24 June 2021
EMA/426468/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Minjuvi

International non-proprietary name: tafasitamab

Procedure No. EMEA/H/C/005436/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
B-ALL	B-cell acute lymphoblastic leukaemia
BMI	Body mass index
BTK	Bruton's Tyrosine Kinase
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum concentration
CMQ	Company MedDRA Query
CR	Complete response
CRi	CR with incomplete count recovery
CT	Computed tomography
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DoR	Duration of response
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FL	Follicular lymphoma
HDC	High-dose chemotherapy
IgG	Immunoglobulin G
iNHL	Indolent NHL
IPI	International Prognostic Index

IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LEN	Lenalidomide
mAb	Monoclonal antibody
MALT	Mucosa-associated lymphoid tissue lymphoma
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
NA	Not applicable
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PE	Pulmonary embolism
PFS	Progression-free survival
PK	Pharmacokinetic
PLL	Prolymphocytic leukaemia
PR	Partial response
R/R	Relapsed or refractory
RT	Richter's Transformation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SD	Standard deviation/ stable disease
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System organ class

SPM	Second primary malignancies
TEAE	Treatment-emergent adverse event
TIA	Transient ischaemic attack
TTNT	Time to next treatment
TTP	Time to progression

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Incyte Biosciences Distribution B.V. submitted on 30 April 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Minjuvi, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2019

Minjuvi, was designated as an orphan medicinal product EU/3/14/1424 on 15 January 2015 in the following condition: treatment of diffuse large B-cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Minjuvi as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/minjuvi.

The applicant applied for the following indication:

Minjuvi is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or refuse, autologous stem cell transplant (ASCT).

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0294/2019 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

Conditional marketing authorisation

The applicant requested a Full Marketing Authorisation at submission however during the procedure, the applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above - mentioned Regulation.

New active Substance status

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

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26/01/2017	EMA/426468/2021	Dr Walter Janssens, Prof. Markku Pasanen
12/10/2017	EMA/426468/2021	Dr Serena Marchetti, Prof. Dieter Deforce
27/06/2019	EMA/CHMP/SAWP/341711/2019	Dr Alexandre Moreau, Dr Ole Weis Bjerrum, Dr Armando Magrelli

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- The adequacy and comprehensiveness of the comparability study for the purpose of demonstrating comparability between pre-change (CMC3) and post-change (CMC4) material;
- The results of the comparability exercise demonstrate that CMC3 and CMC4 materials are comparable;
- The used of the two materials within the Phase II/III clinical trial MOR208C204 (B-MIND trial) for MAA;
- The use of the same validated ligand-binding assay for quantification of MOR00208 in human serum for CMC3 derived material and CMC4 derived material after limited cross-validation and based on the comparability results;
- The waiving of developmental toxicology studies (e.g. an EFD or ePPND study) in the nonclinical development programme of MOR208 for the treatment of relapsed or refractory DLBCL and CLL/SLL.
- The proposed single-arm Phase 2 study design (MOR208C203, L-MIND) in conjunction with the observational, retrospective cohort study of patients with LEN monotherapy (MOR208C206) to support a full approval; the proposed safety database; the overall planned clinical database in

conjunction with the retrospective observational MOR208C206 cohort study to evaluate the risk/benefit ratio of MOR00208 to support a MAA for an indication in adult patients with R/R DLBCL.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	30 April 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	12 May 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	20 May 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 May 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Minjuvi on	24 June 2021
The CHMP adopted a report on non-similarity of Minjuvi with Kymriah, Yescarta and Polivy on 24 June 2021	24 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Minjuvi is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplantation (ASCT).

2.1.2. Epidemiology and risk factors, screening tools/prevention

DLBCL is the most common subtype of Non-Hodgkin lymphomas, constituting 30%–58% of NHL (Tilly et al. 2015 and comprises 60% of all new lymphomas in the elderly population (Thieblemont and Coiffier, 2007). The disease causes approximately 8500 new cases in Europe (Sant et al. 2010) and an estimated 4000 deaths per year (Marcos-Gragera et al. 2011, De Angelis et al. 2015, Howlader et al. 2016). The incidence of DLBCL increases with age, it is mainly as adult/elderly disease. The incidence rises from <1/100,000 in children to 10-15/100,000 in patients aged 65 years and older, with most cases occurring in adults >54 years of age (Sant et al. 2010). A family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL (Morton el al. 2014).

2.1.3. Biologic features

Non-Hodgkin lymphomas (NHL) comprise a heterogeneous group of lymphoproliferative malignancies, which in 90% of cases are derived from B-cells with DLBCL with distinctive prognostic profiles including cell of origin: germinal centre B-cell (GCB) type or activated B-cell (ABC) type. Other prognostic factors are expression of MYC, BCL2 and ENO3 genes (Carreras et al. 2020), TP53 deletion or mutation (Tessoulin et al. 2017), and aberrant microRNA expression (Ting et al. 2019). "Double-expression" (overexpression of MYC and BCL2 proteins), "double-hit" (dual translocation of MYC and BCL2 or BCL6) and "triple-hit" (chromosomal alterations in MYC, BCL2, and BCL6) DLBCL are associated with a particularly poor prognosis (Carreras et al. 2020, Xia and Zhang 2020, Rosenthal and Younes 2017). The ABC (non-GCB) type has been associated with worse outcome (Nowakowski et al. 2015, Hans et al. 2004, Lenz et al. 2008). DLBCL have been categorised into different subtypes with different characteristics, such as T-cell/histiocyte-rich B-cell lymphoma, Epstein-Barr virus (EBV)-positive DLBCL, DLBCL not otherwise specified (NOS) and others.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

DLBCL primarily develops in the lymph nodes, but in about 40% of the patients "extranodal sites" (areas outside the lymph nodes) may be involved, such as the gastrointestinal tract, testes, thyroid, skin, breast, bone, brain, or essentially any organ of the body, being localised or generalised. DLBCL is an aggressive disease with short life expectancy if left untreated. With currently available treatments, around 50% of newly diagnosed patients can be cured. DLBCL may arise as de novo, but it can also arise from a prior/existing low-grade (indolent) lymphoma, such as follicular lymphoma (FL) or marginal zone lymphoma (MZL), it is then commonly referred to as transformed lymphoma.

The most commonly used risk assessment tool in DLBCL is the International Prognostic Index (IPI), which predicts the risk of relapse/non-cure (International NHL Prognostic Factors Project, 1993). The IPI is determined at initial diagnosis, and is based on age, stage of disease according to the Ann Arbor classification, lactate dehydrogenase (LDH) levels, Eastern Co-operative Oncology Group (ECOG) performance score and extranodal involvement. Other factors may also affect prognosis and treatment strategies, including the maximum bulk of the disease (Tilly et al. 2015). While similar considerations apply for treatment of transformed lymphoma, outcomes are somewhat inferior as compared to de novo DLBCL (Lossos et al. 2011, Guirguis et al. 2014).

Most patients are diagnosed with advanced disease, and DLBCL is most frequently diagnosed between the age of 65-74 years, with a median age at diagnosis of 70 years (Smith et al. 2015).

2.1.5. Management

Standard treatment for patients with newly diagnosed DLBCL consists of immuno-chemotherapy with the anti-CD20 monoclonal antibody rituximab (RTX), and CHOP administered for 6-8 cycles (R-CHOP) (Tilly et al. 2015). The addition of RTX has substantially improved the results of CHOP-chemotherapy, but still approximately 30-40% of patients ultimately relapse and are not cured by first-line therapy with R-CHOP, and approximately 20% of patients are refractory to R-CHOP as first-line therapy (primary refractory) (Coiffier et al., 2002).

In patients progressing or relapsing after first-line treatment, the ultimate goal is salvage chemotherapy mainly with platinum- and/or gemcitabine-based regimens, followed by high-dose chemotherapy (HDC) with ASCT. This is a potentially curative treatment, significantly improving the disease-free survival and overall survival (OS) (Philip et al., 1995). Many patients are not fit enough to receive intensive chemotherapy regimens, e.g. because of older age or comorbidities, for these patients, the outcome is dismal with generally no prolonged periods of disease control (Thieblemont and Coiffier 2007). Primary refractory patients who progress through front-line therapy also do very poorly even after receipt of salvage treatment followed by ASCT with a 3–year progression-free survival (PFS) rate of 17% (Vardhana et al. 2017).

Treatment options for patients who have relapsed or progressed after second-line treatment of DLBCL are limited, and there is no consensus regarding the optimal treatment. According to guidelines by the European Society of Medical Oncology (ESMO) (Tilly et al. 2015), recommendations for transplant –non-eligible patients in first relapse mainly include platinum- and/or gemcitabine-based regimens or clinical trials with novel drugs. Of note, none of the agents recommended by the ESMO guidelines (Tilly et al. 2015) is specifically approved as a second-line treatment for DLBCL. Bendamustine +rituximab, may also be used as second line and subsequent therapies, or participation in clinical studies with novel drugs. Of newer therapies, the CAR R-cell therapies represent a treatment option for R/R DLBCL patients who have received two or more lines of systemic therapy (Neelapu et al. 2017a, Schuster et al. 2017), but the manufacturing and distribution process is complex, the patients have to tolerate the conditioning regimen and adverse events such as the risk of neurotoxicity and cytokine-release syndrome must be considered. Pixuvri is also an option as monotherapy for patients with multiply relapsed or refractory aggressive NHL. In January 2020, the novel antibody-drug conjugate polatuzumab vedotin (Polivy), in combination with BR, received a conditional approval as second- or later-line therapy for R/R DLBCL patients who are not candidates for ASCT. Lenalidomide as single agent and in combination with RTX has shown some effect and was well-tolerated in heavily pre-treated patients with R/R DLBCL (Wiernik et al., 2008, Zinzani et al. 2011, Czuczman et al. 2017), however lenalidomide is not approved for the treatment of DLBCL by EMA or FDA. Lenalidomide has been approved for mantle cell lymphoma and follicular lymphoma. Recent approvals of CAR T-cells or POLA-BR in R/R DLBCL have not yet been included in the ESMO guidelines which date back to 2015.

About the product

Tafasitamab is a Fc-enhanced humanised monoclonal antibody (mAb) that binds to the human B-cell surface antigen, CD19. CD19 is expressed throughout normal and malignant B-cell development up to terminal plasma cell differentiation and is present on all malignant B-cells, including DLBCL (Olejniczak et al. 2006). Alteration of two amino acid residues in the constant region of tafasitamab significantly increases binding to Fc gamma receptors (FcγR), including FcγRIIIa (CD16), and FcγRII (CD32), leading to enhanced *in vitro* antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and direct cytotoxic effects (apoptosis) on tumour cells relative to the unmodified antibody (Uckun et al. 1988, Tedder et al. 1994, Sato et al. 1997, Otero and Rickert 2003). The major pharmacological effect of tafasitamab is B-cell depletion.

Type of Application and aspects on development

The applicant requested a Full Marketing Authorisation. The CHMP following discussions during the procedure, support a Conditional Marketing Authorisation (refer to the benefit/risk section).

2.2. Quality aspects

2.2.1. Introduction

Tafasitamab, the active substance contained in Minjuvi, is a humanised CD19-specific monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Minjuvi is presented as a powder for concentrate for solution for infusion containing 200 mg of tafasitamab and formulated with sodium citrate dihydrate, citric acid monohydrate, trehalose dihydrate and polysorbate 20.

Minjuvi is available in a clear type I single-use glass vial with a butyl rubber stopper, aluminium seal and a plastic flip-off cap. Each carton contains 1 vial.

After reconstitution with water for injections (WFI), each mL of solution contains 40 mg of tafasitamab. The reconstituted solution is subsequently diluted with sodium chloride 9 mg/mL (0.9%) solution for injection. The final concentration of the diluted solution is between 2 mg/mL and 8 mg/mL of tafasitamab.

2.2.2. Active Substance

General Information

Tafasitamab is a Fc-engineered humanised monoclonal antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes. Tafasitamab is optimised for increased affinity to Fcγ receptors through two amino acid substitutions at positions 243 and 336 (strongest increase observed for FcγRIIIa). The Fc modification results in enhanced antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Tafasitamab does not mediate complement dependent cytotoxicity (CDC).

