patients were > 70 years of age.. TEAEs were reported for 100% of patients aged ≤ 65 years and for 98.2% of patients aged > 65 years, and for 100% of patients aged > 70 years.

Serious events occurred in 9/25 (36.0%) of patients ≤ 65 years old and 26/55 (47.3%) > 65 years old. The numerical difference in serious events was driven by patients > 65 years of age reporting more cardiac and nervous system events. Grade ≥3 TEAEs occurred in 18/25 (72.0%) patients ≤ 65 years and 43/55 (78.2%) patients >65 years of age.

Incidences of hematological events and infections were similar between the age groups: Patients aged ≤ 65 years and those aged > 65 years had similar incidences of hematological AEs (neutropenia [48.0% and 49.1%, respectively] and thrombocytopenia [32.0% and 30.9%, respectively]).

The overall incidence of infections was also similar between patients aged ≤ 65 years and those aged > 65 years (68.0% and 67.3%, respectively). Events occurring more frequently with a difference of $\geq 10\%$ in patients aged > 65 years compared with those ≤ 65 years included: diarrhea, abdominal pain, asthenia, peripheral edema, decreased appetite, back pain, hyperkalemia, hypokalemia, and hypomagnesemia.

Sex

Out of 80 patients receiving combination treatment in MOR208C203, 43 (53.8%) patients were male and 37 (46.2%) patients were female. Overall, the incidence of TEAEs was similar between male and female patients. Male patients and female patients had a similar rate of hematological events of neutropenia, anemia, thrombocytopenia and leukopenia.

For non-hematological events, the incidence of infusion-related reactions was similar between the sexes. Events occurring with a difference of $\geq 10\%$ in females compared with males included asthenia, nausea, and vomiting. Events occurring with a difference of $\geq 10\%$ in males compared with females included constipation, muscle spasms, back pain, and blood creatinine increased.

Grade ≥ 3 TEAEs occurred in 35/43 (81.4%) of male patients and in 26/37 (70.3%) of female patients. The incidences of Grade ≥ 3 hematologic events of neutropenia, and thrombocytopenia was similar between male and female patients. The overall incidence of infections was also similar.

Serious events occurred in 21/43 (48.8%) male patients and in 14/37 (37.8%) female patients. The incidences of serious neutropenia, thrombocytopenia and infections were similar between male and female patients.

Race

Of the 74 patients receiving combination therapy in MOR208C203 who self-reported race, 72 identified as White and two identified as Non-white. In the pooled monotherapy trials, a total of 131 patients were White and ten patients were Non-White. As the number of Non-White patients is very small, meaningful comparisons could not be made with respect to adverse event patterns between these two groups.

Geography

In the MOR208C203, six patients were from the U.S., and 75 patients were from Europe. Consequently, numbers of patients from the U.S. were too small to provide meaningful comparisons of TEAEs by geographic region.

Manufacturing Process

For the MOR208C203, an analysis of TEAEs by manufacturing process (b) (4) was performed. It was not possible to draw any meaningful conclusions, as there was a great degree of overlap in patients who received tafasitamab manufactured by both processes, leading to confounding. All patients received tafasitamab manufactured by (b) (4); 45 (55.6%) of these patients received tafasitamab from (b) (4) only while 36 (44.4%) switched from (b) (4) to (b) (4) during the course of the treatment. No patients received tafasitamab from (b) (4) only.

The median time to switch from (b) (4) was 11.925 months, indicating a longer co-exposure of the (b) (4) treated patients with lenalidomide as compared to (b) (4) patients. Therefore, the summary of TEAEs by (b) (4) is also confounded with toxicities induced by lenalidomide and is of limited value to compare with (b) (4).

The Applicant’s Position:

The subgroup results were similar to those from the primary analysis for safety, which evaluated factors including age, sex, and race. The incidences of neutropenia, thrombocytopenia and infections were similar between the younger and older patients. Male patients and female patients had a similar rate of hematological events and Grade ≥3 hematologic events.

The FDA’s Assessment:

The FDA subgroup analysis for age and sex is shown below. An analysis of TEAE based on age ≥65 and < 65 was done. For trial MOR208C203, 58 patients were ≥65 and 23 patients were <65. All patients had at least 1 TEAE. TEAE that occurred in more than 10% of patients based on age ≥65 and < 65 are shown in Table 48.

Table 48: TEAE Based on Age ≥ 65 and < 65

	65 and over (N=58)	under 65 (N=23)	Total (N=81)
Table Section 1			
Blood and lymphatic system disorders	38 (65.5)	15 (65.2)	53 (65.4)
Anemia	23 (39.7)	6 (26.1)	29 (35.8)
Febrile neutropenia	6 (10.3)	4 (17.4)	10 (12.3)
Leukopenia	8 (13.8)	4 (17.4)	12 (14.8)
Neutropenia	31 (53.4)	10 (43.5)	41 (50.6)
Thrombocytopenia	17 (29.3)	8 (34.8)	25 (30.9)
Gastrointestinal disorders	37 (63.8)	15 (65.2)	52 (64.2)
Abdominal pain	8 (13.8)	0	8 (9.9)
Constipation	10 (17.2)	4 (17.4)	14 (17.3)
Diarrhea	22 (37.9)	7 (30.4)	29 (35.8)
Nausea	8 (13.8)	4 (17.4)	12 (14.8)
Vomiting	9 (15.5)	3 (13.0)	12 (14.8)

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	65 and over (N=58)	under 65 (N=23)	Total (N=81)
General disorders and administration site conditions	37 (63.8)	10 (43.5)	47 (58.0)
Asthenia	16 (27.6)	3 (13.0)	19 (23.5)
Fatigue	7 (12.1)	7 (30.4)	14 (17.3)
oedemic peripheral	16 (27.6)	3 (13.0)	19 (23.5)
Pyrexia	15 (25.9)	4 (17.4)	19 (23.5)
Infections and infestations	42 (72.4)	17 (73.9)	59 (72.8)
Bronchitis	8 (13.8)	5 (21.7)	13 (16.0)
Lower respiratory tract infection	1 (1.7)	3 (13.0)	4 (4.9)
Nasopharyngitis	5 (8.6)	3 (13.0)	8 (9.9)
Pneumonia	7 (12.1)	1 (4.3)	8 (9.9)
Respiratory tract infection	4 (6.9)	4 (17.4)	8 (9.9)
Upper respiratory tract infection	6 (10.3)	2 (8.7)	8 (9.9)
Urinary tract infection	6 (10.3)	2 (8.7)	8 (9.9)
Investigations	28 (48.3)	11 (47.8)	39 (48.1)
C-reactive protein increased	5 (8.6)	3 (13.0)	8 (9.9)
Metabolism and nutrition disorders	35 (60.3)	7 (30.4)	42 (51.9)
Decreased appetite	13 (22.4)	5 (21.7)	18 (22.2)
Hypokalemia	13 (22.4)	2 (8.7)	15 (18.5)
Hypomagnesaemia	7 (12.1)	1 (4.3)	8 (9.9)
Musculoskeletal and connective tissue disorders	32 (55.2)	8 (34.8)	40 (49.4)
Arthralgia	6 (10.3)	1 (4.3)	7 (8.6)
Back pain	12 (20.7)	3 (13.0)	15 (18.5)
Muscle spasms	8 (13.8)	4 (17.4)	12 (14.8)
Pain in extremity	6 (10.3)	1 (4.3)	7 (8.6)
Nervous system disorders	26 (44.8)	13 (56.5)	39 (48.1)
Headache	1 (1.7)	6 (26.1)	7 (8.6)
Respiratory, thoracic and mediastinal disorders	26 (44.8)	14 (60.9)	40 (49.4)
Cough	12 (20.7)	9 (39.1)	21 (25.9)
Dyspnea	7 (12.1)	3 (13.0)	10 (12.3)
Skin and subcutaneous tissue disorders	26 (44.8)	13 (56.5)	39 (48.1)
Pruritus	6 (10.3)	2 (8.7)	8 (9.9)
Vascular disorders	18 (31.0)	5 (21.7)	23 (28.4)
Hypertension	6 (10.3)	1 (4.3)	7 (8.6)

FDA analysis
 Source: OCS Analysis Studio, Custom Table Tool.
 Columns - Dataset: Demographics; Filter: SAFFL = 'Y', STUDYID = 'MOR208C203'.
 Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >= 10%.

For SAEs, at total of 56.9% (33/58) of patients ≥ 65 years of age had at least 1 SAE compared to 39.1% (9/23) patients <65. SAEs that occurred in more than 10% of patients based on ≥ 65 and < 65 are displayed in Table 49. As shown in the table, patients ≥ 65 had had increase in SAEs in the System Organ Class on Infections and infestations, in particular the SAE of pneumonia.

Table 49: SAEs Based on Age 65 and Over and < 65

	65 and over (N=58)	under 65 (N=23)	Total (N=81)
Table Section 1			
Blood and lymphatic system disorders	4 (6.9)	2 (8.7)	6 (7.4)
Febrile neutropenia	3 (5.2)	2 (8.7)	5 (6.2)
Infections and infestations	16 (27.6)	5 (21.7)	21 (25.9)
Pneumonia	6 (10.3)	0	6 (7.4)

FDA analysis
 Source: OCS Analysis Studio, Custom Table Tool.
 Columns - Dataset: Demographics; Filter: STUDY D = 'MOR208C203', SAFFL = 'Y'.
 Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y'; Percent Threshold: >= 5%.

A similar analysis was done using an age of 75. A total of 31 patients were ≥75 and 50 patients were < 75. TEAE limited to 1 per patient based on the age groups of ≥ 75 and < 75 are displayed in Table 50.

Table 50: TEAE Based on Age ≥ 75 and < 75

	75 and over (N=31)	under 75 (N=50)	Total (N=81)
Table Section 1			
Blood and lymphatic system disorders	23 (74.2)	30 (60.0)	53 (65.4)
Anemia	14 (45.2)	15 (30.0)	29 (35.8)
Febrile neutropenia	6 (19.4)	4 (8.0)	10 (12.3)
Leukopenia	1 (3.2)	11 (22.0)	12 (14.8)
Lymphopenia	0	5 (10.0)	5 (6.2)
Neutropenia	16 (51.6)	25 (50.0)	41 (50.6)
Thrombocytopenia	10 (32.3)	15 (30.0)	25 (30.9)
Gastrointestinal disorders	17 (54.8)	35 (70.0)	52 (64.2)
Abdominal pain	3 (9.7)	5 (10.0)	8 (9.9)
Constipation	4 (12.9)	10 (20.0)	14 (17.3)
Diarrhea	11 (35.5)	18 (36.0)	29 (35.8)
Nausea	2 (6.5)	10 (20.0)	12 (14.8)
Vomiting	2 (6.5)	10 (20.0)	12 (14.8)
General disorders and administration site conditions	19 (61.3)	28 (56.0)	47 (58.0)
Asthenia	7 (22.6)	12 (24.0)	19 (23.5)
Fatigue	3 (9.7)	11 (22.0)	14 (17.3)
Mucosal inflammation	1 (3.2)	5 (10.0)	6 (7.4)
oedemic peripheral	11 (35.5)	8 (16.0)	19 (23.5)
Pyrexia	6 (19.4)	13 (26.0)	19 (23.5)
Infections and infestations	24 (77.4)	35 (70.0)	59 (72.8)
Bronchitis	5 (16.1)	8 (16.0)	13 (16.0)

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	75 and over (N=31)	under 75 (N=50)	Total (N=81)
Nasopharyngitis	2 (6.5)	6 (12.0)	8 (9.9)
Pneumonia	3 (9.7)	5 (10.0)	8 (9.9)
Respiratory tract infection	2 (6.5)	6 (12.0)	8 (9.9)
Upper respiratory tract infection	4 (12.9)	4 (8.0)	8 (9.9)
Urinary tract infection	3 (9.7)	5 (10.0)	8 (9.9)
Investigations	14 (45.2)	25 (50.0)	39 (48.1)
Blood creatinine increased	4 (12.9)	3 (6.0)	7 (8.6)
C-reactive protein increased	1 (3.2)	7 (14.0)	8 (9.9)
Metabolism and nutrition disorders	20 (64.5)	22 (44.0)	42 (51.9)
Decreased appetite	8 (25.8)	10 (20.0)	18 (22.2)
Hypocalcemia	4 (12.9)	1 (2.0)	5 (6.2)
Hypokalemia	6 (19.4)	9 (18.0)	15 (18.5)
Hypomagnesaemia	5 (16.1)	3 (6.0)	8 (9.9)
Musculoskeletal and connective tissue disorders	14 (45.2)	26 (52.0)	40 (49.4)
Arthralgia	1 (3.2)	6 (12.0)	7 (8.6)
Back pain	5 (16.1)	10 (20.0)	15 (18.5)
Muscle spasms	3 (9.7)	9 (18.0)	12 (14.8)
Pain in extremity	1 (3.2)	6 (12.0)	7 (8.6)
Nervous system disorders	14 (45.2)	25 (50.0)	39 (48.1)
Headache	0	7 (14.0)	7 (8.6)
Paranesthesia	4 (12.9)	2 (4.0)	6 (7.4)
Psychiatric disorders	2 (6.5)	11 (22.0)	13 (16.0)
Anxiety	0	6 (12.0)	6 (7.4)
Respiratory, thoracic and mediastinal disorders	11 (35.5)	29 (58.0)	40 (49.4)
Cough	6 (19.4)	15 (30.0)	21 (25.9)
Dyspnea	3 (9.7)	7 (14.0)	10 (12.3)
Skin and subcutaneous tissue disorders	12 (38.7)	27 (54.0)	39 (48.1)
Pruritus	1 (3.2)	7 (14.0)	8 (9.9)
Rash	2 (6.5)	5 (10.0)	7 (8.6)
Vascular disorders	9 (29.0)	14 (28.0)	23 (28.4)
Hypertension	2 (6.5)	5 (10.0)	7 (8.6)
Hypotension	4 (12.9)	2 (4.0)	6 (7.4)

FDA analysis
 Source: OCS Analysis Studio, Custom Table Tool.
 Columns - Dataset: Demographics; Filter: SAFFL = 'Y', STUDYID = 'MOR208C203'.
 Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >= 10%.