With the exception of the two intended amino acid changes, the protein sequence of tafasitamab is identical to human IgG1 in the Fab and hinge regions (through position 242 and at position 331 and identical to human IgG2 in the CH2 and CH3 domains (position 244 through the C terminus, except at position 331).

Tafasitamab is secreted as a disulfide-linked glycosylated tetramer consisting of two identical 451 amino acid heavy chains and two identical 219 amino acid kappa light chains. The heavy chain bears an N-linked glycosylation site at position N301.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Tafasitamab active substance is manufactured at Boehringer Ingelheim, Biberach, Germany. EU GMP compliance of this site and other facilities involved in active substance operations was confirmed.

Tafasitamab is produced in CHO cells in a fed-batch manufacturing process and purified via several affinity chromatographic- (Protein A, cation exchange (CEX), anion exchange (AEX)) and filtration steps (depth, virus, tangential flow (TFF)). The dedicated virus neutralisation steps consist of low-pH and nanofiltration.

The tafasitamab manufacturing process is a standard platform design for monoclonal antibodies produced in CHO cells.

One 12,000 L production bioreactor run results in one purification run providing one batch of tafasitamab active substance. One or multiple batches of tafasitamab active substance can be split and/or pooled into multiple sub-batches to provide the required active substance volume for aseptic filling and lyophilisation to one lot of tafasitamab finished product. Batch size and traceable batch ID is defined from master cell bank (MCB) to finished product.

The formulated active substance (40.0 mg/mL tafasitamab antibody) is either stored frozen for long-term storage until filling, or alternatively the active substance can be processed into tafasitamab finished product directly without freezing.

The only allowed form of reprocessing is refiltration of the virus filtrate or active substance. In the event of an integrity test failure or mechanical failure of equipment, the virus filtrate or active substance material may be reprocessed one additional time. Verification of the active substance refiltration has already been performed during process validation by demonstrating reprocessing on purpose.

Control of materials

A complete listing of the raw materials used for the manufacture of tafasitamab is provided with specifications for the non-compendial raw materials tested according to the respective in-house specifications.

None of the raw materials on the list are considered critical regarding adventitious agents.

The media used for cell banking and cell culture are described in sufficient detail.

Information on the source of the host cell line, the preparation and description of the expression vector, and the establishment of the cell banks is provided. Expression plasmids encoding the tafasitamab heavy chain and light chain were transfected into CHO cell substrate, and the highest producing monoclonal cell was selected to generate an MCB. The MCB was subsequently used to prepare a working cell bank (WCB), which was used for the production of clinical trial material and will be used for commercial supply. The procedures to generate MCB and WCBs are described. Both MCB and WCB were tested and characterised in accordance with ICH guideline requirements and were both confirmed to be of CHO origin. The expression of the expected cDNA sequence was confirmed. The genetic stability of the production cell line has been demonstrated (limit of *in vitro* cell age).

Control of critical steps and intermediates

Controls for critical manufacturing process steps have been established for the manufacture of tafasitamab active substance to ensure consistent process performance and the desired product quality. For all critical process parameters (CPPs) which may affect the quality and safety of the final product relevant controls have been established. The in-process control (IPC) limits and acceptance criteria as well as the proven acceptable ranges (PARs) for the CPP are defined and presented. The justifications provided in the manufacturing process development section are found appropriate.

Process validation

The process control strategy is designed based on a lifecycle approach. The process control strategy is verified at manufacturing scale and a data monitoring/trending plan is established for the commercial manufacturing.

Process validation lifecycle activities include:

- Process evaluation:

  The process control strategy is evaluated by a failure mode risk analysis (FMEA), taking into consideration scientific knowledge, parameter characterisation through laboratory scale studies as well as commercial manufacturing scale data.

- Process verification:

  The effectiveness of the process control strategy is demonstrated at manufacturing scale using qualified equipment. The results of process parameter control, in-process tests and release tests demonstrate that the manufacturing process is controlled effectively and performs reproducibly to yield tafasitamab that meets the desired product quality criteria. Process verification of the manufacturing process was successfully completed by producing consecutive batches at the commercial manufacturing scale using qualified equipment.

  Concurrent validation support activities have been initiated to validate the performance over the lifetimes of chromatography resins and TFF membranes including their cleaning and storage procedures. Verification protocols of the refiltration procedures at the virus filtration and active substance filtration steps were prepared. These activities will continue concurrently with commercial manufacturing.

- Ongoing process verification:

  The validated state of the process control strategy is ensured through an ongoing data monitoring/trending programme.

Process validation of the active substance is considered acceptable.

Manufacturing process development

The control strategy for tafasitamab and the documentation of comparability of the four manufacturing process generations, CMC1, CMC2, CMC3 and CMC4, has been provided and described in sufficient detail.

A Quality by Design (QbD) approach is used for the manufacturing process development of tafasitamab. No design space is claimed.

The Quality Target Product Profile (QTPP) of tafasitamab has been described in sufficient detail as well as the risk-based assessment of tafasitamab quality attributes related to the molecule, the process, the quality and safety. The critical quality attributes (CQA) are controlled as critical process input parameters (CPP) with PARs defined by the process characteristic studies (PCS) and virus validation studies as applicable.

Four manufacturing processes have been used throughout the history of tafasitamab. CMC1 materials was used for toxicological studies and the phase I study. Due to certain limitations, the manufacturing process was thereafter transferred and a number of major changes were introduced to lead to the CMC2 process. Two other process variants (CMC3 and CMC4) were subsequently developed. CMC4 is the commercial process format but both CMC2 and CMC4 have been used in the L-MIND pivotal clinical study which is the focus of this application. Impact of the different processes on comparability has been assessed and specific attention has been brought to comparability between CMC2 and CMC4 materials including head-to-head comparison and extended characterisation. Overall, comparability was shown for each process change showing representativeness across clinical trial materials and to the proposed commercial material. Furthermore, direct comparison between CMC2 and CMC4 corroborated comparable physicochemical, biological and stability/degradation profiles.

The comparability programme is performed in line with CHMP and ICH guidelines. This is acceptable.

Characterisation

The characterisation of tafasitamab and of the process- and product-related impurities is performed with state-of-the-art analytical methods and orthogonal methods. The characterisation is appropriate and described in sufficient detail.

Elucidation of structure

Orthogonal standard and state-of-the-art methods were applied to determine physicochemical and immunological properties, biological activity, purity, impurities and quantity of tafasitamab. Primary and higher order structure, heterogeneity with respect to size, charge, glycosylation, glycation, oxidation as well as biological activity and binding were analysed.

The structure is a combination of IgG1 (Fab and hinge region) and IgG2 (CH2 and CH3 domain). The Fc binding to Fc-γ receptors (FcγRs)) is enhanced through the modification at two amino acids in the CH2 domain.

The heterogeneity characterisation concerned free thiols, oxidised methionine and tryptophan variants, charge variants, isomerisation of aspartate and C-terminal variants.

The charge variant study of deamidated variants characterised deamidation hotspots and the impact on biological function. A deamidation hotspot showed influence on the ability to bind to the target CD19. A proportional impact of deamidation on potency was seen for material generated by forced degradation. The level of deamidated species is controlled during the manufacturing process via process design and the process parameters. Furthermore, the release specifications for active substance and finished product are controlling the level of deamidated species.

N-glycan variants were characterised to influence the biological activity.

Galactose levels were identified not to have influence on the potency. The level of afucosylation is known to have influence on the effector function but was measured at low levels and is therefore of no significant influence on the Fc-binding activity.

Characterisation of size variants showed a high purity No hyper-potent species were identified.

The biological activity was characterised by orthogonal potency tests, as well as cell-based assays. At release, the target binding is analysed via a cell-based CD19 binding assay. ADCC killing activity is determined by measuring the lysis of target cells by using an effector cell line. For characterisation purposes an additional ADCC reporter bioassay and a flow cytometry-based ADCP assay were used. Furthermore, binding to recombinant human CD19 and human Fc gamma receptors and the neonatal Fc receptor (FcRn) was analysed. The results confirmed that tafasitamab binds to all human FcγRs with

higher affinities than reported for non-engineered human IgG1 and that the ADCC as well as the ADCP activities were enhanced.

Impurities

The process- and product-related impurities are identified, and the clearance capacity of the manufacturing process is evaluated to ensure acceptable low levels.

The product-related impurities are CQAs and controlled via the IPCs and process validation. The process-related impurities are also risk assessed and the worst-case scenario exposure (WCSE) was compared to the permitted daily exposure (PDE). A buffer used in the purification step had a WCSE above PDA and the clearance capacity of the manufacturing process was analysed in a spiking study to be below the limit of quantitation (LoQ.) The clearance capacity was also documented for the process-related impurities, e.g. host cell DNA and host cell proteins (HCPs)on all available commercial scale batches. The detection of HCPs was performed with an ELISA using rabbit antibodies.

The risk assessment of the materials in contact with the active substance during the manufacturing process revealed suitability and no risk for safety or quality, hence no extractables and leachables studies were performed.

The risk of presence of elemental impurities in a concentration that has a safety impact is generally considered very low in biotech products due to the chromatography steps and especially TFF, therefore no specific control for elemental impurities is performed. This approach is considered acceptable.

Specification

The specification for the active substance includes control of identity, purity and impurity, potency and other general tests.

Following tightening of the acceptance limit for the ADCC assay and further justification regarding the acceptance criteria for CD19 binding assay and CEX main peak, the specification for the control of the active substance at release and stability is considered acceptable.

The applicant is recommended to evaluate additional data from subsequent batches and re-evaluate the release and shelf life acceptance criteria for active substance and finished product based on statistical evaluation and trend analyses of the results (see Recommendation). The re-evaluation will be done using suitable statistical approaches and will be conducted after at least 25 active substance batches have been produced, including the data from already available CMC4 active substance batches. If changes to the dossier should be necessary, the applicant will submit a variation of appropriate category, as applicable.

Analytical methods

The proposed analytical procedures were satisfactorily validated in line with ICH requirements and they are considered suitable to control the active substance on a routine basis.

Potency is controlled by CD19 binding and ADCC. The CD19 binding assay is a cell-based quantitative method to evaluate binding of tafasitamab to the CD19 receptor relative to the reference material. Acceptance criteria for the CD19 binding assay were set based on a statistical approach and justified by clinical studies. The ADCC bioassay, is a quantitative method to evaluate the relevant mechanism of action of tafasitamab relative to the tafasitamab reference material. The potency of the reference material is set to 100%.

Batch analysis

Batch information and analytical release data from all tafasitamab active substance batches produced so far that were used for clinical supply, stability studies, process verification or are intended for market supply is provided.

All tafasitamab active substance batches were tested to the respective specifications that were in place at the time of release, and which were applicable for the respective stage of development.

All CMC4 batches intended for clinical or commercial use meet the proposed commercial specification acceptance criteria.

Reference standard

The applicant established appropriately characterised in-house primary and working reference standards, prepared from lot representative of production. Working reference standards used in the testing of production lots was calibrated against the primary reference material. Documentation of the qualification, storage conditions and stability programme of primary and working reference standards was provided. A suitable protocol for qualification of future primary and working reference materials was also described.

Container closure system

The active substance container closure system is described in sufficient detail in relation to structure and compatibility. The choice of the container closure system was chosen to pose low risk for extractables and leachables and to provide adequate protection from microbial contamination.

Other types of material that come into contact with the active substance include the filter units for which compatibility has been documented.

Stability

The active substance stability protocol is in compliance with the ICH guidelines. Primary stability studies were performed on batches representative of the commercial manufacturing process. The proposed shelf-life and storage conditions are supported by the stability studies.

No differences in the stability indicating parameters were observed in all stability studies conducted.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the finished product

Tafasitamab finished product is a lyophilised powder for reconstitution and intravenous infusion. The finished product is a white to slightly yellowish lyophilisate for reconstitution with 5 mL WFI, supplied in single-use 20 R glass vials.

All excipients used in the manufacture of tafasitamab are compendial (sodium citrate dihydrate, citric acid monohydrate, trehalose dihydrate and polysorbate 20). No excipients of animal or human origin or any novel excipients are used in the manufacture of tafasitamab.