For patients ≥ 75 years of age, 61.3% (19/31) had at least 1 SAE compared to patients < 75 years of age where 46% (23/50) had at least 1 SAE. SAEs that occurred in 5% or more patients, limited to 1 per patient for both the SAE and System Organ Class are displayed in Table 51.

Table 51: SAEs Based on Age 75 and Over and < 75

	75 and over (N=31)	under 75 (N=50)	Total (N=81)
Table Section 1			
Blood and lymphatic system disorders	4 (12.9)	2 (4.0)	6 (7.4)
Febrile neutropenia	3 (9.7)	2 (4.0)	5 (6.2)
Cardiac disorders	3 (9.7)	3 (6.0)	6 (7.4)
Cardiac failure congestive	2 (6.5)	0	2 (2.5)
Infections and infestations	9 (29.0)	12 (24.0)	21 (25.9)
Pneumonia	2 (6.5)	4 (8.0)	6 (7.4)

FDA analysis
 Source: OCS Analysis Studio, Custom Table Tool.
 Columns - Dataset: Demographics; Filter: STUDY D = 'MOR208C203', SAFFL = 'Y'.
 Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y'; Percent Threshold: >= 5%.

An analysis of TEAE in trial MOR208C203 limited to 1 per patient based on sex is displayed in the Table 52. As shown in the table, the majority of TEAE occurred at similar rates in both males and females. As shown in the table, anxiety was increased > 10% in females.

Table 52: TEAE Based on Sex

	F (N=37)	M (N=44)	Total (N=81)
Table Section 1			
Blood and lymphatic system disorders	26 (70.3)	27 (61.4)	53 (65.4)
Anemia	12 (32.4)	17 (38.6)	29 (35.8)
Febrile neutropenia	6 (16.2)	4 (9.1)	10 (12.3)
Leukopenia	7 (18.9)	5 (11.4)	12 (14.8)
Neutropenia	21 (56.8)	20 (45.5)	41 (50.6)
Thrombocytopenia	12 (32.4)	13 (29.5)	25 (30.9)
Gastrointestinal disorders	28 (75.7)	24 (54.5)	52 (64.2)
Abdominal pain	4 (10.8)	4 (9.1)	8 (9.9)
Constipation	4 (10.8)	10 (22.7)	14 (17.3)
Diarrhea	15 (40.5)	14 (31.8)	29 (35.8)
Nausea	10 (27.0)	2 (4.5)	12 (14.8)
Vomiting	12 (32.4)	0	12 (14.8)
General disorders and administration site conditions	22 (59.5)	25 (56.8)	47 (58.0)
Asthenia	12 (32.4)	7 (15.9)	19 (23.5)
Fatigue	7 (18.9)	7 (15.9)	14 (17.3)
Mucosal inflammation	5 (13.5)	1 (2.3)	6 (7.4)
oedemic peripheral	8 (21.6)	11 (25.0)	19 (23.5)
Pyrexia	10 (27.0)	9 (20.5)	19 (23.5)
Infections and infestations	28 (75.7)	31 (70.5)	59 (72.8)

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	F (N=37)	M (N=44)	Total (N=81)
Bronchitis	6 (16.2)	7 (15.9)	13 (16.0)
Escherichia urinary tract infection	4 (10.8)	0	4 (4.9)
Nasopharyngitis	4 (10.8)	4 (9.1)	8 (9.9)
Pneumonia	5 (13.5)	3 (6.8)	8 (9.9)
Respiratory tract infection	3 (8.1)	5 (11.4)	8 (9.9)
Upper respiratory tract infection	4 (10.8)	4 (9.1)	8 (9.9)
Urinary tract infection	7 (18.9)	1 (2.3)	8 (9.9)
Investigations	20 (54.1)	19 (43.2)	39 (48.1)
Blood creatinine increased	0	7 (15.9)	7 (8.6)
C-reactive protein increased	4 (10.8)	4 (9.1)	8 (9.9)
Metabolism and nutrition disorders	18 (48.6)	24 (54.5)	42 (51.9)
Decreased appetite	9 (24.3)	9 (20.5)	18 (22.2)
Hypokalemia	7 (18.9)	8 (18.2)	15 (18.5)
Hypomagnesaemia	5 (13.5)	3 (6.8)	8 (9.9)
Musculoskeletal and connective tissue disorders	16 (43.2)	24 (54.5)	40 (49.4)
Arthralgia	4 (10.8)	3 (6.8)	7 (8.6)
Back pain	5 (13.5)	10 (22.7)	15 (18.5)
Muscle spasms	3 (8.1)	9 (20.5)	12 (14.8)
Nervous system disorders	19 (51.4)	20 (45.5)	39 (48.1)
Headache	4 (10.8)	3 (6.8)	7 (8.6)
Psychiatric disorders	10 (27.0)	3 (6.8)	13 (16.0)
Anxiety	5 (13.5)	1 (2.3)	6 (7.4)
Renal and urinary disorders	6 (16.2)	9 (20.5)	15 (18.5)
Dysuria	4 (10.8)	1 (2.3)	5 (6.2)
Respiratory, thoracic and mediastinal disorders	20 (54.1)	20 (45.5)	40 (49.4)
Cough	6 (16.2)	15 (34.1)	21 (25.9)
Dyspnea	6 (16.2)	4 (9.1)	10 (12.3)
Skin and subcutaneous tissue disorders	18 (48.6)	21 (47.7)	39 (48.1)
Pruritus	3 (8.1)	5 (11.4)	8 (9.9)
Rash	4 (10.8)	3 (6.8)	7 (8.6)

FDA analysis
 Source: OCS Analysis Studio Custom Table Tool.
 Columns - Dataset: Demographics Filter: STUDY D = 'MOR208C203' SAFFL = 'Y'.
 Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >= 10%.

An analysis of TEAE $\geq$ grade 3 is shown in the Table 53. This analysis was limited to 1 per patient and TEAE that occurred in >10% of patients are shown. As displayed in the table, all TEAE shown in the table are increased in females, however the numbers are small to make a definitive conclusion.

Table 53: TEAE Grade ≥ 3 Based on Sex

	F (N=37)	M (N=44)	Total (N=81)
Table Section 1			
Blood and lymphatic system disorders	24 (64.9)	22 (50.0)	46 (56.8)
Anemia	4 (10.8)	2 (4.5)	6 (7.4)
Febrile neutropenia	6 (16.2)	4 (9.1)	10 (12.3)
Leukopenia	6 (16.2)	3 (6.8)	9 (11.1)
Neutropenia	20 (54.1)	20 (45.5)	40 (49.4)
Thrombocytopenia	7 (18.9)	7 (15.9)	14 (17.3)
Infections and infestations	13 (35.1)	11 (25.0)	24 (29.6)
Pneumonia	4 (10.8)	2 (4.5)	6 (7.4)

FDA analysis
 Source: OCS Analysis Studio, Custom Table Tool.
 Columns - Dataset: Demographics Filter: STUDY D = 'MOR208C203' SAFFL = 'Y'
 Table Section 1 - Dataset: Adverse Events Filter: TRTEMFL = 'Y' AETOXGR = '3' or '4' or '5' Percent Threshold: >= 10%.

The clinical reviewer agrees with the Applicant regarding an analysis based on race and geography and the inability to make meaningful comparisons.

8.2.8. Specific Safety Studies/Clinical Trials

Specific Safety Studies of tafasitamab with or without lenalidomide have not been conducted.

The FDA's Assessment:

The clinical reviewer is in agreement.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In MOR208C203, the median time on tafasitamab in combination with lenalidomide was 190.0 days (range: 3 to 436 days). The cumulative dose administered ranged from 1,567.9 to 88,854.6 mg for tafasitamab and 75.0 to 6,300.0 mg for lenalidomide. The proportion of patients in MOR208C203 who received ≥12 cycles of tafasitamab monotherapy was 42.0%. One patient in MOR208C203 completed 1,170 days (167.1 weeks) of tafasitamab treatment and one patient in MOR208C201 completed 1,998 days (285.4 weeks) of tafasitamab treatment (Table 31). The following five preferred terms were reported in the Combination Therapy phase in MOR208C203, with no event reported in more than one patient: osteoma, prostatic adenoma, squamous cell carcinoma, benign neoplasm of thyroid gland, and lipoma. In the tafasitamab Monotherapy phase, the events of marginal zone lymphoma recurrent and basal cell carcinoma were reported.

The Applicant's Position:

Treatment-emergent AEs of neoplasia were observed with tafasitamab with or without lenalidomide. Carcinogenicity studies have not been conducted, and limited long-term data preclude definitive evaluation of carcinogenicity.

The FDA's Assessment:

The safety database was reviewed for possible secondary malignancies. For trial MOR208C203 a 58-year-old man developed basal cell carcinoma, a 71-year-old man developed prostatic specific antigen increase, a 81-year-old man developed squamous cell carcinoma, an 82-year-old man developed paraneoplastic syndrome and a 68-year-old woman was had a TEAE of myelodysplastic syndrome. On trial MOR208C201 a 69-yearold man had a TEAE of myelodysplastic syndrome and on trial XmAb5574-01 a 84-year-old man had a TEAE of pituitary tumor. Regarding trial MOR208C203 and secondary malignancies, as this is a single arm trial which included lenalidomide, attribution to tafasitamab cannot be determined.

Human Reproduction and Pregnancy

No pre-clinical reproductive and developmental toxicity studies have been conducted to date. The teratogenic potential of tafasitamab with or without lenalidomide has not been established. There are no data on use in pregnant women.

The Applicant's Position:

Use in pregnant women is not recommended.

The FDA's Assessment:

Tafasitamab is used in combination with lenalidomide and the use of lenalidomide is contraindicated in pregnant women. This will be stated in the U.S. Prescribing Information.

Pediatrics and Assessment of Effects on Growth

Diffuse large B-cell lymphoma is a cancer of B cells, a type of lymphocyte that is responsible for producing antibodies. It is the most common form of non-Hodgkin lymphoma among adults, with an annual incidence of 7–8 cases per 100,000 people per year in the U.S. This cancer occurs primarily in older individuals, with a median age of diagnosis of 65 years, although it can occur in young adults and, in rare cases, children. Conducting pediatric studies for tafasitamab with or without lenalidomide in the treatment of relapsed or refractory DLBCL is highly impracticable.

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The Applicant's Position:

No data are available for the use of tafasitamab with or without lenalidomide in combination; use in children is not recommended.

The FDA's Assessment:

The safety and effectiveness of tafasitamab in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is currently no information available regarding overdose with tafasitamab with or without lenalidomide. The highest dose that has been administered is 12.0 mg/kg, and no dose-limiting toxicity has been observed. Drug abuse and dependence with tafasitamab with or without lenalidomide have not been studied and is not likely. No studies have been conducted to specifically assess withdrawal or rebound effects of tafasitamab with or without lenalidomide.

The Applicant's Position:

In the event of overdose, patients should be observed, and appropriate supportive care should be given, if required. Given the nature of tafasitamab and its IV administration by a licensed health care professional, no abuse or dependence is anticipated. Given the disease being treated and the nature of tafasitamab, no withdrawal or rebound effects are anticipated.

The FDA's Assessment:

The clinical reviewer agrees with the statement above.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable, as tafasitamab is not currently registered or approved in the U.S. or any other part of the world.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The clinical reviewer agrees with above.

Expectations on Safety in the Postmarket Setting

Toxicities have been adequately represented in the studies included in this application.

The Applicant's Position:

Routine pharmacovigilance will be conducted in the post-marketing setting to monitor for adverse events.

The FDA's Assessment:

The clinical reviewer agrees with routine pharmacovigilance in the post-marketing setting.

8.2.11. Integrated Assessment of Safety

In decreasing order of frequency in trial MOR208C203, the most frequently reported ($\geq 20\%$ of patients) TEAEs by PT were neutropenia (39/81 [48.8%]), anemia (27/81 [33.8%]), thrombocytopenia (25/81 [31.3%]), diarrhea (23/81 [28.8%]), asthenia (19/81 [23.8%]), edema peripheral (17/81 [21.3%]), pyrexia (17/81 [21.3%]), decreased appetite (16/81 [20.0%]).

When patients completed combination therapy with tafasitamab and lenalidomide and continued with tafasitamab monotherapy the incidences of hematologic TEAEs decreased, and non-hematologic TEAEs tended to decrease, some by as much as 10% (neutropenia, anemia, thrombocytopenia, febrile neutropenia, decreased appetite, asthenia, hypokalemia, constipation, nausea, muscle spasms, and dyspnea).

As of the data cutoff date of June 30, 2019, there were 59 serious TEAEs experienced by 37/141 (26.2%) patients in the three tafasitamab monotherapy trials (MOR208C201, MOR208C202, and XmAb5574-01) and 76 serious TEAEs experienced by 42/81 (51.9%) patients in MOR208C203.

Of these serious TEAEs, a causal relationship to tafasitamab alone was suspected in two serious TEAEs (febrile neutropenia and tumor lysis syndrome) reported for 2/27 (7.4%) patients in XmAb5574-01; four serious TEAEs (genital herpes zoster, febrile neutropenia, myelodysplastic syndrome, and infusion-related reaction) reported for 4/92 (4.3%) patients in MOR208C201; six serious TEAEs (fungal infection, pneumonia viral, febrile neutropenia, cholangitis sclerosing, and tumor lysis syndrome [x2]) reported for 4/22 (18.2%) patients in MOR208C202; and four serious TEAEs (pneumonia, *Streptococcal* sepsis, pyrexia, and cytomegalovirus infection) reported for 4/81 (4.9%) patients in MOR208C203.

In the pooled monotherapy trials, 14/141 (9.9%) patients experienced neutropenia Grade ≥ 3 compared with 40/81 (49.4%) patients in MOR208C203. In the pooled monotherapy trials, 7/141 (5.0%) patients experienced febrile neutropenia Grade ≥ 3 compared with 10/81 (12.3%) patients in MOR208C203. One patient in MOR208C203 experienced Grade 3 neutropenic sepsis while receiving combination therapy.

Most Grade ≥ 3 neutropenia events (preferred terms of neutropenia, febrile neutropenia, neutropenic sepsis, neutrophil count decreased) were non-serious (140 events in 64 patients). Onset of Grade ≥ 3 neutropenia events occurred earlier in the pooled monotherapy trials compared with MOR208C203. The median duration of events was similar in pooled monotherapy trials and MOR208C203 (7 to 8 days).

Grade 3 or higher infections were reported for 43 patients in total with 19/141 (13.5%) patients with 27 events in the pooled monotherapy trials and 24/81 (29.6%) patients with 36 events in MOR208C203 overall. The majority of these events of infections were pneumonia events (20/63) in 17 of 222 (7.7%) patients including the preferred terms of pneumonia, pneumonia viral, pneumonia pneumococcal, pneumonia klebsiella, pneumonia hemophilis. The IgG profile was investigated; patients from trials MOR208C203 and MOR208C201 were grouped in two categories: IgG levels < 400 mg/dL and ≥ 400 mg/dL. Patients with IgG levels < 400 mg/dL did

have a higher incidence of infections of interest (in particular pneumonias) than patients with IgG levels $\geq$ 400 mg/dL.

The incidences of neutropenia, thrombocytopenia and infections were similar between the younger and older patients. Male patients and female patients had a similar rate of hematological events and Grade $\geq$ 3 hematologic events. Regardless of age and race, hematologic events were manageable and rarely led to dose discontinuation.

The Applicant's Position:

Combination therapy in MOR208C203 was well tolerated and resulted in long-term therapy adherence for the 30/80 (37.5%) patients who completed 12 cycles of combination therapy. Of these, 23/80 (28.8%) subsequently went on to complete > 12 cycles of tafasitamab monotherapy.

The safety analyses indicate that the safety profile of the combination is mainly driven by lenalidomide side effects. Adding tafasitamab to lenalidomide therapy does not substantially change the incidence of AEs nor the type of AEs reported. Infections are an expected AE with monoclonal antibody therapy due to its B-cell depleting properties. Grade 1 or 2 infections were experienced by 35/81 (43.2%) patients in MOR208C203. The most common infections were bronchitis (16.0%), nasopharyngitis (9.9%), pneumonia (9.9%), respiratory tract infection (9.9%), upper respiratory tract infection (9.9%), and urinary tract infection (9.9%).

Infusion-related reactions related to tafasitamab occurred in 5/81 (6.2%) patients; all were Grade 1, occurred during the first infusion, and did not require discontinuation of treatment. Prior to infusion, all patients received premedication with H1 blockers, antipyretics, and/or glucocorticosteroids. Infusion-related reactions were easily managed with appropriate standard supportive therapy.

In MOR208C203 a total of 20 (24.7%) patients discontinued study medication due to a TEAE. Of these, 8 patients discontinued lenalidomide alone, 10 discontinued both tafasitamab and lenalidomide, and 2 patients discontinued only tafasitamab.

The combination of tafasitamab and lenalidomide can cause neutropenia, including febrile neutropenia. Complete blood counts should be monitored prior to initiation of tafasitamab and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, tafasitamab may require dose interruption or treatment discontinuation.

The incidence and severity of hematologic TEAEs observed in MOR208C203 Combination Therapy are similar to those published for lenalidomide. The incidence of hematologic and non-hematologic TEAEs decreased when patients after completion of the combination therapy phase continued with tafasitamab monotherapy. Tafasitamab monotherapy showed lower rates of hematologic TEAEs compared with published lenalidomide monotherapy trials or with the Combination Therapy.

Overall, tafasitamab was well tolerated at the proposed dose of 12.0 mg/kg according to the schedule noted above in the target population of patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for, or refuse ASCT. Adverse events were generally manageable by dose modification and standard clinical practice.

The FDA's Assessment:

The safety of the combination of tafasitamab and lenalidomide was evaluated in trial MOR208C203, this was supported by three monotherapy trials.

For the pivotal trial, MOR208C203, a total of 46 patients (56.8%) were exposed to tafasitamab for > 6 months, a total of 34 patients (42.0%) were exposed for greater than 1 year and a total of 19 patients (23.5%) were exposed for > 2 years.

The exposure to tafasitamab is longer for patients in trial MOR208C203 compared to the pooled monotherapy trials. For trial MOR208C203, 35 patients received ≥ 12 cycles of treatment compared to the pooled monotherapy safety population where 11 patients received ≥ 12 cycles of tafasitamab. For the pooled monotherapy population, 84.4% of the patient population (119 patients) received between 1-5 cycles.

For trial, MOR208C203, the median age was 72 years with a range of 41-86 years and for the pooled monotherapy trials the median age was 63 with range of 16-90 years. Most patients in both the pivotal trial MOR208C203 and the pooled monotherapy population were white. In trial MOR208C203, 99.9% enrolled were white, 2.5% Asian, 0% Black/African American, 1.2% other and 7.4% missing. In the pooled monotherapy patient population, 92.9% were white, 0.7% Asian, 3.5% Black/African American, and 2.8% other.

The majority of the patient population in MOR208C203 had a higher ECOG status compared to the pooled monotherapy trials. A total of 55.6% of patients in trial MOR208C203 had an ECOG status of 1, while 55.3% in the pooled monotherapy population had an ECOG status of 0. For trial MOR208C203, 8 patients (9.9%) died within 30 days of the last dose. The majority of deaths within 30 days of last dose were due to disease progression, 5 patients. A total of 4 patients died as a result of TEAEs, 1 of these deaths occurred at day 68 although the TEAE of PML started prior. The TEAEs which resulted in death included CVA, sudden death, respiratory failure likely as a result of infection and PML.

There were more patients who experienced at least 1 SAE on trial MOR208C203, 42/81 (51.9%) patients compared to the pooled monotherapy trials 37/141 (26.2%) patients. For trial MOR208C203, the majority of SAEs were in the System Organ Class of Infections and infestations with pneumonia being the most common SAE in this System Organ Class. The only SAE that occurred in >5% of patients on trial MOR208C203 was febrile neutropenia at 6.2%. A total of 20 patients (24.7%) discontinued either both drugs or either drug due to a TEAE. Neutropenia was the most frequent TEAE that lead to discontinuation in 3 patients. At the SOC

level, 5 patients (6.2%) had a TEAE in infections and infestations that led to withdrawal and 4 patients (4.9%) in the SOC of blood and lymphatic system disorders.

TEAE that occurred in more than 20% of patients on the L-MIND trial include neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, peripheral edema, pyrexia, respiratory tract infection, and decreased appetite. The more common grade ≥ 3 TEAE which occurred in more than 10% of patients on the L-MIND trial are neutropenia, thrombocytopenia and febrile neutropenia.

SUMMARY AND CONCLUSIONS

8.1. Statistical Issues

The FDA's Assessment:

The activity of tafasitamab in combination with lenalidomide (tafa+LEN) was investigated in Study MOR208C203 (L-MIND), a single arm study. Per FDA's analysis, the estimated ORR was 55% (95% CI: 43%, 67%) in patients with centrally-confirmed DLBCL. Because this is a combination therapy, the contribution of effect question that is being raised is whether the observed ORR 55% is attributable to lenalidomide (in part or in whole). Per the MOR208C201 study, an estimated investigator-assessed ORR for single agent tafasitamab was approximately 26% (95% CI: 13%, 43%) in DLBCL patients. The Applicant also cited single agent lenalidomide (LEN) data from the literature showing ORR estimates that range from 21% to 29%. As the Applicant noted, the comparison of trial results with external results to learn about contribution of effect is not straightforward for a number of reasons, including differences in the target population.

The primary objective of Study MOR208C206 (RE-MIND) was to learn about LEN single agent activity in DLBCL patients in non-clinical trial settings. The RE-MIND study induced a LEN external cohort that resembled patients in the tafa+LEN cohort from the L-MIND trial and compared their estimated ORRs, with a view towards eliciting supportive information to clarify the contribution of effect question. At face value, the results of the RE-MIND study suggested that tafa+LEN is a substantial improvement over LEN as the respective ORRs per FDA's analyses were 59% (95% CI: 46%, 71%) and 32% (95% CI: 21%, 43%). Had this been a randomized study, these results would resolve the contribution of effect question. In an observational study context however, the interpretation of these RE-MIND results are not straightforward as they are likely to be contaminated by external factors, some of which include

- Outcome misclassification

- Covariate misclassification
- Residual confounding
- Length-biased sampling

This raises the question of whether the difference in the size of the estimated ORRs between the tafa+LEN and LEN cohorts are credible or whether the difference can be ascribable to these contaminants, in part or in whole. Unfortunately, these issues cannot be resolved in an unambiguous way. FDA performed additional analyses to address some of these issues.

Outcome Misclassification

Outcome misclassification occurs when the reported response data are not correct. For example, a patient may be incorrectly reported as a non-responder when in fact the patient was a responder (false negative). Similarly, a patient may be incorrectly reported as a responder when in fact the patient was a non-responder (false positive). The L-MIND trial captured both IRC- and INV- assessed disease status, which enabled an assessment of ORR based on IRC. In the RE-MIND study, the response in the LEN cohort was physician-reported.

As part of the RE-MIND study, some LEN patients were selected for a validation study where their disease status were retrospectively assessed by a review committee. Although the validation study sampled approximately 70 patients, the study was small in the sense that only 22 physician-reported responders were sampled; thus, the utility of the results of the validation study is an open question. It is likely that the outcome misclassification process is differential between the tafa+LEN and LEN cohorts in the RE-MIND study.

As outcome misclassification is likely to be differential between patients in the LEN and tafa+LEN cohorts, FDA conducted additional analyses to assess the variability of the RE-MIND results. The setting for the analyses assumes that IRC-assessed response status is the desired endpoint while physician-reported response status is subject to potential misclassification. This implies that the response status of patients in the LEN cohort who were not in the validation study were considered subject to misclassification. Assuming a true positive of no less than 75%, the most favorable scenario to the LEN cohort is a true negative of 100% which leads to an estimated adjusted ORR of 39% (95% CI: 26%, 51%) for the LEN cohort. This resulted in an ORR difference between tafa+LEN and LEN of 21% (95% CI: 3%, 38%). While the true positive of lower than 75% can lead to higher adjusted LEN ORRs, the plausibility of such scenarios is less plausible as it would imply a false negative of more than 25% in the assessment of patients' disease status in clinical practice. It is not clear a false negative of 25% or more in clinical practice is plausible.

Assuming other aspects of the data are valid, FDA's sensitivity analyses suggest that the observed results were robust to outcome misclassification.

Residual Confounding

Residual confounding stems from the fact that regardless of attempts to analytically address confounding when comparing two cohorts in an observational study, the efforts may not be sufficient. Reasons for the insufficiency include the following.

Prognostic for ORR. The nine factors used in the RE-MIND study are potentially prognostic for OS/PFS. However, there appears to be little data to suggest that they are prognostic for ORR. To the extent that this is true, achieving balance on these nine covariates would not address the issue of confounding. At this time, it is unclear that the nine covariates are prognostic for ORR.

Remaining Imbalance. Assuming that the factors being controlled for are prognostic for ORR, it is clear that some of the attributes were not balanced. For example, the marginal distribution of Ann Arbor staging, ECOG, and number of prior lines were not balanced and were more favorable to the tafa+LEN cohort. To this point, FDA performed an additional propensity score analysis (results not shown) on the MAS25 analysis set to induce greater balance on all 9 covariates. The results of this analysis were similar to the Applicant's results and thus did not change the general conclusion. However, the similarity of results between FDA and the Applicant's analyses should be interpreted carefully as it could simply mean that the covariates were weakly or not prognostic for ORR.