After reconstitution with WFI, tafasitamab is presented at a concentration of 40 mg/mL in a citrate buffered, isotonic solution at pH 6.0. The target pH is achieved by the molar ratio of sodium citrate dihydrate and citric acid monohydrate. the surfactant polysorbate 20 (PS20) and the osmolyte trehalose are used. The reconstituted finished product solution is unchanged with regard to concentration and

composition compared to the active substance solution. Each vial is designed to deliver 200 mg of tafasitamab.

To ensure that 5.0 mL, corresponding to 200 mg, can be extracted from the 20 R vials after reconstitution, an overfill of is applied.

Pharmaceutical development

Four different processes, CMC1 to CMC4, were used during development of tafasitamab finished product. The final concentration, pharmaceutical form, formulation composition and primary container closure of the CMC4 process have been evaluated in phase II and III clinical studies and in a 13-week repeat-dose toxicity study and are considered both toxicologically and clinically qualified.

The finished product formulation developed from a liquid to a lyophilised formulation. The lyophilised dosage form was introduced to improve product stability. The resulting formulation remained unchanged through CMC2, CMC3 and CMC4 and was selected as the commercial formulation.

Finished product release data from all batches used in clinical development from CMC1 to CMC4 have been compared, and a side-by-side analysis of CMC2 and CMC4 finished product material was conducted. The results show that material from all four manufacturing processes were comparable. Characterisation of the active substance from CMC1 to CMC4 confirmed comparability and no additional changes were identified in finished product characterisation. Therefore, evaluation of the analytical comparability show that the developmental changes made to the finished product manufacturing process did not affect finished product quality.

As for active substance, the applicant has applied QbD principles in the development of the finished product and their manufacturing process. No design space is claimed for the manufacturing process of the finished product. The development includes definition of the QTPP, CQA and CPP identification through prior knowledge, risk assessments and characterisation studies. Data provided to justify the finished product control strategy are comprehensive. Materials used in the manufacturing (filtering and filling) of finished product have been evaluated with respect to extractables and leachables. All potential leachables from materials used in production were at a level below the PDE dose at rough extraction conditions. The same is true for elemental impurities originating from sources in contact with the final finished product (active substance, equipment, water, excipients and container closure system). Therefore, material leachables or elemental impurities are evaluated to pose no risk to patients using tafasitamab.

The container closure system has been evaluated to be suitable for storage of finished product through extractable/leachables studies, stability studies and shipping validation. It is in compliance with Ph. Eur. requirements.

Tafasitamab finished product contains no preservative. The microbiological quality complies with EU requirements for sterile products and is ensured by a combination of various measures - sterile product-contact components, sterile in-line filtration, environmental and media monitoring - and is confirmed by microbiological IPC testing as well as sterility release testing. Container closure integrity, to maintain sterility during storage, has been validated and is continuously controlled as part of the stability specification.

The finished product is intended to be administered via intravenous infusion using WFI (for reconstitution) and sodium chloride 9 mg/mL (0.9%) solution (for dilution). Physicochemical stability of the reconstituted solution and the diluted infusion were demonstrated for the durations and conditions as listed in the product information. From a microbiological point of view, although microbial challenge tests demonstrated that microbial proliferation was not observed in any reconstituted and diluted tafasitamab solutions, the product should be used immediately. Compatibility between finished product

and the plastic material used for infusion was confirmed in a 24-hour contact study comprising of the most commonly used containers, infusion lines and sterile filters.

Manufacture of the product and process controls

Manufacture

Tafasitamab finished product is manufactured and tested at EU GMP compliant sites.

The manufacturing process of tafasitamab finished product is well described. It is a simple process where the already formulated active substance is thawed, sterile filtered, filled into vials and lyophilised. Upon completion of the lyophilisation cycle, vials are fully stoppered and crimped, and a 100% visual inspection is performed before shipping for secondary packaging and labelling. Adequate CPPs and IPCs are in place. Acceptable process ranges were established and supported by process development studies.

The batch size varies based on commercial needs.

Process validation

Each step of the finished product manufacturing process (sterile filtration, aseptic filling, lyophilisation, crimping and 100% visual inspection) have been properly validated.

The sterile filters have been validated and certified by the supplier. Additionally, the suitability of the filter membrane was verified through a bacterial retention study. Filter validation has been performed in accordance with the *Guideline on the sterilization of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMPQWP/850374/2015)*. Filter integrity pre- and post-filtration has been validated and is controlled in routine production by in-process filter integrity controls pre and post filtration. A consistency validation study confirmed that finished product quality was unchanged prior to and post sterilisation for all three process verification batches. Possible leaching from filter material was found to be very low and not considered to pose any toxicological risk to patients using tafasitamab.

All hold- and light-exposure times for finished product were within the predefined criteria for all three process verification batches, and the final finished product was within the specifications valid at the time of process validation.

Product specification

The specification for the finished product includes control of identity, purity and impurity, potency and other general tests.

The finished product specification was established in line with ICH Q6B and Ph. Eur. monograph 2031 on monoclonal antibodies for human use.

For the finished product specific specifications (appearance of cake, reconstitution time, residual moisture and polysorbate 20), the acceptance criteria are set based on data from clinical CMC3 and CMC4 finished product batches, which have consistently provided the same results, and on formulation robustness studies.

The finished product specification is considered acceptable.

The potential presence of elemental impurities in the active substance and finished product has been assessed on a risk-based approach in line with the ICH Q3D guideline for elemental impurities. The risk of carryover of elemental impurities from reagents and materials used for manufacture is considered negligible and no additional control is required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC)

No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or finished product. Therefore, no additional control measures are deemed necessary.

Analytical procedures

Several analytical procedures for finished product are also used at active substance level and have thus been described and validated in the active substance part of the dossier.

The methods appearance (coloration, clarity and opalescence), subvisible particles, content uniformity, and sterility are compendial methods with predefined acceptance criteria for monoclonal antibodies and injections in general.

For the finished product non-compendial methods for appearance and description, functional tests and excipients have all been appropriately qualified/validated.

Batch analysis

Data for CMC4 batches supports batch consistency and uniformity of the finished product. The same is true for CMC1, CMC2 and CMC3 batches, underlining that the finished product manufacturing process has been robust throughout development and manufacturing of tafasitamab finished product.

Reference material

The reference standard used for tafasitamab finished product is the same as the reference standard used for active substance.

Container closure

The choice of the container closure system is in line with pharmaceutical standards and the components comply with pharmacopoeial requirements. Both vials and rubber stoppers have been analysed with respect to extractables according to Ph. Eur. and the results are acceptable.

Stability of the product

Stability testing was performed per ICH and CHMP guidelines.

One CMC3 and six CMC4 batches are used as primary stability batches. Sixty months stability data are available for the CMC3 batch and 18-48 months data are available for the six CMC4 batches. Therefore, the proposed shelf life is covered by real-time data from the CMC3 batch and two CMC4 batches. The use of a CMC3 batch in stability studies has been justified by the similarities in manufacturing and formulation between CMC3 and CMC4, the comparability between CMC3 and CMC4 active substance and finished product and the same container closure system being used for material from the two processes. CMC4 batches were used for post-reconstitution stability, one of which was also used in the in-use stability study.

All long-term stability data remain within the specification presented.

Stability after reconstitution has been investigated by reconstituting the lyophilised finished product with WFI and storing it up to 24 hours at up to 25°C. The results support the post-reconstitution stability claim of 24 hours at 2-25°C. In-use stability has been assessed by diluting the reconstituted finished product in saline solution and storing it for 36h at 5±3°C followed by up to 24 hours at up to 25°C. All physico-chemical in-use stability results were within acceptance criteria of the chosen subset of specification test, and no increase in microbial count was observed. The results thus support the in-use stability claim of 36 hours at 2-8°C followed by up to 24 hours at maximum 25°C.

An in-use shaking study was performed supporting that tafasitamab finished product can be transported after reconstitution and dilution. A photostability study showed that the finished product should be protected from light as stated in the SmPC.

The post-approval stability protocol and stability commitment are acceptable.

Container closure integrity is tested to confirm container closure integrity. The provided data confirm container closure integrity for up to 12 months for the finished product process verification batches and up to 36 months for an additional finished product batch; and the applicant commits to continue the testing according to the stability protocol and inform the authorities in case of any out-of-specification results.

The data presented support the claimed shelf life for the finished product of 36 months under the proposed storage conditions of 5 ± 3°C protected from light.

Adventitious agents

Testing of starting materials and monitoring of process intermediates during manufacturing provides high assurance that no viral or non-viral adventitious agents are introduced into the manufacturing process of tafasitamab. Raw materials containing human- or animal-derived material were only used for development and generation of the host cell line and MCB. These materials are certified as non-BSE/TSE containing and the high dilution during cell culture expansion and the subsequent virus reducing steps of the manufacturing process makes it unlikely that BSE/TSE would be present in the final finished product.

Qualified scale-down models were used in the virus validation study, which was carried out in accordance with ICH Q5A. The model viruses used were xenotropic Murine Leukemia Virus (xMuLV), Minute Virus of Mice (MVM), Pseudorabies Virus (PRV) and Reovirus type 3 (Reo-3). These model viruses were selected based on ICH Q5A to represent a broad range of virus types and characteristics. Global reduction factors were satisfactory regarding the virus removal/inactivation for enveloped viruses as well as for non-enveloped viruses.

Lastly, the active substance is tested for bacterial endotoxins and bioburden at release and the finished product is tested for sterility and bacterial endotoxins at release, providing assurance that no bacterial contamination is present in the final finished product.

Adventitious agents safety is considered satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the Minjuvi quality dossier is of high quality and the documentation for the manufacture, control and stability of tafasitamab is provided in sufficient detail.

The control strategy uses a QbD approach with a defined QTPP that is found acceptable.

Four manufacturing processes have been used during development and comparability has been shown.

All relevant product-related variants and impurities are controlled in the manufacturing process via IPCs or release specifications.

The stability of both finished product and active substance has been analysed according to relevant guidelines and the proposed shelf lives are supported by real-time data.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Minjuvi is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

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

The applicant agreed to a Recommendation.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical testing strategy for tafasitamab consisted of *in vitro* and *in vivo* pharmacology, pharmacokinetic, toxicokinetic and toxicology studies. Non-clinical studies with tafasitamab were designed to support human clinical trials in CD19 positive hematologic malignancies and the marketing authorisation application of tafasitamab.

The pivotal toxicology studies supporting the development of tafasitamab were conducted in accordance with GLP regulations at test facilities/test sites, which were part of EU or an OECD GLP monitoring programme. Safety pharmacology was included in the pivotal toxicology studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

Binding to CD19

Tafasitamab binding to human CD19 was analysed by flow cytometry with HEK 293T cells transiently expressing human CD19 and a half-maximal effective concentration (EC50) of 4.8 nM was observed (TR07098). EC95 (i.e. 95% receptor occupancy) was derived from the binding curve obtained and was determined at 90.4 nM (or 13.6 µg/ml; TR07098 Addendum 1).

Table 1: Effective concentration at a given % maximal binding of tafasitamab to CD19 expressing HEK cells (EC_F)

Unit	EC50	EC90	EC95
µg/mL	0.7156	6.4404	13.5964
mol/L	4.76067E-09	4.2846E-08	9.04527E-08

Further flow cytometry analysis of tafasitamab cross-reactivity with lymphocytes of various species demonstrated that the antibody recognizes CD19 from human as well as cynomolgus and rhesus monkeys, but not common laboratory animals such as the mouse, rat, rabbit, or dog (XC9-23209). In summary, tafasitamab binds to human CD19 as expected, predicated on its parental murine 4G7 binding pattern. Interestingly, the humanisation and affinity maturation also resulted in binding of tafasitamab to macaque CD19, which supported the use of cynomolgus monkeys for toxicological evaluation of tafasitamab.

Table 2: B lymphocyte staining with XmAb5574 (tafasitamab), anti-CD20, and anti-CD45

Species	XmAb5574-FITC (%)	CD20-APC (%)	# Donors Tested
Human	19.6 (± 6.2)	19.6 (± 6.6)	4*
Cynomolgus monkey	31.4 (± 7.8)	33.6 (± 8.7)	5
Rhesus monkey	26.1 (± 5.1)	25.8 (± 4.9)	5
	XmAb5574-FITC (%)	**CD45-PE (%)**	
Dog	3.3 (± 0.4)	54.7 (± 5.1)	3
Rabbit	1.3 (± 0.4)	44.3 (± 3.1)	3
Rat	0	ND	3
Mouse	0.1 (± 0)	ND	3*

Results are shown as percentage of cells stained and are expressed as mean (± standard deviation). *For mouse, three different pools of blood were used for the analysis. For human, one single donor was tested on 4 different days. ND: not done.