We also note that similarity in the marginal distributions is not sufficient to justify claims of achieving balance as it must also be supported by similarity in the joint distributions. Due to the small size of the RE-MIND study, it is not feasible to adequately assess similarity of the joint distributions of baseline characteristics. However, we noted in Section 8.1.3 that the joint distributions of refractory to last line, number of prior lines, and primary refractory disease do not appear to be balanced in the MAS25 matched analysis set.

Unmeasured Confounding. Even if it was feasible to perfectly balance the pre-specified factors, the fact still remains that there are yet to be determined/unmeasured factors (e.g., cytogenetics) that are prognostic for ORR in the studied population and may be less favorable to the LEN cohort. Addressing unmeasured confounding is analytically difficult despite methods that suggest otherwise (e.g., Schneeweiss 2006; Lin et al 1998; VanderWeele et al 2017). Furthermore, the results of such analyses are often over-interpreted. This difficulty stems from the fact that the underlying assumptions cannot be rigorously justified and from the fact that it is difficult to conclude whether the results of such analyses are plausible. Consider FDA Table 54 below. This table was obtained through an FDA simulation study that examined the sensitivity of the observed results to various distributional scenarios of an unmeasured binary confounder, denoted as U, across the tafa+LEN and LEN cohorts and across responders (ORR=1) and non-responders (ORR=0). FDA's analyses examined over 2700 scenarios. The results in FDA Table 54 were obtained after selecting only scenarios where the 95% confidence interval of the difference in ORR rates contains 0, and after eliminating all scenarios that were viewed as not

likely to occur.

- Column 1 is the difference in ORR rates between tafa+LEN and LEN after adjusting for an unmeasured confounder U.
- Column 2 (Γ_0) is the relative odds of responding between patients who are U-positive and U-negative in the LEN cohort.
- Column 3 (Γ_1) is the relative odds of responding between patients who are U-positive and U-negative in the tafa+LEN cohort.
- Column 4 is the prevalence of patients who are U-positive in the LEN cohort.
- Column 5 is the prevalence of patients who are U-positive in the tafa+LEN cohort.

From this analysis, there are two things to note. First, potentially there exists an unmeasured binary confounder that may lead to a lack of statistical difference. The simulation study also suggested that difference in the prevalence would have to be at least 27% for the simulation results to be credible. While this is statistically possible, it is not clear that it is plausible given that the study employed inclusion/exclusion criteria that were similar to L-MIND and adjusted for 9 potentially prognostic covariates. Second, it is unclear how Γ_0 and Γ_1 in columns 2 and 3 could be used to make decisions. Row 1 for example says that a binary unmeasured confounder U will induce a lack of statistical difference in ORR if we believe the following:

- The prevalence of U-positives in the LEN cohort is 36% while it is 70% in the tafa+LEN cohort.
- In the LEN cohort, the odds of responding among U-positives is 2.85 times that of U-negatives.
- In the tafa+LEN cohort, the odds of responding among U-positives is 1.89 times that of U-negatives.

Again, while these are possible, there is little information to suggest that these values are credible.

Table 54: A Sensitivity Analysis of Unmeasured Confounding Looking at Scenarios of an Unmeasured U that Results in Lack of Statistical Difference in ORR

Difference in ORR Rate	Γ_0	Γ_1	P(U=1 LEN)	P(U=1 tafa+LEN)
16% (95% CI: -0.4% , 32.8%)	2.85	1.89	0.36	0.70
16% (95% CI: -1.1% , 34.0%)	1.56	3	0.37	0.73
15% (95% CI: -1.4% , 31.6%)	2.33	1.86	0.39	0.71
14% (95% CI: -3.2% , 30.7%)	2.33	2.67	0.39	0.76
16% (95% CI: -0.4% , 31.7%)	2.85	1	0.39	0.76
14% (95% CI: -3.2% , 31.4%)	1.22	1.89	0.41	0.76

17% (95% CI: -0.7% , 33.7%)	2.85	1.89	0.41	0.79
16% (95% CI: -0.6% , 32.3%)	1.83	3	0.42	0.73
15% (95% CI: -2.2% , 32.1%)	2.85	2.67	0.42	0.74
15% (95% CI: -1.3% , 31.4%)	2.85	2.33	0.42	0.76
16% (95% CI: -0.7% , 32.3%)	2.33	2.67	0.5	0.77
13% (95% CI: -3.4% , 29.5%)	1.83	2.15	0.5	0.79

SOURCE: FDA-analysis

8.1. Conclusions and Recommendations

The FDA's Assessment:

Study MOR208C203 (L-MIND) was the primary study upon which the activity of tafa+LEN was assessed in DLBCL patients who had relapsed after or were refractory to at least 1, but no more than 3 previous systemic regimens, and who were not candidates for high dose chemotherapy and subsequent ASCT (or relapsed after ASCT). The results from the L-MIND study (per FDA's analyses) suggested that tafasitamab in combination with lenalidomide resulted in an estimated ORR of 55% (95% CI: 43%, 67%), CR of 37% (95% CI: 25%, 49%), and PR of 18% (95% CI: 10%, 29%) in the 71 patients with central pathology confirmed diagnosis of relapsed/refractory DLBCL patients. Estimated DOR was 21.7 months. Based on the ORR and DOR and the lack of approved therapies for this patient population, the efficacy results from the L-MIND trial are considered to provide a meaningful treatment benefit for the intended patient population.

Additionally, the activity of single agent tafasitamab was assessed in Study MOR208C201, which showed an estimated ORR of 26% (95% CI: 13%, 43%). Although study MOR208C206 (RE-MIND), an observational study, was designed to learn about the contribution of effect question, due to the limitations of the study however, it can only be concluded that the results from the study regarding LEN activity were consistent with what was reported in the literature.

Based on the favorable risk-benefit profile of tafasitamab in combination with lenalidomide, the clinical and statistical reviewers recommend approval of tafasitamab in combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

Kunthel By, PhD
Primary Statistical Reviewer

Yu-te Wu, PhD
Statistical Team Leader

Alexandria Schwarsin, MD
Primary Clinical Reviewer

Bindu Kanapuru, MD
Clinical Team Leader

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Version date: July 24, 2019 (ALL NDA/ BLA reviews)

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

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No Oncology Drug Advisory Committee (ODAC) Meeting or other external consultations are required for the application.

10. Pediatrics

The Applicant's Position:

Tafasitamab received Orphan Drug Designation on December 1, 2014. Drugs with orphan drug designation have a statutory exemption under Section 505B(k)(1) of the FD&C Act from the requirement to conduct pediatric studies under the Pediatric Research Equity Act; therefore, pediatric studies are not required for tafasitamab.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

11. Labeling Recommendations

The table below summarizes changes to the proposed prescribing information made by FDA. See the final approved prescribing information for MONJUVI (tafasitamab) accompanying the approval letter for more information.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
1 Indications and Usage	Indication includes initial combination with lenalidomide (b) (4). (b) (4).	Added two statements to acknowledge the drug was approved based upon accelerated approval and that the continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial(s) as stated in the "Labeling for Human Prescription Drug and Biological Products Approved Under Accelerated Approval Regulatory Pathway" guidance for industry.
2 Dosage and Administration	2.2 Included premedication to reduce risk of IRRs. 2.3 Dose modification and management table provided for IRR and myelosuppression.	Created a "Recommended Premedications" subsection to describe premedications based on recommendations found in "Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format" guidance for industry. Limited dosing information for lenalidomide and referenced the lenalidomide USPI. Move some information from dosage moderations for adverse reactions table to Warnings and Precautions [21 CFR 201.57(6)(i)].
5 Warnings and Precautions	Included infusion-related reactions, myelosuppression, and infections.	Revised each proposed W&P to provide the percentage of patients who experienced the reaction in the L-MIND population of 81 patients overall (including combination and monotherapy phases) and to include a description of the most frequent symptoms, time to onset and the percentage of patients who required a dosage modifications where applicable. (b) (4)

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling (b) (4)
		Added a W&P for embryo-fetal toxicity, because MONJUVI causes immune cell depletion. Added reference to the labeling for lenalidomide, because lenalidomide is contraindicated in pregnant women.
6 Adverse Reactions	Text provided above ADR table. Common adverse reactions table included.	Reorganized subsection 6.1 Clinical Trials Experience for consistency with current OOD labeling practices. Added exposure information consistent with recommendations regarding description of data sources found in "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format" guidance for industry. Added a description of adverse reactions that required a dosage interruption. Revised the table to include only adverse reactions with all grades and grades 3 or 4 reactions listed for the overall study population (both combination and monotherapy phases). Moved relevant description of infusion-related reactions, myelosuppression and infections to W&P. Included description of chemistry laboratory abnormalities separately only as there was incomplete capture of hematology labs in the laboratory dataset.
8 Use in Specific Populations	Terminology and formatting consistent with current PLLR guidance and best labeling practices.	Added a description of the clinical considerations of MONJUVI in pregnant women (§ 201.57(c)(9)(i)(C)) to provide information to further inform prescribing and risk-benefit counseling, because MONJUVI may cause depletion of fetal CD19 immune cells following in utero exposure. Added reference to lenalidomide labeling

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		in subsections 8.2 and 8.3 because of the added risks associated with lenalidomide.
11 Description	...	Revised the established pharmacologic class to conform to the format of numerous other antibodies. Added the molecular weight, dosage form and the resulting concentration after reconstitution and the pH (21 CFR 201.57(c)(12)). Placed the inactive ingredients in alphabetical order per USP General Chapters <1091>: Labeling of inactive ingredients.
12 Clinical Pharmacology	Details provided.	(b) (4) (b) (4) As per ICH E14 Q&A (R3) 6.3, thorough QT studies are not recommended for monoclonal antibodies. Added a measure of dispersion (i.e., SD or min to max) for all PK parameters as recommend in the guidance Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.
14 Clinical Studies	Included ORR and DoR from pivotal study. ORR from RWD for lenalidomide monotherapy provided.	Revised efficacy results to only describe study population and outcomes for patients with confirmed diagnosis of DLBCL. Only included a description of the overall response rate (n, % and 95% CI) and duration of response (median, range), as well as the CR and PR rate. (b) (4)

The Applicant's Position:

The USPI for tafasitamab meets the regulatory requirements for providing a summary of the essential scientific information needed for its safe and effective use and is consistent with current FDA guidance and best labeling practices.

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

The FDA's Assessment:

The FDA's assessment is included in the table above.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

This section is not applicable.

13. Postmarketing Requirements and Commitment

The FDA's Assessment:

The final PMR and PMC language remains pending at this time. A PMR to confirm the benefit of tafasitamab in a randomized controlled trial will be issued. A PMC will be issued to further characterize the safety and efficacy of tafasitamab in combination with lenalidomide in the underrepresented racial and ethnic minority patients with DLBCL.

14. Division Director (DHOT) (NME ONLY)

*Haleh Saber, PhD
Deputy Division Director
OOD/DHOT*

15. Division Director (OCP)

*Brian Booth, PhD
Division Director
OCP/DCPI*

16. Division Director (OB)

Thomas Gwise, PhD
Division Director
OB/DBIX

17. Division Director (Clinical)

Nicole J. Gormley, MD
Division Director
OOD/DHM2

18. 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.

*Marc Theoret, MD
Deputy Director (Acting) and Associate Director for Immunotherapeutics
OOD*

19. Appendices

19.1. References

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The FDA's References:

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19.2 Financial Disclosure

The Applicant's Position:

The Applicant disclosed all financial interests/arrangements with clinical investigators as per 21 CFR Part 54. None of the investigators or sub-investigators involved in the clinical trials had financial interests to disclose or arrangements that required disclosure. Limited instances of missing financial disclosure information occurred for 6 sub-investigators across the studies. Of these six, three did not see any patients while delegated on the study, one was delegated for one month only, and information was missing for the remaining two.

The lack of disclosures across investigators in the clinical trials does not raise concerns about the overall integrity of study data. The three studies were conducted over multiple sites and in multiple countries, thus limiting the potential for a single investigator or sub-investigator to make a significant contribution to the data. Further, all efficacy assessments were conducted by an IRC, or both the Investigator and an IRC.

The FDA's Assessment:
 [FDA will complete this section.]

Covered Clinical Study (Name and/or Number):* MOR208C203

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>296</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: n/a	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: n/a	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>3</u>		
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.

19.3 Nonclinical Pharmacology/Toxicology

Data:

None

The Applicant's Position:

None

The FDA's Assessment:

N/A

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Summary of Bioanalytical Method Validation and Performance

Tafasitamab concentrations in human serum were quantified using validated ligand binding assays. The pivotal Study **MOR208C203 (L-MIND)** used the 2nd generation PK assay, an electrochemiluminescence (ECL) assay based on MSD technology. Briefly, tafasitamab was captured on the surface of a MSD plate coated with the Fab-fragment AbD18759.1 (human monoclonal idiotypic anti-tafasitamab antibody), and the bound analyte was detected using the antibody 6B11-E5-ECL, an ECL-labeled mouse monoclonal idiotypic anti-tafasitamab antibody. The lower limit of quantification was 50 ng/mL in human serum. Other than Phase 1 Study **XmAb5574-01**, this PK assay was used in all other clinical studies (**L-MIND**, **COSMOS**, **MOR208C201**, **MOR208C202**). The PK assay has been validated for intended use. Summary method performance of the bioanalytical method to measure tafasitamab in human serum, with method performance in pivotal Study **L-MIND**, is shown in **Table 55**.