Binding of Tafasitamab to Mouse, Cynomolgus Monkey and Human Fcγ Receptors

Binding of tafasitamab to murine, cynomolgus monkey and human FcγRs was characterised using surface plasmon resonance (SPR) analysis and was compared to the native IgG1 version of the antibody (TR08137). The engineering of the constant region of tafasitamab lead to increased binding affinity for Fc gamma receptors (FcγR) in all tested species.

The binding affinity of Fc regions of therapeutic antibodies to the human activating receptors FcγRIIIa and FcγRIIa is known to impact clinical efficacy. Cancer patients carrying FcγR alleles with a higher binding affinity have been reported to respond better to immunotherapy than those with lower affinity alleles (Cartron G et al., 2002; Cheung NK et al., 2006). The protein engineering strategy in the design of tafasitamab (MOR00208) was to create an antibody with increased binding affinity to FcγRs, independent of the patient's allelic genotype. Notably, the affinities of tafasitamab for the human activating Fcγ receptor RIIIa were increased 47 and 130-fold (V158 and F158 allele) relative to the unmodified IgG1 antibody. Binding affinities for the human activating Fcγ receptor RIIa (R131 and H131 allele) were increased 11 and 5.4-fold over the unmodified IgG1, respectively.

Binding characteristics of tafasitamab to FcγRs from humans and cynomolgus monkeys were similar, further validating the cynomolgus monkey as the appropriate non-clinical species for evaluation of the

pharmacological and toxicological properties of the enhanced effector function properties of tafasitamab. Finally, tafasitamab binds with substantially greater affinity to mouse FcγRs compared to the native human IgG1 antibody. Hence, human xenograft mouse tumour models allow for testing of the anti-tumour efficacy of tafasitamab in vivo.

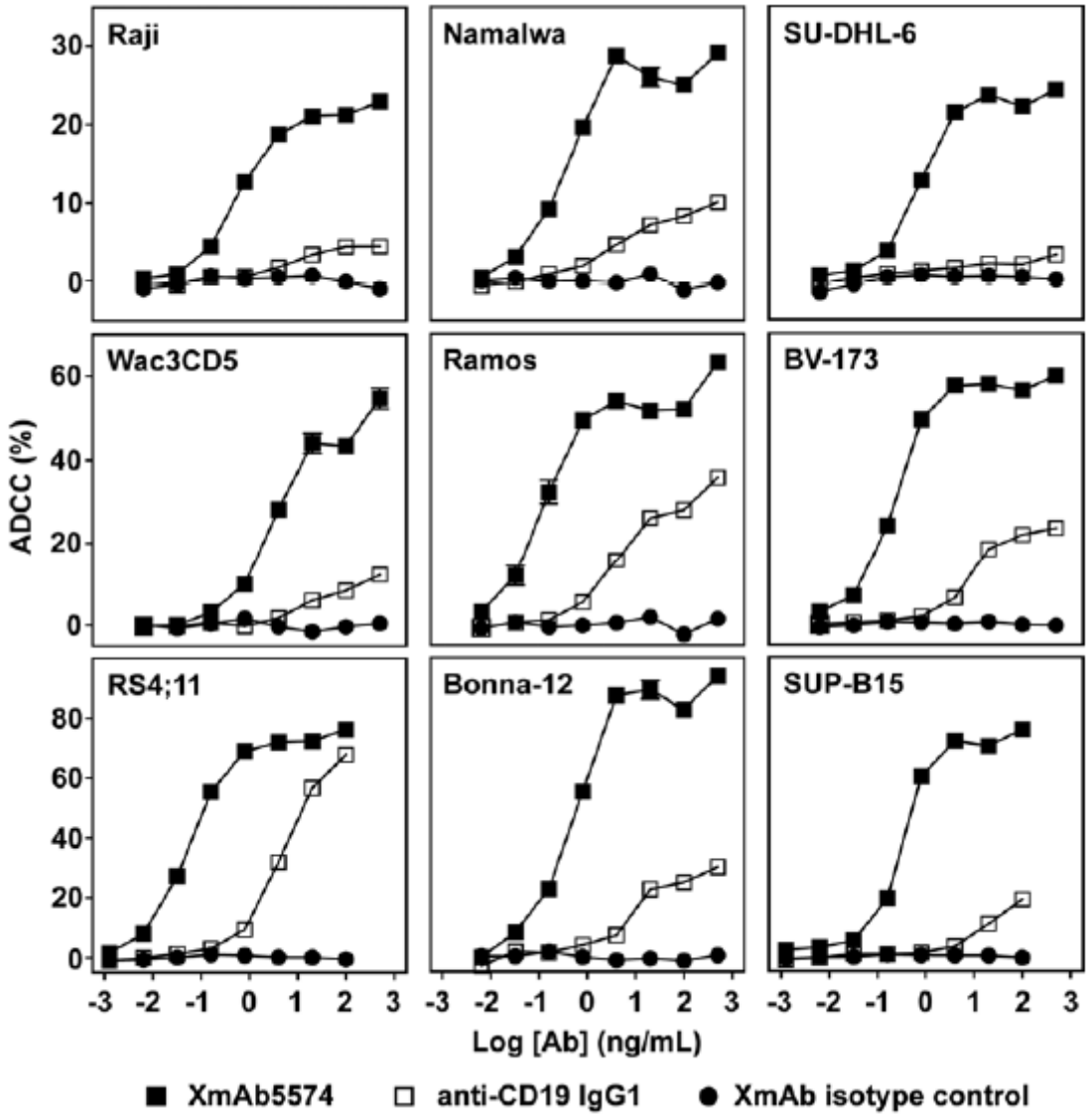
Table 3: Binding affinities of XmAb5574, native IgG1, Fc-KO antibodies to human, cyno, and murine FcγRs.

Receptor	Native IgG1		XmAb5574	
	K_D (M)	SD	K_D (M)	SD
Human FcγRI	3.3×10^{-10}	1.8×10^{-11}	1.4×10^{-10}	1.6×10^{-11}
Human H131 FcγRIIa	8.7×10^{-07}	1.1×10^{-07}	1.6×10^{-07}	8.5×10^{-09}
Human R131 FcγRIIa	8.5×10^{-07}	4.2×10^{-08}	7.5×10^{-08}	4.2×10^{-09}
Human FcγRIIb	1.4×10^{-06}	2.1×10^{-08}	1.1×10^{-07}	1.0×10^{-08}
Human V158 FcγRIIIa	2.2×10^{-07}	1.5×10^{-08}	4.7×10^{-09}	2.5×10^{-10}
Human F158 FcγRIIIa	2.0×10^{-06}	7.1×10^{-09}	1.5×10^{-08}	7.1×10^{-10}
Cyno FcγRI	1.2×10^{-09}	2.3×10^{-10}	3.5×10^{-10}	9.2×10^{-11}
Cyno FcγRIIa	3.9×10^{-06}	5.2×10^{-07}	1.5×10^{-07}	4.9×10^{-09}
Cyno FcγRIIb	1.2×10^{-06}	4.9×10^{-08}	7.6×10^{-08}	5.4×10^{-09}
Cyno FcγRIIIa	1.1×10^{-07}	7.1×10^{-09}	1.9×10^{-09}	9.2×10^{-11}
Murine FcγRI	1.2×10^{-07}	6.5×10^{-09}	2.4×10^{-09}	1.7×10^{-10}
Murine FcγRIIb	1.2×10^{-06}	1.6×10^{-07}	1.1×10^{-07}	2.9×10^{-08}
Murine FcγRIV	3.4×10^{-08}	1.2×10^{-09}	2.3×10^{-10}	9.6×10^{-11}

Mode of Action: ADCC, ADCP and Direct Cytotoxicity (Apoptosis)

The Fc-mediated effector function properties of tafasitamab were evaluated using *in vitro* cell-based assays with isolated human NK cells (TR08139), gamma delta T cells (MOR208L029) or macrophages (TR08139) as effector cells. Tumour cell lines tested included Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), chronic myeloid leukemia (CML), diffuse large B cell lymphoma (DLBCL) and acute lymphoblastic leukemia (ALL), all of which expressed varying levels of CD19 antigen ranging from 15,000 to 105,000 molecules/cell.

Figure 1: ADCC activity of XmAb5574 against multiple tumour cell lines

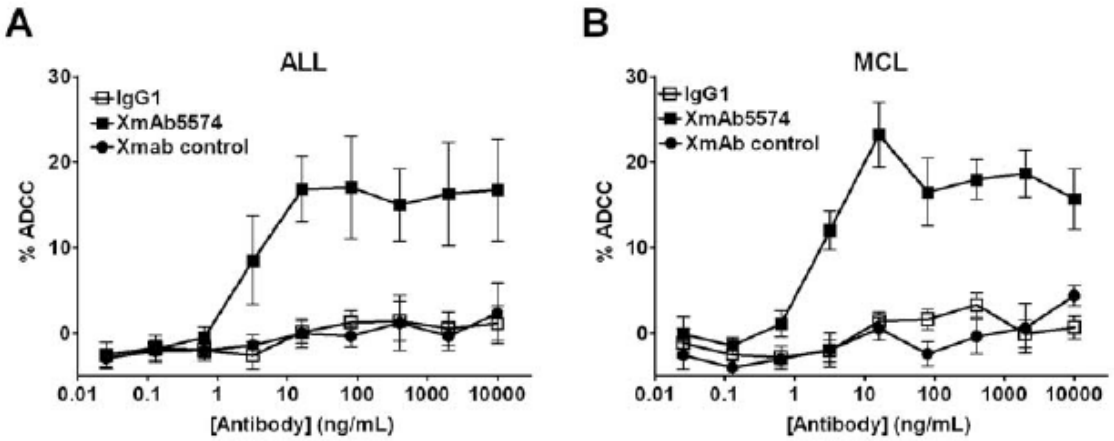


ADCC was measured with an LDH release assay using purified IL-2-activated NK cells as effectors and nine lymphoma or leukemia cell lines as targets. The target cell lines used and the corresponding number of CD19 molecules/cell (in parentheses) were as follows: Burkitt's Lymphoma: Raji (105,000), Namalwa (37,000), Ramos (56,000); DLBCL: SU-DHL-6 (15,000); CLL: Wac3CD5 (38,000); CML: BV- 173 (80,000); ALL: RS4;11 (43,000), SUP-B15 (49,000); HCL: Bonna-12 (29,000). Target cells were opsonised with antibodies and mixed with NK cells at a cell ratio of 1:5; LDH release was measured 4 hours later. Data were obtained in triplicate; error bars indicate standard deviations (SD).

Tafasitamab mediates potent ADCC against CD19 expressing tumour cell lines as well as primary ALL, MCL and CLL cells. Furthermore, tafasitamab mediates potent ADCP of CD19 expressing tumour cell

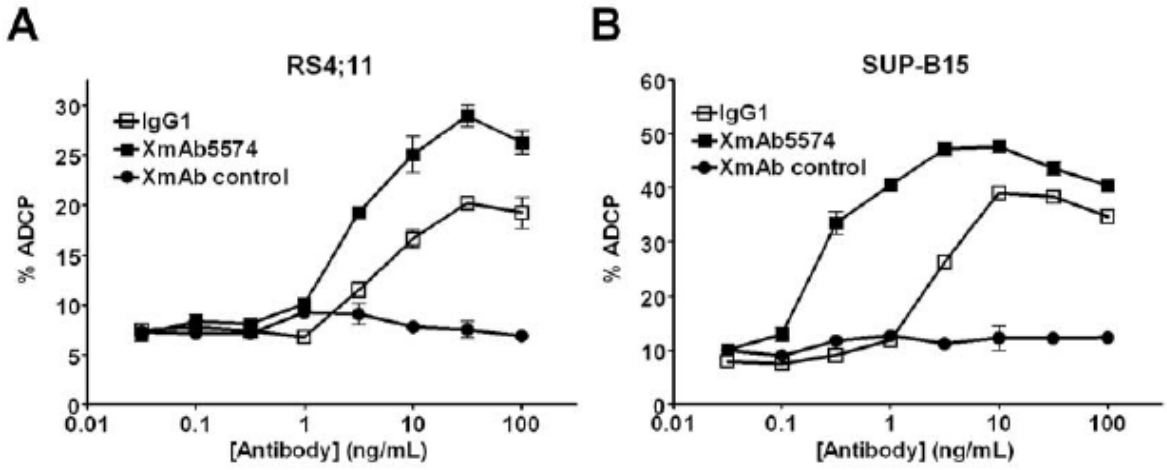
lines. The Fc engineering of tafasitamab resulted in significant increases in ADCC and ADCP activity relative to the native IgG1 control antibody leading to increased potency as well as maximal cell killing.