Table 55: Summary Method Performance of the Bioanalytical Method to Measure Tafasitamab Concentrations in Human Serum

Bioanalytical method validation report name, amendments, and hyperlinks	Method validation report MOR208L016 , entitled: “Immunoassay validation of an ECL method for the determination of MOR00208 ((b)(4) production process) in human serum from DLBCL patients, CLL patients and healthy volunteers.” Method validation report MOR208L016 Amendment 1 , entitled: “STABILITY STUDY REPORT: Stability evaluation of MOR00208 ((b)(4) production process) in human serum from DLBCL patients, CLL patients and healthy volunteers”
Method description	Ligand binding assay based on MSD technology, employing capture with Fab-fragment AbD18759.1 (human monoclonal idiotypic anti-tafasitamab antibody) and detection using the antibody 6B11-E5-ECL (an ECL-labelled mouse monoclonal idiotypic anti-tafasitamab antibody). Electrochemiluminescence (ECL) readout on MSD instrument.
Materials used for calibration curve & concentration	Tafasitamab from ((b)(4) production process (Development Standard 02 (MP1-01, DS02))
Validated assay range	50 ng/mL to 10 000 ng/mL in 100% serum
Material used for QCs & concentration	Tafasitamab from ((b)(4) production process (Development Standard 02 (MP1-01, DS02))
Minimum required dilutions (MRDs)	1:100
Source & lot of reagents (LBA)	- Fab-fragment AbD18759.1 (human monoclonal idiotypic anti-tafasitamab antibody): MorphoSys AG, Lot.Nr.: 140602_110TWO3 6B11-E5-ECL (an ECL-labelled mouse monoclonal idiotypic anti-tafasitamab antibody): MorphoSys AG, Lot.Nr.: 150902_129RSII9
Regression model & weighting	5-parameter logistic fit with $1/y^2$ weighting

Validation parameters	Method validation summary		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision [^]	Number of standard calibrators from LLOQ to ULOQ	8	Table 10 of report MOR208L016
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-0.67% to 2.11%	Table 10 of report MOR208L016
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.71%	Table 10 of report MOR208L016
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 5 QCs.</u> QCs: 50.00 / 100.0 / 500.0 / 6000 /10 000 ng/mL in neat serum	-0.39% to 15.73%	Table 13 of report MOR208L016
	<u>Inter-batch %CV</u> QCs: 50.00 / 100.0 / 500.0 / 6000 /10 000 ng/mL in neat serum	≤ 18.45%	Table 13 of report MOR208L016
	<u>Total Error (TE)</u> QCs: 50.00 / 100.0 / 500.0 / 6000 /10 000 ng/mL in neat serum	≤ 28.11%	Table 13 of report MOR208L016
Selectivity & matrix effect	<u>Healthy volunteer serum:</u> 10/10 individual lots were within ±20% bias at LQC and HQC, and tested BLQ when not spiked with drug. Range of observed bias: -9.62% to 7.39%. <u>CLL patient serum:</u> 10/10 individual lots were within ±20% bias at LQC and HQC, and tested BLQ when not spiked with drug. Range of observed bias: -16.23% to 6.12%. <u>DLBCL patient serum:</u> 9/10 individual lots were within ±20% bias at LQC and HQC, and tested BLQ when not spiked with drug. Range of observed bias: -12.93% to 515.04%.		Table 23 of report MOR208L016 (healthy volunteers); Table 24 of report MOR208L016 (CLL patients); Table 25 of report MOR208L016 (DLBCL patients)

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Interference & specificity	Lenalidomide (up to 1 µg/mL), Venetoclax (up to 4 µg/mL), Bendamustine (up to 10 µg/mL), Idelalisib (up to 4 µg/mL) did not interfere with detection of tafasitamab at LLoQ and ULoQ levels (1 sample each, range of observed bias: -16.24% to 7.15%); and blank serum spiked with concomitant drug quantified <LLoQ.	Tables 26, 27, 28, 29 of report MOR208L016
Hemolysis effect	1 hemolyzed sample tested within selectivity assessment at LQC and HQC; range of observed bias: -5.42% to -1.41%; blank hemolyzed sample quantified <LLoQ	Table 23 of report MOR208L016
Lipemic effect	Not applicable	
Dilution linearity & hook effect	Absence of prozone effects confirmed (Samples at 50,000 ng/mL (highest concentration tested) in neat serum quantify >ULOQ). Dilution linearity confirmed for 1:10 and 1:100 beyond MRD (i.e. 1:1000 and 1:10 000 total dilution). Range of observed bias: -20.92 % to -11.44%.	Tables 30 and 31 of report MOR208L016
Bench-top/process stability	Stable 4 hours at RT after a freezing period at -20°C or -80°C in pooled human serum from healthy volunteers, or from CLL patients, or from DLBCL patients (Specification: At least 2 of 3 samples at each QC level (LQC and HQC) within ± 20.00% deviation from nominal and %CV <20%).	Table 38 of report MOR208L016 (healthy volunteers); Table 39 of report MOR208L016 (CLL patients); Table 40 of report MOR208L016 (DLBCL patients)
Freeze-Thaw stability	Stable after 5 freeze (at -20°C or -80°C) and thaw (RT) cycles in pooled human serum from healthy volunteers, or from CLL patients, or from DLBCL patients (Specification: See Bench-top/process stability).	Table 41 of report MOR208L016 (healthy volunteers); Table 42 of report MOR208L016 (CLL patients); Table 43 of report MOR208L016 (DLBCL patients)
Long-term storage	Stable at least 719 days (pooled serum from CLL patients) / 725 days (pooled serum from DLBCL patients) / 728 days (pooled serum from healthy volunteers) at -20°C and -80°C.	Tables 44-49 of report MOR208L016; Tables 21-29 of MOR208L016 Amendment 1
Parallelism	Confirmed within PK sample assessment in clinical study L-MIND. 3 study samples diluted to three concentrations within the quantifiable range. %CV across dilutions ≤3.47%.	Table 14 of PK bioanalytical report L-MIND
Carry over	Not applicable	

Method performance in study L-MIND (MOR208C203): INTERIM BIOANALYTICAL REPORT: Quantification of MOR00208 in Human Serum Samples of Clinical Study MOR208C203 by using a Ligand Binding Assay with Electrochemiluminescence (ECL) Detection		
Assay passing rate	82/100 runs (82.0%) passed	Table 7 of PK bioanalytical report L-MIND
Standard curve performance	- Cumulative bias range: not calculated - Cumulative precision (%CV): not calculated	Table 8 of PK bioanalytical report L-MIND
QC performance[^]	- Cumulative bias range: -5.26% to 2.24% - Cumulative precision (%CV): ≤52.82% - Total Error: not calculated	Table 10 of PK bioanalytical report L-MIND
Method reproducibility	Incurring sample reanalysis (ISR) was performed in 150/1420 (10.6 %) of study samples and 120/150 (80.0%) of ISR samples met the pre-specified criteria.	Table 12 of PK bioanalytical report L-MIND
Study sample analysis/stability	<u>Length of storage for Standards/QCs:</u> Standards were prepared freshly for each run. QC samples were stored at -80°C as study samples and used within the validated long-term stability period. <u>Length of storage for study samples:</u> All study samples were analyzed within the validated long term stability, i.e. 725 days at -20°C and -80°C in DLBCL serum.	

[^] Statistics excluded rejected runs. In addition, a “QCVH (QC Very High) sample” was analyzed in case study samples were diluted beyond MRD in a run. The QCVH sample dilution was performed in an identical manner as the study samples to ensure correct sample handling.

Source: Table 10 of Applicant’s Summary of Biopharmaceutical Studies and Associated Analytical Methods

19.4.2 Pharmacometrics Review

A population pharmacokinetics (PPK) model was developed by the Applicant to characterize the PK of tafasitamab in patients with either relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), R/R Non-Hodgkin’s lymphoma (NHL) (including diffuse large B-cell lymphoma (DLBCL)), or R/R acute lymphoblastic leukemia (ALL). Patients intrinsic and extrinsic factors which influence the PK and PK variability of tafasitamab were identified. Individual tafasitamab exposure metrics were generated for subsequent exposure-response (E-R) analyses for efficacy and safety. In this review, the FDA Pharmacometrics Reviewer verified the Applicant’s PPK model and E-R analyses for both safety and safety.

1. Population PK analyses

Four clinical trials were included in the PPK analyses: XmAb5574-01, MOR208C201, MOR208C202 and MOR208C203/L-MIND. In L-MIND, subjects received tafasitamab in combination with lenalidomide (LEN), whereas in the other trials tafasitamab was administered

as monotherapy. The final PPK analysis was conducted based on 221 subjects and 3972 measurable tafasitamab serum concentrations.

The intrinsic and extrinsic factors of sex, age, body weight, race, ethnicity, disease type, tumor size, LDH, cancer stage, ECOG, B-cell count (time-varying), absolute lymphocyte count, immunogenicity, total protein, ALB, liver enzymes, CrCL and LEN administration were analyzed in the analysis.

The final model was a 2-compartment model with time-dependent elimination. The time-dependent clearance was defined as $CL \cdot \exp(-t^{\gamma}/(T_{50}^{\gamma} + t^{\gamma}))$ to describe the increasing C_{min} in L-MIND trial observed beyond one year of treatment. The effect of baseline body weight (WTB) was found to be significant on CL and V. The effects of ALB on CL, sex on V and disease type on V were also included in the final PPK model. The final model parameters are shown in Table 56. The covariate effects on exposures were generally moderate (5th percentile – 95th percentile of the respective covariate range caused a change of < ±50% of the respective primary PK parameter or derived exposure parameter).

Table 56: Final Model Parameter Estimates for Tafasitamab

Parameter	Estimate	se	CV%	PHX 95% CI	Bootstrap 95% CI	IIV (%)	Shrinkage (%)
CL [L/day]	0.413	0.0108	2.61	(0.392, 0.434)	(0.397, 0.433)	32.4	7.08
V [L]	5.47	0.243	4.44	(5.00, 5.95)	(5.12, 5.97)	19.1	8.04
CL2 [L/day]	0.978	0.0761	7.79	(0.828, 1.13)	(0.842, 1.17)	54.4	22.2
V2 [L]	3.85	0.241	6.26	(3.38, 4.32)	(3.46, 4.21)	69.9	13.8
γ	3.28	0.153	4.66	(2.98, 3.58)	(2.23, 4.30)	–	–
T_{50} [day]	495	5.98	1.21	(483, 507)	(445, 567)	–	–
CL-WTB	0.860	0.122	14.2	(0.620, 1.10)	(0.682, 1.05)	–	–
CL-ALB	-1.08	0.192	-17.8	(-1.46, 0.704)	(-1.41, -0.768)	–	–
V-WTB	0.403	0.0752	18.7	(0.255, 0.550)	(0.255, 0.564)	–	–
V-SEX	-0.139	0.031	-22.3	(-0.200, -0.0781)	(-0.211, -0.0737)	–	–
V-DIS23	-0.318	0.0472	-14.8	(-0.411, -0.226)	(-0.410, -0.251)	–	–
CMixRatio	0.133	0.00973	7.30	(0.114, 0.152)	(0.0382, 0.581)	–	–
stdev	1.39	0.0956	6.86	(1.21, 1.58)	(0.344, 4.26)	–	6.86

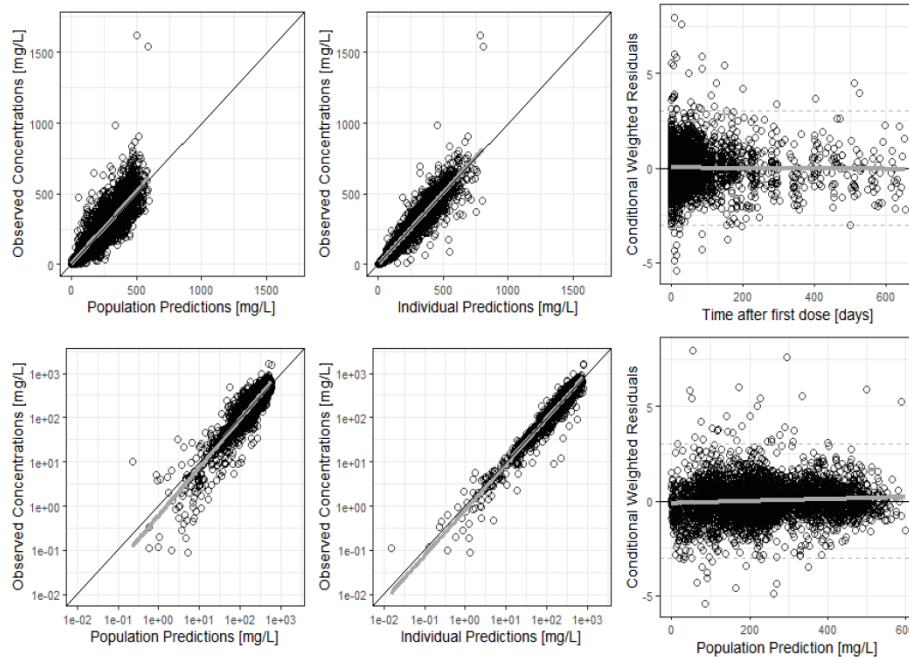
Item 4. Note: IIV% is calculated as $(100 \times \sqrt{e^{\omega^2} - 1})$, where ω^2 is the variance of a normal distribution with mean 0

Abbreviations: ALB = serum albumin at baseline, ALL = acute lymphoblastic leukemia, CI = confidence interval, CL = clearance, CL2 = inter-compartmental clearance, CV = coefficient of variation, DIS23 = NHL and ALL, γ = sigmoidicity factor, IIV = inter-individual variability, NHL = Non-Hodgkin's lymphoma, PHX = Phoenix™ NLME, se = standard error, stdev = standard deviation, T_{50} = time to half of the maximum decline in CL, V = central volume of distribution, V2 = peripheral volume of distribution, WTB = body weight at baseline.