Figure 2: ADCC activity of XmAb5574 against primary tumour cells



Target primary tumour cells were obtained from patients with ALL (A) or MCL (B). All samples showed high CD19 expression. Tumour cells were labeled with 51Cr (100 µCi /106 cells), opsonized with antibodies, and mixed with PBMCs at a cell ratio of 1:80 for 4 hours; ADCC was determined using 51Cr release. Shown are averages of three experiments from three different PBMC donors; error bars indicate SD.

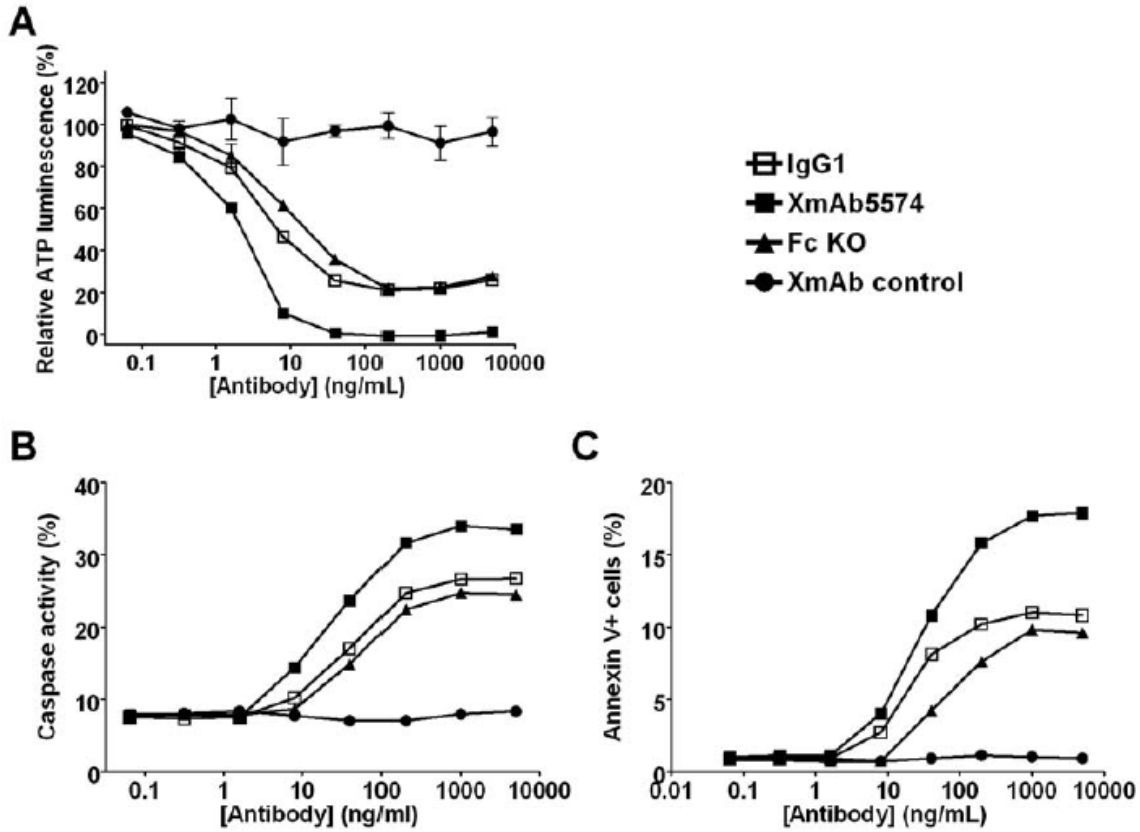
Figure 3: ADCP activity of XmAb5574 against tumour cell lines



ADCP was determined by flow cytometry using RS4;11 (A) or SUP-B15 (B) cells as targets and monocyte-derived macrophages (MDM) as effector cells. % ADCP was calculated as the number of double positive cells divided by the total number of tumour cells. Data were obtained in triplicate; error bars indicate SD.

In addition, tafasitamab exhibits direct cytotoxic and antiproliferative effects mediated by caspase-induced apoptosis (TR08138). Induction of apoptosis in B cell non-Hodgkin lymphoma SU-DHL-6 cells was demonstrated by annexin V staining and caspase activation. The increased antiproliferative activity of tafasitamab relative to the unmodified IgG1 analog in a FcγR crosslinking assay format, suggests a role of the optimised Fc binding to FcγRs in mediating this effect.

Figure 4: Anti-proliferative and caspase-mediated apoptosis activity of XmAb5574 against CD19+ tumour cells



Studies were performed on SU-DHL-6 cells using a human FcRIIIa-GST fusion receptor to provide antibody crosslinking. A, proliferation assay: cross-linked antibodies were incubated with 6·103 cells for 72 hours, and cell titres were analysed using a luminescent cell viability assay. Data were obtained in triplicate; error bars indicate SD. B and C, apoptosis was assayed using caspase activation (B) and annexin V staining (C). Cross-linked antibodies were incubated with SU-DHL-6 cells for 48 h. Caspase activity was quantitated using a fluorometric assay. For the annexin V assay, cells were labeled with annexin V-PE and 7-amino-actinomycin D, and fluorescence was analysed by flow cytometry. For both B and C, data are from a single experiment.

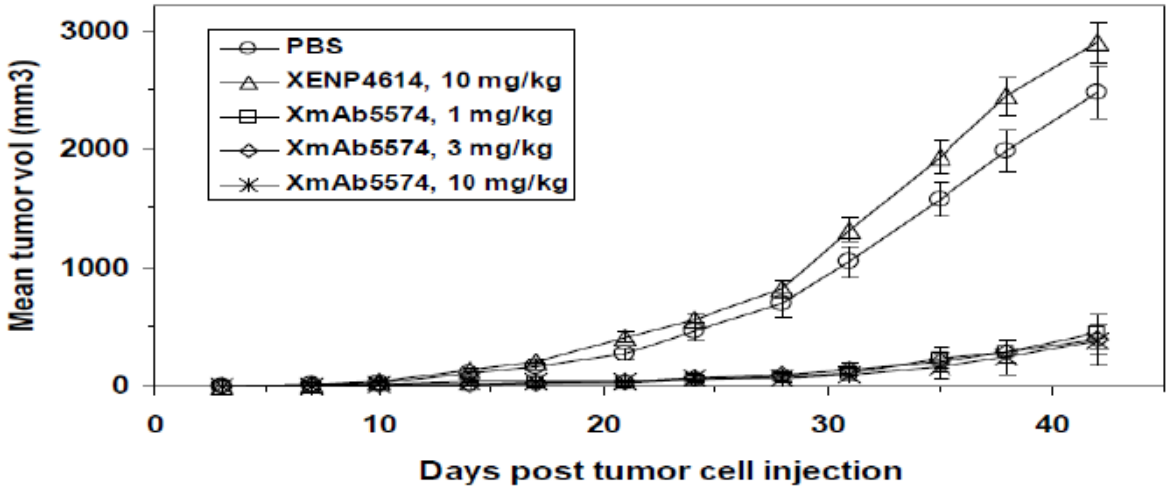
Moreover, it was shown that γδ T cells can act as an additional effector cell population to NK cells and macrophages in antibody-mediated tumour cell lysis (MOR208L029). Tafasitamab demonstrated ADCC activity mediated by γδ T cells towards several lymphoma and leukemia cell lines as well as primary patient-derived CLL, MCL and B-ALL cells. Tafasitamab activity was distinctly enhanced compared to the IgG1 analog.

Tafasitamab does not induce CDC activity against any of the tested B cell lymphoma cell lines (TR08139).

In Vivo Anti-tumour Efficacy of Tafasitamab in SCID Mice Bearing Subcutaneously Implanted Human Raji and RAMOS Lymphoma

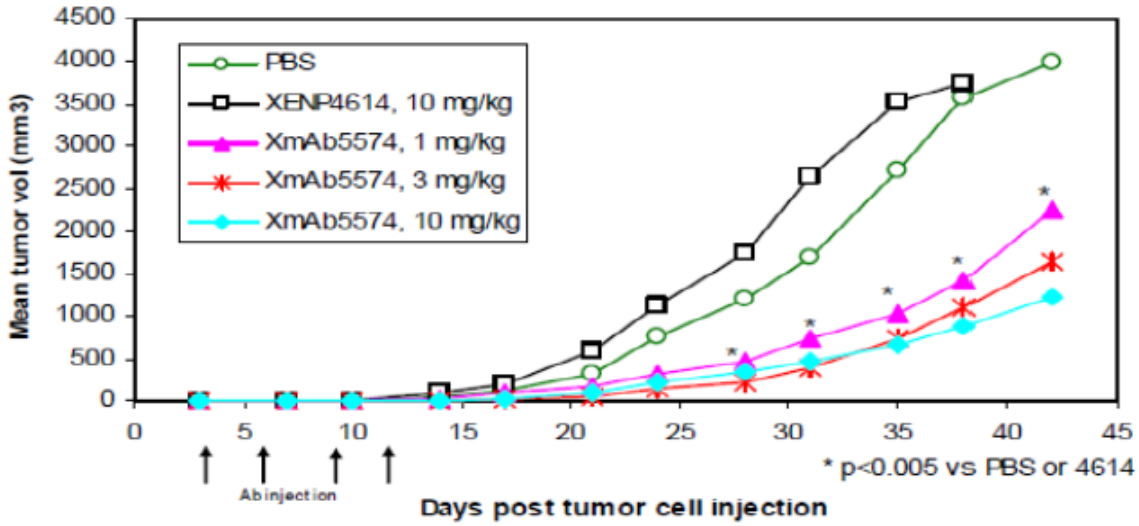
The in vivo efficacy of tafasitamab was evaluated using subcutaneous xenograft models in SCID mice engrafted with human Burkitt's lymphoma Raji or RAMOS cells. Mice bearing s.c. injected Raji tumour cells and treated with 1, 3 or 10 mg/kg tafasitamab (intraperitoneal (i.p.) injection on Days 3, 6, 10 and 13 after tumour cell inoculation) exhibited a statistically significant reduction in tumour growth compared to phosphate buffered saline (PBS) vehicle treatment. In addition, 33% (2/6) of mice in the 10 mg/kg tafasitamab-treated group were tumour free at Day 42 after injection of tumour cells (XC9-05407).