Source: Applicant's MOR208I032 population PK study report

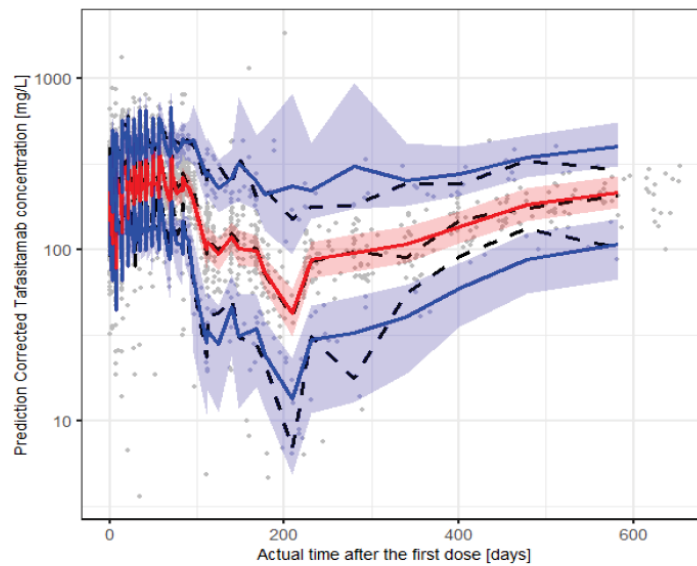
The goodness-of-fit (GOF) plots for the final model are shown in Figure 18. The pcVPC for the final model is shown in Figure 19.

Figure 18: Goodness-of-Fit Plots for Tafasitamab Final PPK Model



Source: Applicant's MOR208I032 population PK study report

Figure 19: Prediction-Corrected VPC for the Final PPK Model



Median (lines) and 95% Prediction Intervals (shaded regions)

— Simulated Median — Simulated 5th and 95th Percentile - - Observed

Source: Applicant's MOR208I032 population PK study report

In addition, the overall prevalence and incidence of anti-drug antibodies (ADA) was low across studies (8/27 subjects in XmaB5574-01, 5/92 subjects in MOR208C201, 0/22 subjects in

MOR208C202 and 2/92 subjects in MOR208C203/L-MIND). All subjects tested positive were ADA-positive already at baseline. No treatment-emergent or treatment-boosted ADAs were detected. There appears to be no impact of ADA on the PK of tafasitamab at the studied dose levels.

Next, the Applicant derived exposure parameters (AUC_{0-28} (simulated cumulative exposure in treatment cycle 1, i.e. from 0-28 days), AUC_{0-56} (simulated cumulative exposure in treatment cycle 1 and 2, i.e., from 0-56 days), average C_{min} , the highest C_{min} , C_{max} after the first dose, and overall maximal C_{max}) for each subject based on post hoc analysis of the final PPK model. The calculated exposure metrics were used in the exposure-response analyses that will be discussed in the following sessions.

Reviewer's comments: Overall, the Applicant's PPK model appears reasonable. The significant effect of body weight on PK, with higher CL and V expected at higher body weight, supports the proposed mg/kg dosing regimen. The Applicant investigated the effect of renal function by evaluating CrCL on CL as a continuous variable, and hepatic function by evaluating AST, ALT, ALKP and GGT on CL as continuous variables. Upon information request, the Applicant conducted additional sensitivity analysis to re-evaluate the effect of renal and hepatic impairment using classification of renal and hepatic function (normal, mild, moderate, or severe) as categorical variables.

The Applicant's sensitive analysis is summarized as below:

In the PPK analysis dataset, the 221 subjects were categorized as following:

- For renal impairment:
 - 109 (49.3%) subjects with normal renal function ($CrCL \geq 90$ mL/min),
 - 76 (34.4%) subjects with mild renal impairment ($CrCL: 60-89$ mL/min) and
 - 36 (16.3%) subjects with moderate renal impairment ($CrCL: 30-59$ mL/min).
- For hepatic impairment (based on NCI-ODWG criteria):
 - 174 (78.7%) subjects with normal hepatic function (aspartate aminotransferase (AST) and total bilirubin (BILI) levels $\leq$ the upper limit of normal [ULN]),
 - 42 (19.0%) subjects with mildly impaired hepatic function (AST $>$ ULN and BILI $\leq$ ULN, or AST any value and BILI $> 1.0 - 1.5 \times$ ULN); and
 - 5 (2.3%) subjects with moderately impaired hepatic function (AST any value and BILI $> 1.5 - 3 \times$ ULN).

The Applicant conducted a sensitivity analysis using stepwise covariate modelling (scm) in order to elucidate a potential influence of renal and hepatic impairment categories on tafasitamab clearance (CL). The analysis result showed that, neither hepatic nor renal impairment categories were significant covariates. The sensitivity scm run resulted in the same covariates (i.e. body weight on CL and V, albumin on CL, sex on V, and disease type on V) as the original analysis.

Reviewer's comments: FDA Reviewer agrees with the Applicant's assessment that mild and moderate renal impairment, as well as mild hepatic impairment did not impact the exposure of tafasitamab. For other renal and hepatic impairment categories, no conclusion could be drawn as too few or no subjects were available in such categories.

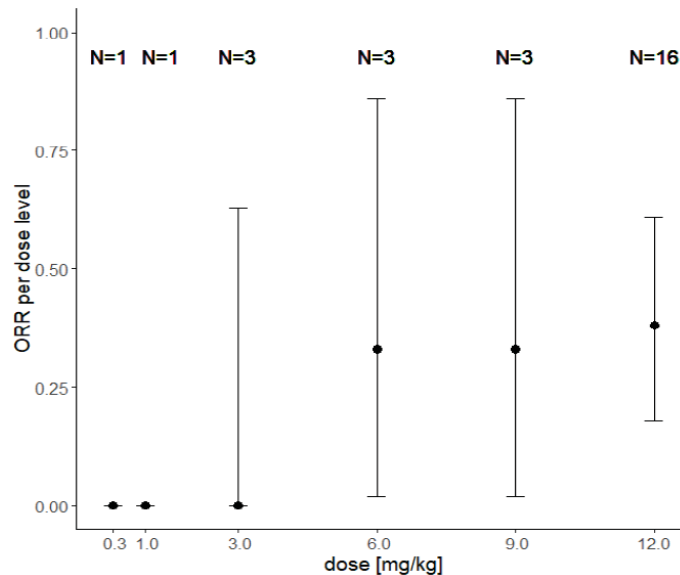
2. Exposure-response analyses for efficacy

The Applicant conducted exposure-response (E-R) analysis using ORR and PFS for each of the studies separately (XmAb5574-01, MOR208C201 and MOR208C203/L-MIND). AUC_{0-28} , AUC_{0-56} and maximal Cmin level were selected as exposure metrics for the current analysis, in which, AUC_{0-28} is the most relevant PK measure. In study XmAb5574-01, the dose levels tested were 0.3 mg/kg, 1 mg/kg, 3mg/kg, 6 mg/kg, 9 mg/kg and 12 mg/kg, while in other two studies, the tested dose level was 12 mg/kg only. In the following sessions, the E-R analyses for efficacy for each study will be reviewed.

2.1 E-R analysis for efficacy of study XmAb5574-01

Twenty-seven (27) patients with R/R CLL/SLL were included in the analysis. The objective response rate per dose level is shown in Figure 20. Overall, the ORR appears to increase in a dose dependent manner, with highest response rate observed at 12 mg/kg QW dosing group.

Figure 20: Objective Response Rate Versus Dose Group in the Phase I Dose Escalation Study XmAb5574-01

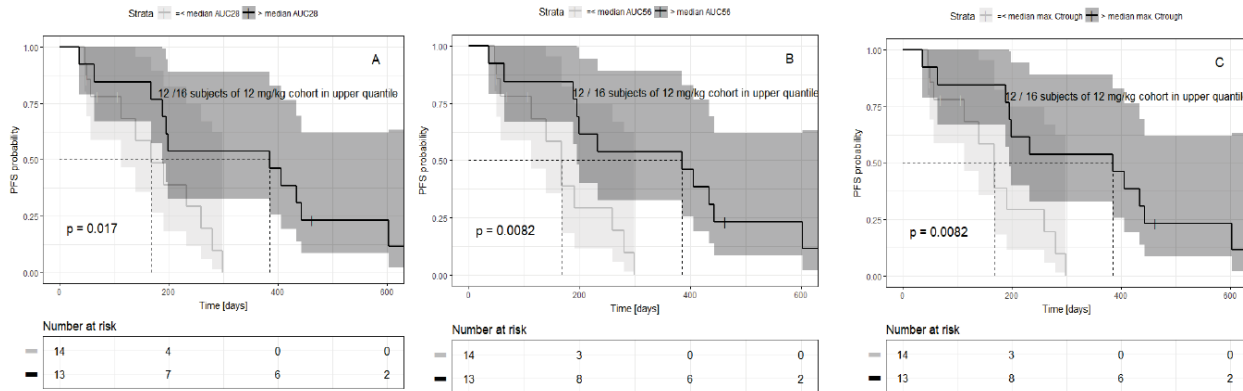


Source: Applicant's exposure-response for efficacy study report MOR208I035

For the E-R analysis using PFS, a longer PFS for patients having higher exposures was observed for all of the three PK metrics (Figure 21). In a sensitivity analysis that excluded the subjects

received additional doses after the end of cycle 2, the overall trend of longer PFS for subjects with higher exposure was still visible (plots not shown in this review).

Figure 21: Kaplan-Meier Plots for PFS Stratified by 50% Percentiles of Measures of Exposure in the Phase I Dose Escalation Study XmAb5574-01



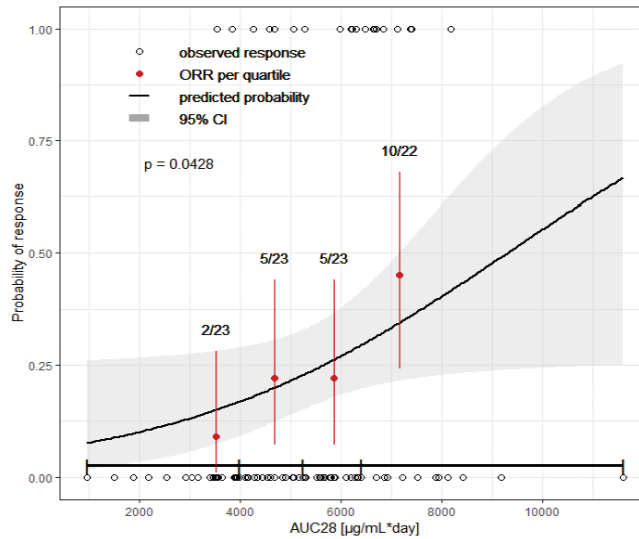
Source: Applicant's exposure-response for efficacy study report MOR2081035

Reviewer's comment: A positive E-R relationship for efficacy was observed in this FIH study. However, very low number of subjects were enrolled in most of the dose cohorts in this study, and the variability in the analysis for ORR and PFS is considered large. Thus, the observed E-R relationship for ORR and PFS should be interpreted with caution.

2.2 E-R analysis for efficacy of study MOR208C201

Ninety-one (91) patients with different NHL subtypes were included in the analysis. All of the subjects received 12 mg/kg QW tafasitamab for up to 3 cycles. Based on univariable logistic regression, positive E-R relationships for probability of response were observed for all tested exposure metrics. Figure 22 shows the univariable logistic regression result using AUC₀₋₂₈ as the predictor variable. A similar positive trend was observed in a sensitivity analysis, which excluded 6 subjects who did not received the full number of planned doses during cycle 1 due to early drop out (plots not shown in this review).

Figure 22: Uni-Variable Logistic Regression of Objective Response Versus AUC₂₈ for Study MOR208C201 (N=91)



Source: Applicant's exposure-response for efficacy study report MOR208I035

In addition, the Applicant explored the potential confounding factors impacting the analysis in Figure 22 and concluded that no pronounced imbalance of baseline characteristics identified among the exposure quartiles (Table 57). It should be noted that the record for IPI risk was missing for 12 subjects and NK cell count was missing for 20 subjects. Baseline characteristics and corresponding ORR were also summarized by means of a forest plot (Figure 23). The applicant concluded that no pronounced imbalances in ORR among the various covariate quantiles or categories were noticed.

Table 57: Distribution of Subject Baseline Characteristics Over AUC28 Quartiles (Study MOR208C201) (N=91)

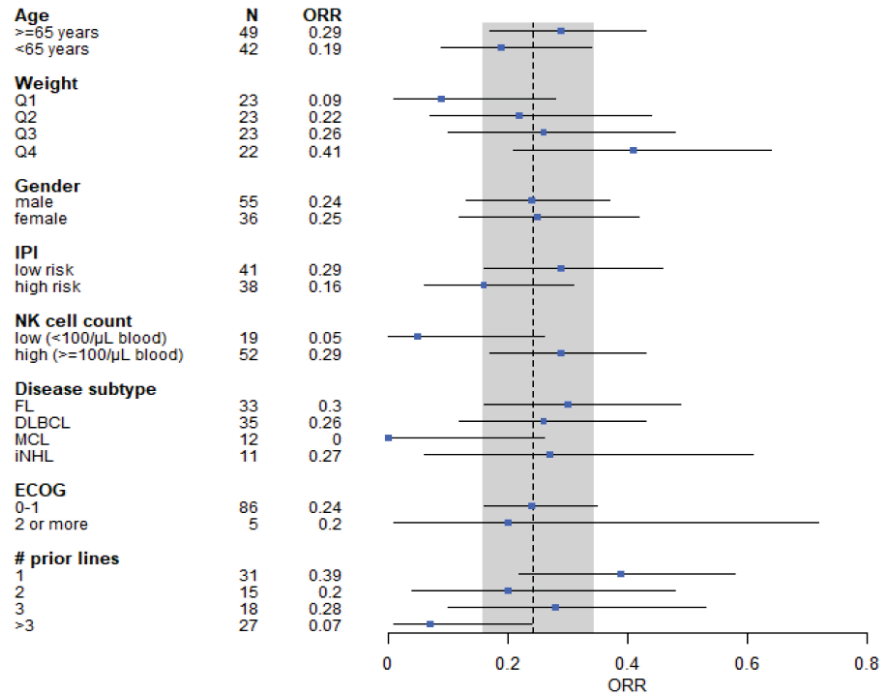
AUC28 quartiles	median AUC28 [µg/mL*day]	Median age [years]	Median BW [kg]	females	males	ECOG 0-1	ECOG 2-4	IPI low risk	IPI high risk
Q1	3523.97	73	63.4	10	13	22	1	5	16
Q2	4685.54	71	73.4	6	17	21	2	9	9
Q3	5862.59	60	77	8	15	21	2	14	8
Q4	7167.26	62.5	82.5	12	10	22	0	13	5

AUC28 quartiles	median AUC28 [µg/mL*day]	NK* high	NK* low	FL	DLBCL	MCL	iNHL	Prior Line = 1	Prior Line = 2	Prior Line = 3	Prior Line = >3
Q1	3523.97	11	7	4	12	5	2	5	3	5	10
Q2	4685.54	12	7	6	10	2	5	8	4	3	8
Q3	5862.59	15	5	11	8	3	1	9	5	4	5
Q4	7167.26	14	0	12	5	2	3	9	3	6	4

*NK high: NK cells $\geq 100/\mu\text{L}$ blood; NK low: NK cells $< 100/\mu\text{L}$ blood; BW=body weight; ECOG=Eastern Cooperative Oncology Group; IPI=International Prognostic Index; NK=Natural Killer; FL=Follicular Lymphoma; DLBCL=Diffuse Large B-Cell Lymphoma; iNHL=indolent Non-Hodgkin Lymphoma

Source: Applicant's exposure-response for efficacy study report MOR208I035

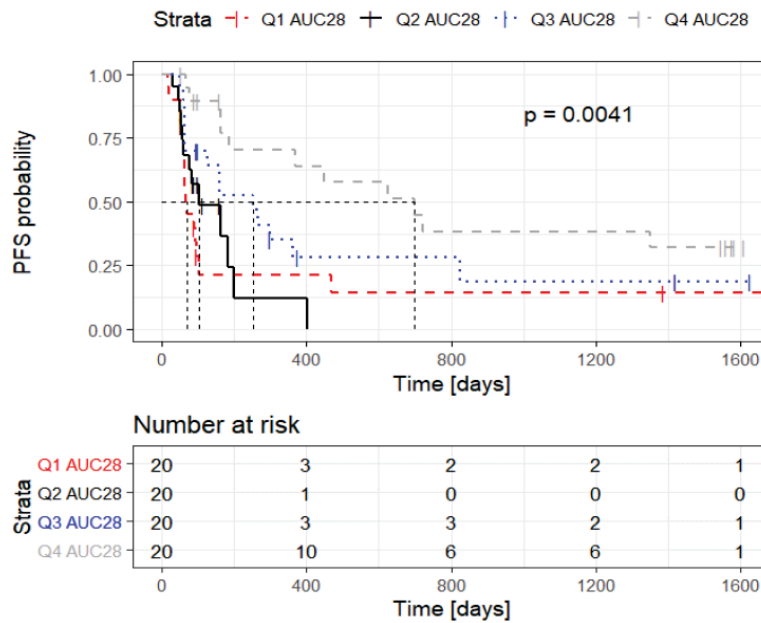
Figure 23: Forest Plot Summarizing ORR According to Baseline Characteristics in Study MOR208C201 for the Full Analysis Set (N=91)



Source: Applicant’s exposure-response for efficacy study report MOR208I035

In the E-R analysis using PFS (Full NHL set for PFS, N=80), the Applicant demonstrated that higher tafasitamab exposure was associated with longer PFS (Figure 24). Supporting analyses of AUC56 and maximal C_{min} revealed similar results. In addition, the Applicant claimed no pronounced imbalances of covariate distributions amongst the exposure quartiles (Table 58).

Figure 24: Kaplan-Meier Plot Showing Analysis of PFS Stratified by AUC28 Quartiles in Study MOR208C201 Using the Full Analysis Set (N=80)



Source: Applicant's exposure-response for efficacy study report MOR208I035

Table 58: Distribution of Subject Baseline Characteristics Over AUC28 Quartiles (Study MOR208C201) (N=80)

AUC28 quartiles	median AUC28 [µg/mL*day]	Median age [years]	Median BW [kg]	females	males	ecog 0-1	ecog 2-4	IPI low risk	IPI high risk
Q1	3548.42	74	67.5	9	11	19	1	3	15
Q2	4971.03	67.5	75.5	2	18	18	2	11	6
Q3	6150.84	60	78.9	8	12	18	2	12	7
Q4	7295.12	61	82	12	8	20	0	11	5

AUC28 quartiles	median AUC28 [µg/mL*day]	NK* high	NK* low	FL	DLBCL	MCL	iNHL	Prior Line = 1	Prior Line = 2	Prior Line = 3	Prior Line = >3
Q1	3548.42	9	5	3	10	5	2	6	3	4	7
Q2	4971.03	12	5	7	8	2	3	7	3	4	6
Q3	6150.84	11	5	11	5	3	1	8	5	2	5
Q4	7295.12	13	0	10	5	2	3	8	3	6	3

*NK high: NK cells $\geq 100/\mu\text{L}$; NK low: NK cells $< 100/\mu\text{L}$; BW=body weight; ECOG=Eastern Cooperative Oncology Group; IPI=International Prognostic Index; NK=Natural Killer; FL=Follicular Lymphoma; DLBCL=Diffuse Large B-Cell Lymphoma; iNHL=indolent

Source: Applicant's exposure-response for efficacy study report MOR208I035

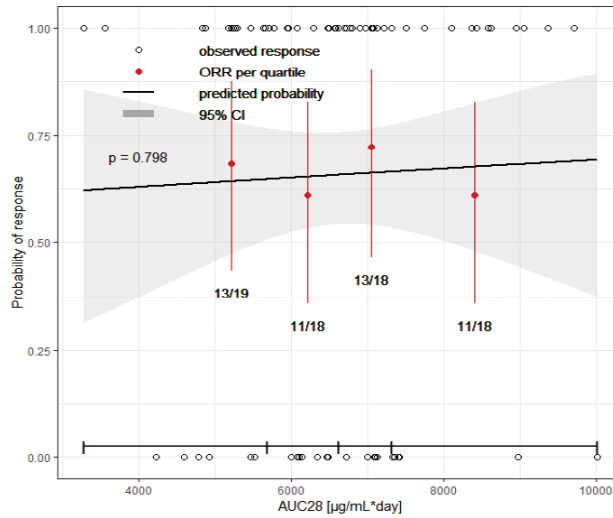
Furthermore, the Applicant conducted E-R assessment using PFS in R/R DLBCL subgroup (N=28) of clinical study MOR208C201. The measures of exposure were split into 50% percentiles instead of quartiles due to the low number of subjects and events. The analysis identified a significant positive E-R relationship ($p=0.044$). However, potential confounding factors were not analyzed due to the low number of events.

Reviewer's comment: Overall, the Applicant's E-R assessment for efficacy appears acceptable. In the monotherapy trial (study MOR208C201), higher tafasitamab exposures were associated with the better efficacy (ORR and PFS). However, based on the distribution of available baseline prognostic factors there appears to be some imbalance in IPI risk index, NK cell count and prior lines for therapy across the exposure quartiles (Table 57 and Table 58). The patients in Q1 appears to be associated with higher IPI risk, lower NK cell counts, and more >3 prior lines of therapy compared with those in Q4, which may have contributed to lower response in this group and the overall positive E-R relationships for efficacy (Figure 22, Figure 23 and Figure 24). A trend of higher in ORR was observed in patients with higher body weight (Figure 23), which may be due to the higher exposure at higher body weight (Table 57).

2.3 E-R analysis for efficacy of study MOR208C203/L-MIND

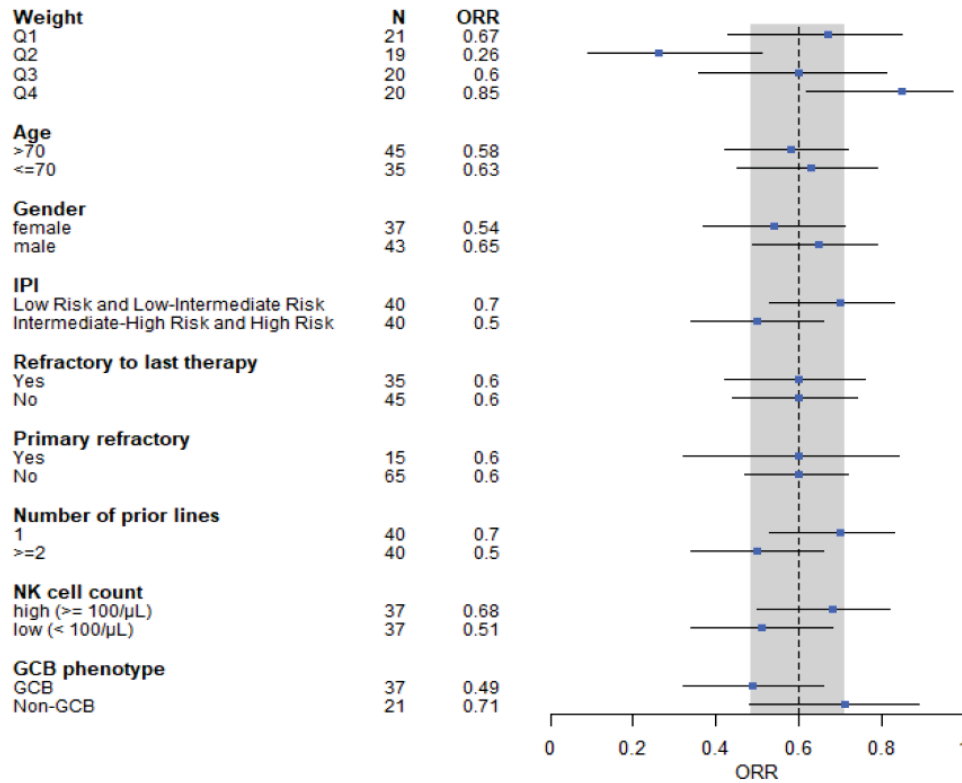
In study MOR208C203/L-MIND, clinical effectiveness of tafasitamab was studied in combination with LEN in subjects with R/R DLBCL. Tafasitamab was administered at a dose level of 12 mg/kg. A slightly positive but not significant ($p=0.093$) E-R relationship was observed in a uni-variable logistic regression using ORR versus AUC_{0-28} in the MOR208C203/L-MIND study. However, in a sensitivity analysis that excluded 7 subjects who did not receive the full number of planned doses during cycle 1 due to early drop out, a flat E-R relationship for ORR from a uni-variable logistic regression was observed (Figure 25). In addition, the Applicant noticed that ORR from study MOR208C203/L-MIND were generally higher compared to that observed in study MOR208C201. The covariate analysis did not reveal any pronounced dependency of ORR on baseline characteristics (Figure 26).