Figure 5: Anti-tumour efficacy of tafasitamab (XmAb5574) in SCID mice with subcutaneous Raji cell xenografts from study XC9-05407



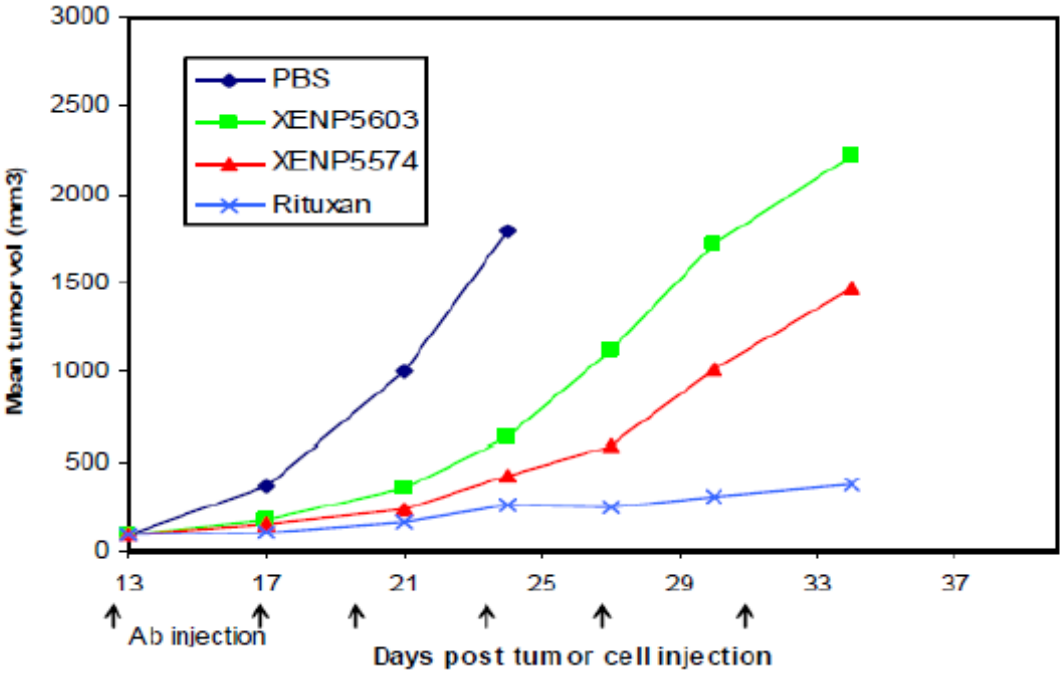
Furthermore, mice bearing established s.c. RAMOS tumours were treated with 10 mg/kg tafasitamab (i.p. twice per week for 3 weeks) and exhibited a statistically significant reduction in tumour growth compared to treatment with PBS vehicle and an unmodified IgG1 (XC9-05607).

Figure 6: Anti-tumour efficacy of tafasitamab (XmAb5574) in SCID Mice Bearing s.c. RAMOS xenografts from Study XC9-05607



Efficacy of tafasitamab was compared to rituximab in a similar study in SCID mice bearing subcutaneously implanted human Ramos lymphoma. Tumour growth inhibition increased in the order of rituximab > tafasitamab > XENP5603 > PBS.

Figure 7: Tumour growth of mice bearing s.c. RAMOS lymphoma and treated with 10 mg/kg tafasitamab (XmAb5574), XENP5603 or rituximab (Rituxan) from study XC9-10008



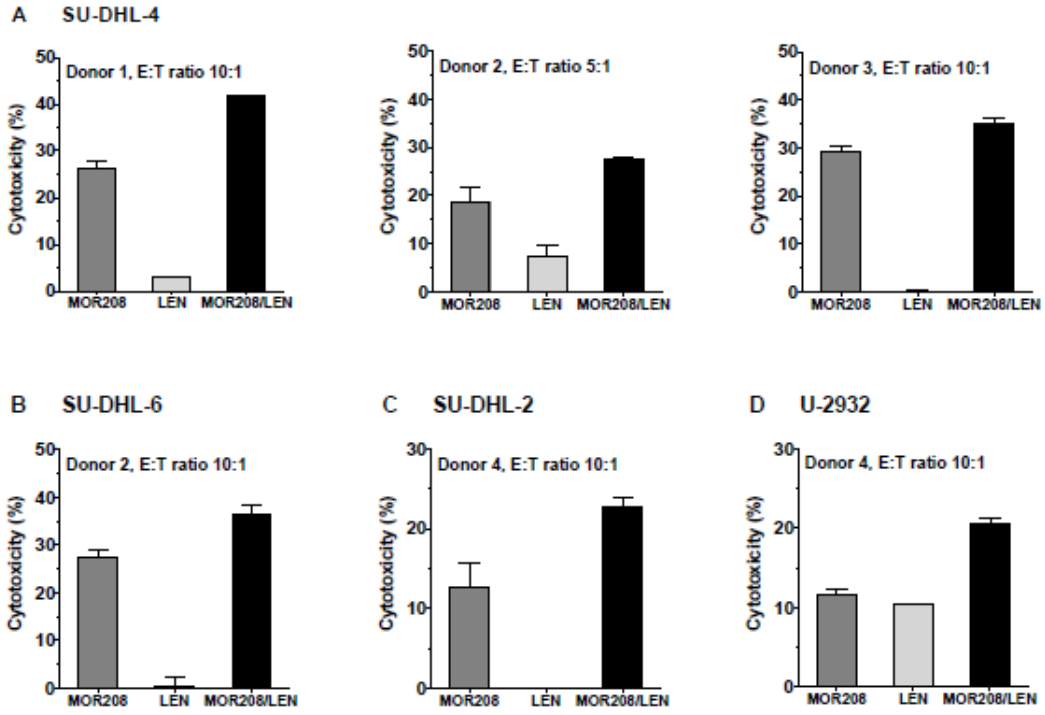
In summary, statistically significant reductions in tumour growth were observed in tafasitamab treated SCID mice engrafted with CD19 expressing human lymphomas.

Combination with lenalidomide

The combination of tafasitamab with the immunomodulatory drug lenalidomide was investigated for enhanced antitumour activity. Lenalidomide activates T cells to release the cytokines interferon gamma (IFN-γ) and interleukin-2 (IL-2), which stimulate NK cell activity and induce an increase in NK cell numbers (Kotla et al., 2009; Gribben et al., 2015). In addition, lenalidomide increases NK-cell expression of FcγRIII, the receptor with high-affinity binding to tafasitamab (Lapalombella et al., 2008). The enhancement of tafasitamab-mediated NK-cell activation and ADCC activity by lenalidomide was demonstrated in previously published *in vitro* experiments (Awan et al., 2010).

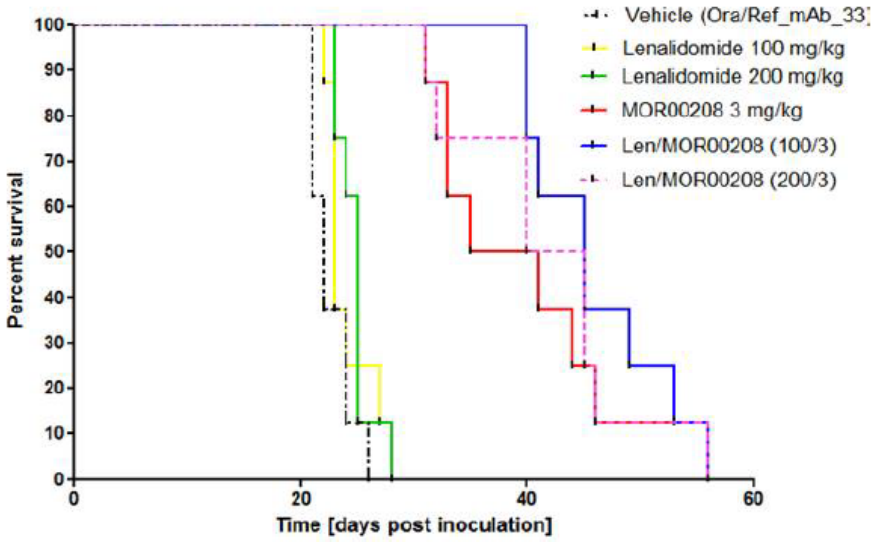
The combination of tafasitamab with lenalidomide was evaluated with several DLBCL cell lines *in vitro* and in a disseminated RAMOS lymphoma model in vivo. Human peripheral blood mononuclear cells (PBMC) were incubated with lenalidomide and used as effector cells in cytotoxicity assays with tafasitamab and SU-DHL-2, SU-DHL-4, SU-DHL-6 and U2392 DLCBL derived tumour cell lines. The combination of tafasitamab with lenalidomide treated PBMCs from various healthy donors resulted in ADCC enhancement of tafasitamab in cytotoxicity assays with all tested DLBCL cell lines (MOR208L039). These data are in line with the described mode of action of lenalidomide as an activator of NK cells (Kotla et al.; 2009, Gribben et al., 2015), as NK cells are the main effector cell population in PBMC mediated ADCC assays.

Figure 8: PBMC mediated cytotoxicity of tafasitamab (MOR208) alone or in combination with lenalidomide (LEN) against SU-DHL-4, SUDHL- 6, SU-DHL-2 and U-2932 cells (MOR208L039)



Tafasitamab and lenalidomide combination therapy was also investigated in a disseminated RAMOS non-Hodgkin lymphoma survival model. Lenalidomide (100 or 200 mg/kg) was administered p.o. for 28 consecutive days and tafasitamab (3 mg/kg) was administered i.v. twice weekly for three weeks. The combination of tafasitamab and lenalidomide resulted in increased anti-tumour activity compared to both monotherapy regimens in vivo (MOR208P009). These findings support combination treatment of CD19 positive tumours with the Fc-domain engineered antibody tafasitamab and the NK cell activating drug lenalidomide. Due to their complementary modes of action, the two drugs act cooperatively against tumour cells expressing CD19.

Figure 9: Effect on tumour growth of Tafasitamab (MOR00208) in combination with lenalidomide as compared to either monotherapy in an i.v. RAMOS SCID mouse model (MOR208P009)



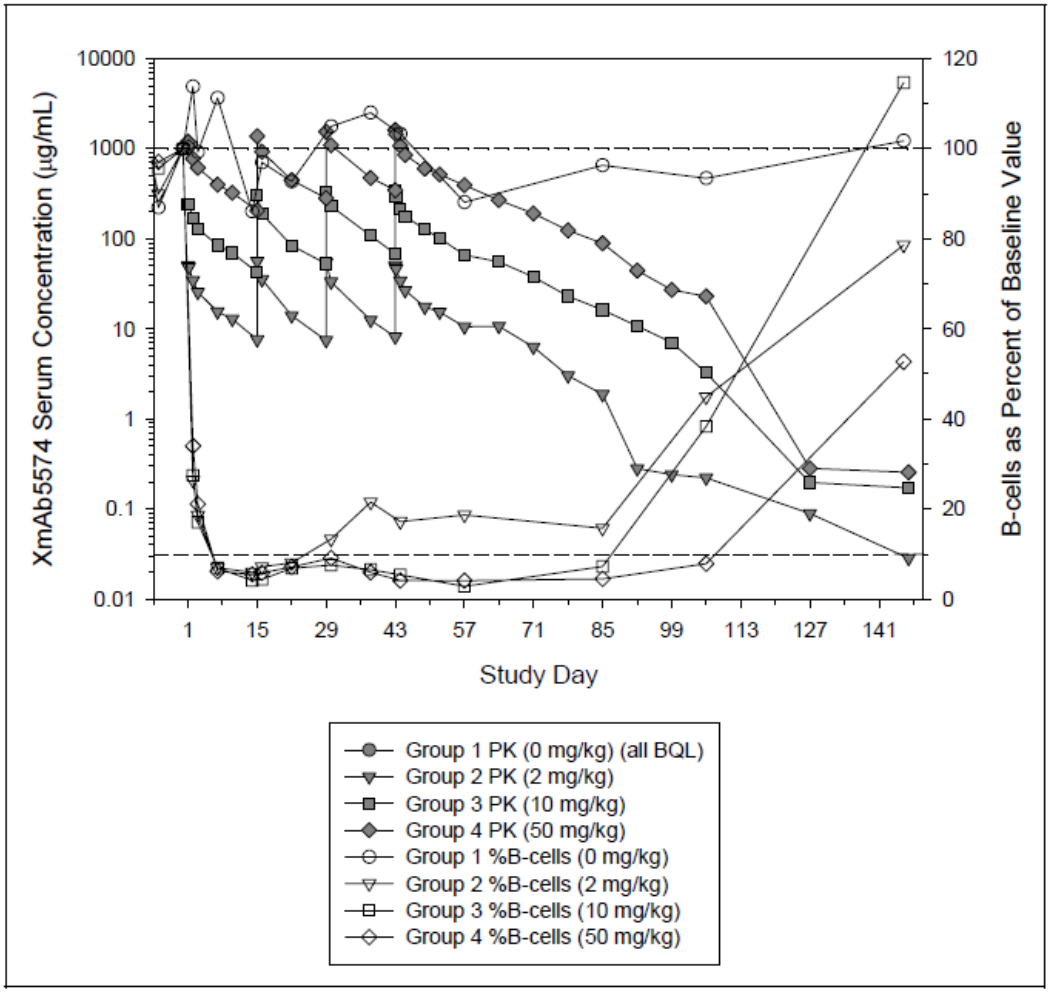
Secondary pharmacodynamic studies

Effects on B-lymphocytes were investigated in an 8-week toxicity study of tafasitamab administered i.v. every two weeks (XC9-14408) and a 13-week toxicity study of tafasitamab administered weekly (MOR208P008).