Figure 25: Uni-Variable Logistic Regression of Objective Response Versus AUC28 for Clinical Study MOR208C203/L-MIND (N=80)



Source: Applicant's exposure-response for efficacy study report MOR208I035

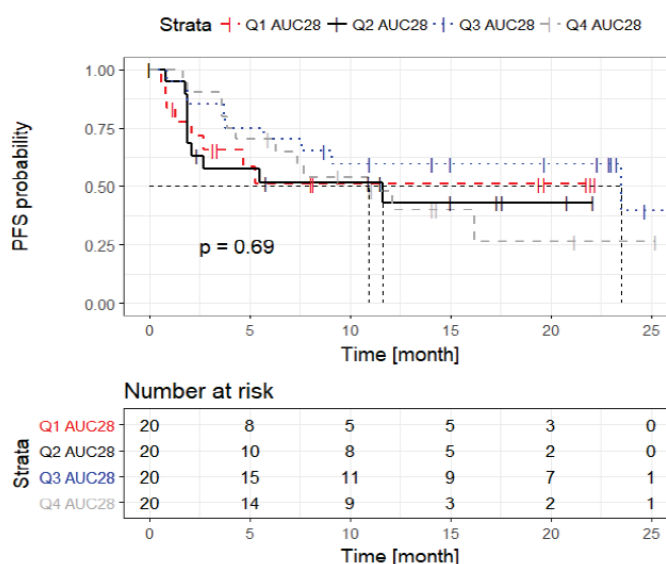
Figure 26: Forest Plot Summarizing Objective Response Rates (ORR) According to Baseline Characteristics in Study MOR208C203/L-MIND



Source: Applicant's exposure-response for efficacy study report MOR208I035

Similar to ORR, exposure-efficacy assessment using PFS also revealed a flat E-R relationship in PFS amongst exposure quartiles in the L-MIND study (Figure 27). After adjusting for potentially confounding baseline covariates (“IPI score” and “primary refractoriness”), quartiles of AUC28 were still not significant predictors of PFS, thus confirming the finding of a flat E-R relationship in the MOR208C203/L-MIND study.

Figure 27: Kaplan-Meier Plot Showing Analysis of PFS Stratified by Quartiles of AUC28 in Study MOR208C203/L-MIND (Tafasitamab in Combination with LEN)



Source: Applicant’s exposure-response for efficacy study report MOR208I035

Reviewer’s comment: FDA Reviewer agrees with the Applicant’s assessment. In contrast to a positive E-R relationship observed in monotherapy study MOR208C201, the efficacy of tafasitamab appeared to reach the plateau in the combination therapy study MOR208C203/L-MIND. Thus, from the efficacy perspective, the proposed dosing regimen of tafasitamab at a dose of 12 mg/kg is reasonable in the combination therapy with LEN.

3. Exposure-response relationship for clinical safety

The Applicant conducted assessment for exposure-response for clinical safety. Adverse events (AEs) were analyzed vs tafasitamab exposure for R/R NHL subjects (study MOR208C201, including R/R DLBCL subjects) and R/R DLBCL subjects (study MOR208C203/L-MIND). AUC₀₋₂₈ and C_{max} were used in the analyses. The individual exposure metrics were separated into exposure quartiles and analyzed against TEAEs, each AESI and Neutropenia ≥ Grade 3.

The TEAEs that have been evaluated included Anaphylactic Reactions, Drug-Related Hepatic Disorders, Torsade de pointes/QT Prolongation, Tumor Flare Reaction, Tumor Lysis Syndrome, Non-haematological malignant tumors, Infusion Related Reactions, Grade 3 or Higher Hypersensitivity, Cytokine Release Syndrome, Overdose, Diarrhea, Non-allergic Rash/Skin

Reactions, Embolic and Thrombotic Events, Infections, Neutropenias and Acute Renal Failure. Overall, there were no obvious trends within each study for increasing TEAEs for any SOC with increasing exposure.

Reviewer's comment: *The Applicant's E-R analysis for safety appears acceptable. Apparent E-R relationships were observed for several AESIs. However, the increase in odds ratio with increasing exposure quartiles for these TEAEs was moderate, and the incidence rates per exposure quartiles were low (<20%). Therefore, the Applicant's proposed dosing regimen of tafasitamab at a dose of 12 mg/kg in the combination with LEN is supported by the E-R relationships for safety.*

In conclusion, the Applicant developed a PPK model that reasonably described the PK behavior of tafasitamab in patients with either R/R CLL/SLL, R/R NHL (including DLBCL), or R/R ALL. Body weight had a statistically significant impact on both tafasitamab CL and V, supporting the body weight-based dosing regimen. A positive E-R relationship was observed for tafasitamab monotherapy clinical studies, while in combination with LEN, tafasitamab exhibited a flat E-R relationship, whereas ORRs increased almost two folds compared to tafasitamab monotherapy. Based on above findings, the proposed dosing regimen for tafasitamab administered at a dose of 12 mg/kg as IV infusion Q1W for three cycles and Q2W afterwards, in combination with LEN is reasonable for patients with R/R-DLBCL.

19.4.3 Genomics

FCGR Polymorphisms and Tumor Response

FCGR2A and FCGR3A polymorphisms affecting the binding affinity of the Fc region of therapeutic monoclonal antibodies to FCGRs have been reported to influence treatment outcomes in different cancers (Mellor et al., 2013; Nagelkerke et al., 2019). According to the Applicant, tafasitamab was engineered to allow increased binding affinity to FCGRs, independent of the patient's FCGR genotype. Binding affinities of tafasitamab for FCGR3A (p.158V and p.158F alleles) were increased 47 and 130-fold relative to the unmodified IgG1 antibody and binding affinities for FCGR2A (p.131R and p.131H alleles) were increased 11 and 5.4-fold relative to the unmodified IgG1, respectively.

The Applicant conducted exploratory analyses of responses by FCGR genotype in studies MOR208C203 (L-MIND) and MOR208C201 (DLBCL Subset). Germline DNA samples were collected with mucosal cheek swabs from consented patients and centrally genotyped for FCGR2A p.H131R (also denoted as p.H166R, rs1801274) and FCGR3A p.V158F (also denoted as p.V176F, rs396991) polymorphisms. Approximately 70% of patients in Study 203 and 66% in Study 201 had evaluable samples with response assessment. Almost all patients were White in both analyses.

The number of patients and overall response rate (ORR) in subsets defined by the FCGR genotype are summarized in Table 59. High affinity subgroups included patients homozygous for high affinity alleles (FCGR2A p.131H, FCGR3A p.158V), while low affinity subgroups included patients heterozygous or homozygous for the low affinity alleles. Although response rates were nominally lower in the subgroup of patients homozygous for the high affinity FCGR3A p.158V allele, results are limited by small numbers, missing data, and the exploratory nature of the analyses and are not conclusive.

Table 59: Exploratory Subgroup Analyses of Response by FCGR Genotype in Studies MOR208C203 (L-MIND) and MOR208C201 (DLBCL Subset)

	Study MOR208C203 Tafasitamab + LEN (IRC, FAS), N= 80*		Study MOR208C201 Tafasitamab (INV, ITT), N= 35*	
	FCGR2A p.H131R Genotype Categories			
Response	High Affinity (HH), N= 25	Low Affinity (HR+RR), N= 34	High Affinity (HH), N= 11	Low Affinity, (HR+RR), N= 21
CR or PR (ORR), n (%)	16 (64)	18 (53)	4 (36)	5 (24)
No response assessment, n (%)	1 (4)	2 (6)	4 (36)	5 (24)
	FCGR3A p.V158F Genotype Categories			
Response	High Affinity (VV), N= 15	Low Affinity, (VF+FF), N= 46	High Affinity (VV), N= 5	Low Affinity (VF+FF), N= 27
CR or PR (ORR), n (%)	7 (47)	29 (63)	0	9 (33)
No response assessment, n (%)	1 (7)	2 (4)	2 (40)	7 (26)

Source: Reviewer-generated table based on Applicant’s exploratory analyses. LEN= Lenalidomide; IRC= Independent Radiology/Clinical Review Committee; INV= Investigator; ITT= Intention-to-Treat; FAS= Full Analysis Set; ORR= Overall Response Rate; CR= Complete Response; PR= Partial Response. *Study MOR208C203: Missing genotype data: FCGR2A n=21, FCGR3A, n=19; Study MOR208C201: Missing genotype data: FCGR2A, n=3, FCGR3A, n=3. Patients with no response assessment were included as non-responders in the analyses.

19.5 Additional Safety Analyses Conducted by FDA

The FDA’s Assessment:

This section is not applicable.

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Assessment Aid Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ramadevi Gudi, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: Ramadevi Gudi -S Digitally signed by Ramadevi Gudi -S DN: c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Ramadevi Gudi -S, 0.9.2342.19200300.100.1.1 2000462985 Date 2020.07.14 07:59:45 -04'00'			
Nonclinical Team Leader (Acting)	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S DN: c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Brenda Gehrke -S, 0.9.2342.19200300.100.1.1 0012062023 Date 2020.07.13 19:59:45 -04'00'			
Nonclinical Team Deputy Division Director	Haleh Saber, PhD	OOD/DHOT	Sections: 5, 14	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 2020.07.24 14:13:13 -04'00'			
Pharmacometrics Reviewer	Ruojing Li, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Ruojing Li -S (Affiliate) Digitally signed by Ruojing Li -S (Affiliate) DN: c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Ruojing Li -S (Affiliate), 0.9.2342.19200300.100.1.1 2002080834, cn Ruojing Li -S (Affiliate) Date 2020.07.13 19:18:04 -04'00'			
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6, 19.4	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 2020.07.13 16:48:24 -04'00'			
Genomics Reviewer	Kate Drozda, PhD	OCP/DTPM	Sections: 6	Select one: ☒ Authored ☐ Approved
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Genomics Team Leader	Rosane Charlab Orbach, PhD	OCP/DTPM	Sections: 6	Select one: ☒ Authored ☒ Approved
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Clinical Pharmacology Reviewer	Vicky Hsu, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Vicky Hsu -S Digitally signed by Vicky Hsu -S DN: c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Vicky Hsu -S, 0.9.2342.19200300.100.1.1 2000996657 Date 2020.07.13 17:22:31 -04'00'			

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Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☒ Authored
	Signature: Ruby Leong -S3 Digitally signed by Ruby Leong -S3 DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Ruby Leong -S3, 0.9.2342.19200300.100.1.1 2000548953 Date: 2020.07.25 12:11:54 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15	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 Date: 2020.07.24 08:38:45 -04'00'			
Statistical Reviewer	Kunthel By, PhD	OB/DBIX	Sections: 7,8	Select one: ☒ Authored ☐ Approved
	Signature: Kunthel By -S Digitally signed by Kunthel By -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Kunthel By -S, 0.9.2342.19200300.100.1.1 2000860014 Date: 2020.07.27 13:04:39 -04'00'			
Statistical Team Leader	Yu-te Wu, PhD	OB/DBIX	Sections: 7,8	Select one: ☒ Authored ☒ Approved
	Signature: Yute Wu -S Digitally signed by Yute Wu -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Yute Wu -S, 0.9.2342.19200300.100.1.1 1300369006 Date: 2020.07.14 07:51:19 -04'00'			
Biostatistics Division Director	Thomas Gwise, PhD	OB/DBIX	Sections: 7, 8, 16	Select one: ☐ Authored ☒ Approved
	Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 1300369224, cn Thomas E. Gwise -S Date: 2020.07.24 08:24:14 -04'00'			
Clinical Reviewer	Alexandra Schwarsin, MD	OOD/DHM2	Sections: 2, 3, 4, 7, 8, 9, 10, 12, 13, 19	Select one: ☒ Authored ☐ Approved
	Signature: Alexandria J. Carney -S Digitally signed by Alexandria J. Carney -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=001188 8 1, cn=Alexandria J. Carney -S Date: 2020.07.30 10:13:51 -0'00'			
Associate Director for Labeling	Stacy Shord, PharmD	OOD	Sections: 11	Select one: ☒ Authored ☒ Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Stacy Shord -S, 0.9.2342.19200300.100.1.1 2000356537 Date: 2020.07.13 16:46:34 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Bindu Kanapuru, MD	OOD/DHM2	Sections: All	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: 2020.07.30 08:50:17 -04'00'			
Clinical Division Director (Acting)	Nicole Gormley, MD	OOD/DHM2	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Nicole J. Gormley -S Digitally signed by Nicole J. Gormley -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, 0.9.2342.19200300.100.1.1 0012754803, cn Nicole J. Gormley -S Date: 2020.07.13 16:46:00 -04'00'			

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Deputy Director (Acting) and Associate Director for Immunotherapeutics	Marc Theoret, MD	OOD	Sections: All	Select one:
	Signature: See appended signature page below.			☐ Authored ☒ Approved
OOD: Office of Oncologic Diseases				
DHOT: Division of Hematology, Oncology, Toxicology				
OCP: Office of Clinical Pharmacology				
DPM: Division of Pharmacometrics				
DTPM: Division of Translational and Precision Medicine (DTPM)				
DCPI: Division of Cancer Pharmacology I				
OB: Office of Biostatistics				
DBIX: Division of Biometrics IX				
DHM2: Division of Hematologic Malignancies 2				

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BINDU N KANAPURU
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MARC R THEORET
07/31/2020 01:43:01 PM

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