Effects on Lymphocyte Populations in Peripheral Blood; 'An 8-Week Toxicity Study of XmAb5574 Administered by Intravenous Infusion Every Two Weeks to Cynomolgus Monkeys, with a 90-Day Recovery Period'

Changes in the lymphocyte subsets including T-, B-, and NK-cells in peripheral blood of cynomolgus monkeys were assessed in response to tafasitamab administered as an i.v. infusion at doses of 2, 10, or 50 mg/kg every two weeks for 8 weeks in cynomolgus monkeys (XC9-14408). Tafasitamab substantially depleted total B-lymphocyte (CD3-CD20+) in the peripheral blood of treated cynomolgus monkeys. The CD3-CD20+ cell population decreased on Day 2 in the peripheral blood and then remained at a decreased level for the remaining study time points during the dosing phase. By the end of the 90-day recovery period on Day 146, B-lymphocytes recovered to 79% and 115% of baseline levels for the 2 mg/kg and 10 mg/kg dose groups), while only a 53% recovery was observed in the 50 mg/kg dose group.

Figure 10: Plots of mean tafasitamab serum concentration and mean B-cells (CD3-CD20+) as percent of baseline absolute counts versus time for all animals. 5M/5F animals to day 57, thereafter 2M/2F animals to day 147 in study XC9-14408

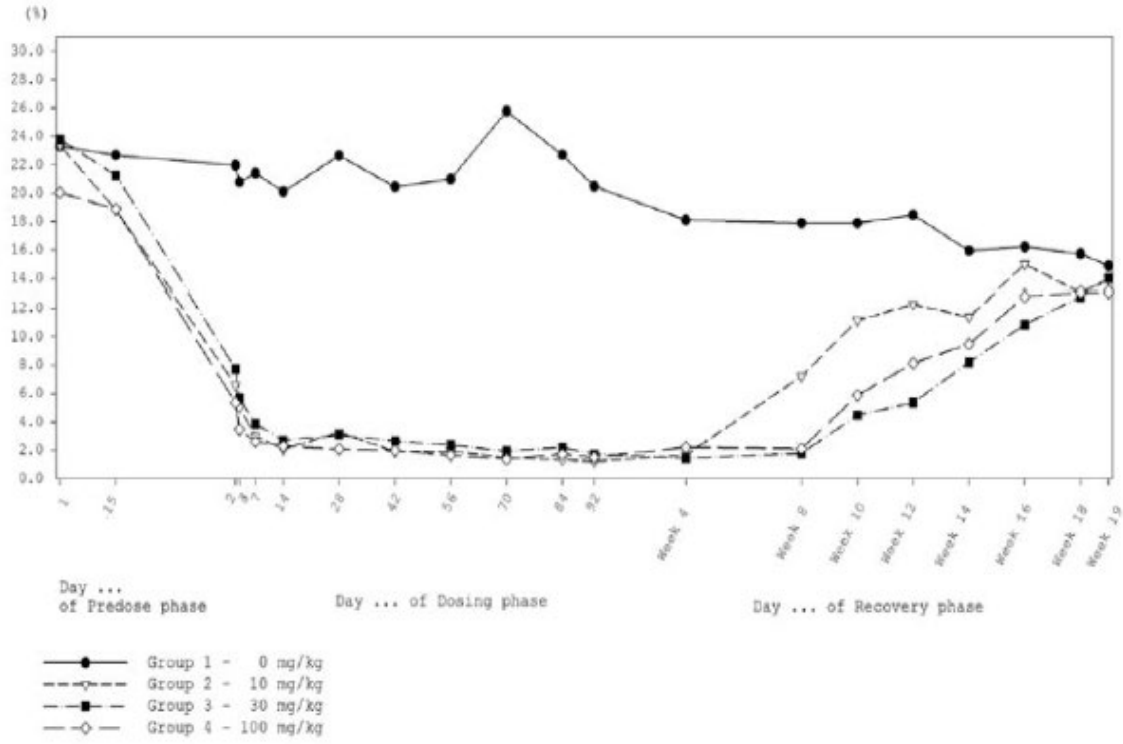


A measurable decrease in NK cells (CD3-CD20-) was observed at the first post-treatment time point for all groups (including the vehicle group) with recovery towards baseline in between treatments. No change in absolute counts of T-lymphocytes was observed, the relative percent increase of T-lymphocytes during dosing was reflective of the concurrent elimination of the B-lymphocytes.

Evaluation of Effects on Lymphocyte Populations in Peripheral Blood from '13-Week Intravenous Infusion Toxicity Study in the Cynomolgus Monkey with a 132 Day Recovery Period' (MOR208P008)

Changes in lymphocyte subsets including T-, B-, and Natural Killer (NK) cells in peripheral blood of cynomolgus monkeys were assessed in response to tafasitamab administered as an i.v. infusion every week at dose levels of 10, 30 and 100 mg/kg for 13 weeks with a 132-day recovery (MOR208P008). Consistent with slightly reduced lymphocyte counts, a tafasitamab-induced reduction of CD20+ B cells was observed at all dose levels in both sexes. There were only minor differences between the dose levels and a distinct decrease was observed within the first two weeks of treatment which persisted until the end of the treatment period. A gradual recovery of the depleted B cell populations was observed following the end of active tafasitamab treatment. By Week 19 of the recovery period, B cell counts reached the range of the control group. Consistent with B cell depletion observed in peripheral blood, a reduction in B cells in bone marrow, spleen and inguinal lymph nodes was noted in all dose groups. Partial to complete recovery was observed at the end of the recovery period. Peripheral CD20+ B cell counts were reduced throughout the treatment period. The B cell depletion effect was reversible within the recovery period.

Figure 11: B lymphocytes counts (CD3-CD20+) from females in study MOR208P008



Safety pharmacology programme

No stand-alone safety pharmacology studies were performed. Monitoring of safety pharmacology parameters for vital organ functions (cardiovascular, respiratory and central nervous system) was incorporated into the 8-week and 13-week repeat-dose toxicology studies in cynomolgus monkeys (XC9-14408 and MOR208P008), in accordance with guidance provided in ICH S6(R1), ICH S9 and ICH S7a.

In the *'8-Week Toxicity Study of XmAb5574 Administered by Intravenous Infusion Every Two Weeks to Cynomolgus Monkeys, with a 90-Day Recovery Period' (XC9-14408), a*ll the electrocardiograms were qualitatively and quantitatively interpreted and within normal limits. No arrhythmias were found. All the electrocardiograms evaluated in this study were considered normal for cynomolgus monkeys. No abnormalities in rhythm were found. There were no abnormal electrocardiographic findings attributable to the administration of tafasitamab at doses up to 50 mg/kg.

In the *'13-Week Intravenous Infusion Toxicity Study in the Cynomolgus Monkey with a 132 Day Recovery Period' (MOR208P008)'* there was no electrocardiographic evidence of cardiotoxicity or arrhythmogenesis. Minor changes in the individual recordings did not show a trend and are most likely explained by random changes in the surface electrocardiographic parameters over time and by the normal limitations of analysis accuracy. Evaluation of blood pressure yielded normal variations, no tafasitamab treatment-related effect was observed. The respiratory rates remained within the normal limit of variation for manually restrained animals. There was no tafasitamab-related effect on neurobehavioral endpoints during the study. Although, statistical analysis revealed significant differences when compared to control, the body temperature variation of tafasitamab-treated animals was generally in the normal range of variation for this species.

Tafasitamab treatment at doses up to 100 mg/kg/week (iv) in cynomolgus monkeys had no effect on neurobehavioral function, body temperature, blood pressure, respiratory rate or electrocardiography.

Pharmacodynamic drug interactions

The efficacy of tafasitamab in combination with other anti-cancer therapeutics has been studied. No other pharmacodynamic drug interaction studies were performed.

2.3.3. Pharmacokinetics

Methods of analysis

The bioanalytical programme of tafasitamab employed two different platforms, ELISA and ECLA for both tafasitamab and antidrug antibodies against tafasitamab. Bioanalytical and antidrug antibody methods were validated and qualified when used in non-GLP studies in non-clinical studies. Bioanalytical methods used in the pivotal repeat-dose toxicity studies were validated according to current guidelines under QA audit programs and were GLP-compliant.

For the 13-week toxicity study the quantitative ECLA bioanalytical method and the antidrug antibody ECLA method appeared to be robust and well-suited for purpose. Bioanalytical method validation included dilution integrity and up to one-year stability at both -20 and -80°C. Free drug interference was determined for the anti-tafasitamab assay. At 75.0 ng/mL and 5000 ng/mL of cynomolgus anti-tafasitamab antibodies, addition of 5 µg/mL and 50 µg/mL of tafasitamab, respectively, still resulted in a positive response.

ISR was evaluated in the 13-week study (MOR208P008). A total of 91.54% of tafasitamab ISR results (130 samples) were within the predefined acceptance criteria, demonstrating the accuracy of the analytical method.

The bioanalytical ELISA method and the anti-tafasitamab antibody ECLA assay employed in the 8-week study (XC9-14408 conducted in 2008/2009) was validated in compliance with GLP. Stability of tafasitamab in serum was demonstrated for more than 500 days at -70°C. Free drug interference of the anti-tafasitamab antibody assay was as follows: At both 60 ng/mL and 2000 ng/mL of anti-tafasitamab antibody positive control antibody, the assay tolerates 50.0 µg/mL of tafasitamab and still results in a

positive signal. Addition of 500 µg/mL of tafasitamab results in the signal of both the 60 and 2000 ng/mL positive controls dropping below the cut point.

A metabolite/degradation product without biological activity was also captured by the bioanalytical methods. However, after a thorough investigation, it was concluded that the impact on the general pharmacokinetic assessments in non-clinical studies during the dosing phases was limited.

In bioanalytical reporting of tafasitamab serum/plasma concentrations, the unit of ng/mL was used consistently. In pharmacokinetic evaluations, e.g. Cmax was generally reported in µg/mL.

Single dose studies

The pharmacokinetics of a single dose of tafasitamab was evaluated in NMRI mice. The dose of 15 mg/kg was administered i.v. or i.p. I.p. administration showed almost 100% bioavailability and terminal half-life of 6.4 hours. This route was used in several in vivo pharmacology studies in SCID mice. No PK studies were performed in SCID mice, hence the data obtained in NMRI mice can be considered as a surrogate for proof of exposure. Maximal plasma concentration for 15 mg/kg i.p. administration was in the neighbourhood of 100 µg/mL. PK after 1 mg/kg i.v. could not be properly evaluated, since 2 out of three mice appeared to be dosed extravascular and not intravenous as intended. SCID mice showed effect at doses of 1-10 mg/kg i.v. or i.p. twice weekly in pharmacology studies.

Pharmacokinetics after single dose in monkey was evaluated in three studies at doses in the range of 0.3 to 10 mg/kg of 1-hour infusion. In the first study (XC9-07907, doses 0.3, 1 and 3 mg/kg, N=2), clearance was slightly higher for the 0.3 mg/kg dose indicating target mediated elimination as expected for a monoclonal antibody. ADA induced increased clearance between day 8 and Day 14 in one animal in the low and one animal in the high dose. Otherwise the PK was similar for the 1 and 3 mg/kg doses with clearance of 4.3 to 4.8 mL/day/kg, respectively. Vss of approximately 50 mL/kg was correlating with the serum compartment. Half-life was observed in the range of 7.7 to 9.1 days, which is in the normal range for IgG antibodies in monkeys.

Toxicokinetics

XC9-14408: 8 weeks at 2, 10 and 50 mg/kg/2 weeks (4 doses)

Cynomolgus monkeys were dosed via single 1-hour iv infusion at 0 (control) 2, 10 and 50 mg/kg of tafasitamab every two weeks for a total of four doses. Serum concentrations of tafasitamab were interpreted within the context of the ADA response. Additional whole blood samples were collected for determination of absolute counts of lymphocyte subsets consisting of T-cells (CD3+/CD20-), B-cells (CD3-/CD20+) and NK-cells (CD3-/CD20-). These were compared to tafasitamab serum concentration-time profiles. See Section of Secondary Pharmacodynamics.

A strong anti-drug antibody response was observed in this study. This response was greatest at 2 mg/kg (8 of 10 animals), less at 10 mg/kg (3 of 10 animals) and at 50 mg/kg (3 of 10 animals). There was a relationship between tafasitamab antibody-mediated clearance and decline in tafasitamab concentrations and concomitant recovery of B-cells, especially at the low dose. Therefore, several animals were excluded from PK analysis. Nevertheless, the number of animals were deemed sufficient for proper PK analysis. This is supported.

Tafasitamab TK exposure parameters (Cmax and AUC0-t) were similar in female and male animals, and no obvious gender differences could be determined by comparing serum concentration over time profiles in males and females.

Tafasitamab TK exposure parameters (Cmax and AUC0-56days) were proportional to dose based on linear regression in all animals as well as in ADA-negative animals only.

The clearance of tafasitamab in ADA-negative animals was consistent across dose levels and was approximately 5.2 to 5.5 mL/kg/day. Vss was determined between 74 to 124 mL/kg. Terminal elimination half-life averaged 10.2, 12.4 and 14.2 days at 2, 10 and 50 mg/kg, respectively.

MOR208P008: 13 weeks at 10, 30 and 100 mg/kg/week (13 doses)

Plasma concentrations of MOR00208 were below the lower limit of quantification (BLOQ) in all samples of animals in Group 1 (control) and at pre-dose on Day 1 for all animals in study groups 2-4.

Following the first and repeated weekly intravenous infusions of tafasitamab, Cmax of tafasitamab was reached (tmax) on average at 1.25 to 3.2 h after start of the 1-hour infusion. Dose normalised Cmax and AUC were similar across the dose range and sampling occasions, supporting a direct dose linear relationship between the 3 dose levels tested (10 mg/kg, 30 mg/kg and 100 mg/kg). Following 4, 7, and 13 repeated weekly administrations of tafasitamab, mean maximum concentrations (Cmax) and exposures (AUC0-144h) of tafasitamab were greater than those determined following the first administration.

The mean terminal elimination half-life of tafasitamab, as determined from the recovery phase, were 8.0 to 17.4 days. The mean terminal elimination half-life over all dose groups as determined from the recovery phase was 12.7 days. The average accumulation ratios over all dose levels were 1.5, 1.7 and 1.9, for Cmax after 4, 7 and 13 repeated administrations, respectively, and were 1.7, 2.1 and 2.3 for AUC0-144h. Thus, steady state can be assumed after the 7th dose (Day 43), expected around 4-5 half-lives (12.7*5=64 days).

There was no evidence in the concentration-time profiles to suggest significant anti-tafasitamab antibody formation, which is also supported by the anti-tafasitamab antibody assessments. It should however be mentioned that the high concentrations of tafasitamab in this study may have interfered with the antidrug antibody assay. Nevertheless, there was no signs of increased clearance as a result of antidrug antibody development.

Mean Cmax and AUC0-144h after the 13th dose for animals dosed at 100 mg/kg (NOAEL) were 5220 µg/mL and 449000 µg/mL*h and 3970 µg/mL and 333000 µg/mL*h for males and females, respectively. The sex ratio (male/female) for mean Cmax ranged from 1.1 to 1.4 and, for mean AUC0-144h, ranged from 1.1 to 1.4, i.e. males showed on average a slightly higher maximal plasma concentration and exposure than females.

Safety margins of 7.9-fold to patient exposure were calculated based on AUC0-144 h at steady state for cynomolgus monkeys and NHL patients. For Cmax, a 9.4-fold higher value was estimated in cynomolgus monkeys compared to NHL patients at steady state.

Distribution

No dedicated studies have been performed to investigate the in vivo tissue distribution of tafasitamab in animals. Tafasitamab exhibited a volume of distribution at steady state (Vss) between 52.6 mL/kg and 124.3 mL/kg across studies, indicating distribution between plasma volume and extracellular Volume.

Protein Binding

No plasma protein binding studies were performed with tafasitamab (see discussion on non-clinical aspects).

Metabolism

No metabolism studies were performed (see discussion on non-clinical aspects).

Excretion

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

Pharmacokinetic drug interactions

No dedicated non-clinical drug interaction study has been performed with tafasitamab (see discussion on non-clinical aspects).

2.3.4. Toxicology

The toxicological profile of tafasitamab has been evaluated in non-clinical studies in agreement with relevant guidelines. The toxicity studies were conducted in cynomolgus monkeys (Macaca fascicularis), as a tafasitamab cross-reactivity study with lymphocytes of various species concluded that the antibody recognised CD19 from human and macaques, but not from common laboratory animals such as mouse, rat, rabbit or dog (XC9-23209). Therefore, the cynomolgus monkey was selected as the relevant species for safety and toxicology assessment of tafasitamab.

Toxicology studies of tafasitamab in cynomolgus monkeys include three non-GLP single dose pharmacodynamic/pharmacokinetic/toxicity studies (XC9-07907, XC9-08007, XC9-05707), and two GLP compliant repeat-dose toxicity studies: an 8-week study of repeated i.v. tafasitamab administration every two weeks with a 90-day recovery period (XC9-14408) and a 13-week study of repeated weekly i.v. tafasitamab administrations with a 132-day recovery period (MOR208P008). Local tolerance was assessed as a part of the 13-week repeat-dose study (MOR208P008) and no evidence of local irritation or other adverse effects was noted at the administration site. Additionally, tissue cross-reactivity studies in tissue panels from healthy humans (XC9-17208a) and cynomolgus monkeys (XC9-17208b) were evaluated to identify possible target tissues for tafasitamab binding. No studies on genotoxicity, carcinogenicity or reproduction and developmental toxicity have been conducted.

All general toxicology studies performed used the intended route for human use (i.e., intravenous administration via infusion) and included concomitant toxicokinetics (which was assessed in detail in the pharmacokinetic section of the assessment report).

Single-dose toxicity

Three non-GLP tafasitamab single-dose i.v. infusion studies with doses ranging from 0.3 to 10 mg/kg were conducted in cynomolgus monkeys (XC9-07907, XC9-08007, XC9-05707). Tafasitamab caused depletion of B-lymphocytes at all doses. At the highest dose tested (10 mg/kg), depletion of B-lymphocytes was observed in peripheral blood, spleen, lymph nodes and bone marrow and correlated to histopathological findings of reduced germinal centre size with decreased immunohistochemical staining for B-cells. Additionally, a transient decrease in NK-cells were noted, which could theoretically have an impact on tafasitamab mediated B-cell lysis.

Tafasitamab was well tolerated within the examined dose range and beside the above-mentioned B-cell depletion, which is considered to be within the anticipated pharmacological effect, no adverse effects were observed. However, when assessing the three single-dose studies, it appears like the studies primarily were conducted to estimate dose ranges and to examine pharmacodynamic/pharmacokinetic

effects of tafasitamab. Evaluation of toxicity in the single-dose studies seemed more secondary, as the selected dose range with a maximum dose of 10 mg/kg (corresponding to a HED of 3.2 mg/kg*), were lower than the intended clinical dose of 12 mg/kg. Additionally, systemic exposure measured by C_{max} in the monkeys was approximately half that observed in humans (294 ± 23.9 µg/mL in monkeys versus 547.4 µg/mL in humans in the MOR208C201 study). As single dose toxicity studies are not required (as per guideline), the lack of any safety margins to the clinical dose is acceptable. However, the observed lack of toxicity cannot be reassuring for the clinical setting, as toxicologically relevant exposure has not been achieved in these studies.

Repeat-dose toxicity

Two GLP compliant tafasitamab repeat-dose toxicity studies were conducted in cynomolgus monkeys.

In the 8-week study (XC9-14408), doses of 2, 10 and 50 mg/kg tafasitamab was administered by i.v. infusion once every two weeks for 8 weeks i.e. a total of 4 consecutive doses. A recovery period of 90-days was included for 2/5 animals of each sex per treatment group.

Tafasitamab was well tolerated at all doses and the NOAEL were therefore determined to be 50 mg/kg. As an anticipated pharmacological effect, a marked decrease in B-lymphocytes (CD3-CD20$^+$) in peripheral blood were noted at all dose levels and corresponded with histopathological findings of reduced cellularity of germinal centres in the spleen. A tendency toward a gender specific increase in incidence, severity and splenic weight were seen in males in the 8-week study but was not observed in the 13-week study. Furthermore, the decrease in absolute and relative splenic weights noted in the terminal male animals in the 8-week study, appeared to be driven by an extraordinarily high splenic weight in one of the control males. The B-lymphocytes in the peripheral blood and the splenic changes were additionally, reversed in most animals at the end of the 90-day recovery period. The onset of the recovery in peripheral blood was dose-dependent.

Findings of decrease in neutrophilic granulocytes and/or platelets were noted in approximately half the monkeys in the two highest dose groups (10 and 50 mg/kg). The findings could, however, not be related to any other findings (e.g. haemorrhages) or changes in clinical pathology parameters. In the second repeat-dose toxicity study (MOR208P008), dose of 10, 30 and 100 mg/kg tafasitamab was administered by i.v. infusion to sexually mature male and female cynomolgus monkeys once weekly for 13 weeks. A recovery period of 19 weeks was included for two males and two females from each group to evaluate the reversibility of the findings. The 13-week repeat-dose toxicity study was performed with clinical trial material (test article) from the commercial formulation (40 mg/mL of tafasitamab, 25mM citrate buffer, 200mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0). Therefore, the local tolerance assessment included in this study is considered supportive for the commercial formulation.

No adverse effects were noted, and the NOAEL was determined to be 100 mg/kg (the highest dose tested). However, findings of anticipated pharmacological effect were observed and correlated well with the findings from the previous repeat-dose study. A decreased peripheral CD20$^+$ B-lymphocyte count at all dose levels indicated according to the applicant a complete CD19-saturation even at the lowest dose tested (10 mg/kg). The findings correlated with reduced IgG concentration in serum and a reduction in primary and secondary antibody response to keyhole limpet haemocyanin (KLH) and tetanus toxoid (TT) respectively, in an assessment of the T-cell dependent antibody response (TDAR). Additionally, the effect of tafasitamab on B-cells was seen histopathologically as a decrease in cellularity of germinal centres in lymphoid follicles in spleen and lymph nodes in all dose group with no clear dose-dependency and varying frequency between groups. Recovery of all B-cell related changes were observed during the treatment free recovery period.

The effect of tafasitamab on reproductive endpoints (i.e. effect on menstrual length and histopathology of male and female reproductive organs), revealed no changes in the monkeys under the conditions of the current study.

The clinical treatment regimen of tafasitamab changes throughout the treatment period, with the first three cycles being administered once weekly (except for cycle 1, where infusions are administered on day 1, 4, 8, 15 and 22 of the cycle), followed by the cycle 4 with treatments every two weeks. The 13-week study (MOR208P008) were in line with the ICH S9 requirements of a study of minimum 3 months duration following the intended clinical treatment schedule, which in this case is once weekly for the majority of times in the first 3 cycles. The treatment schedule of the 8-week study (XC9-14408) was more aligned with cycle 4 treatments (every second week).

Slight tremor occurred occasionally in some animals of all treatment groups including controls and severe body tremor was find in one animal in the high dose group.

In both repeat-dose studies and in the single-dose studies an effect of NK-cells was noted, as a transient decrease.

In the 8-week repeat-dose study (XC9-14408), an antidrug antibody response was seen in 8/10 animals at 2 mg/kg, 3/10 animals at 10 mg/kg, and 3/10 animals at 50 mg/kg and the findings had an impact on the determination of toxicokinetic parameters in these animals. In contrast, in the 13-week repeat-dose study (MOR208P008), no anti-tafasitamab antibodies were formed. Further elaboration on the observed difference in ADA formation between the 8-week repeat-dose study (XC9-14408) and the 13-week repeat-dose study (MOR208P008) was presented.

Interspecies comparison

The choice of the cynomolgus monkeys as the relevant species for toxicity testing is supported based on the argumentation that no antibody binding was noted to lymphocytes in other common laboratory animal species. It is therefore supported that no studies were conducted in rodents, and this is also in line with ICH S6(R1) and the 3R's.

When comparing animal to human exposure for the determined NOAEL values, safety margins based on AUC values revealed 9.77 to 10.24-fold for the 8-week study and 15.18 to 20.46-fold for the 13 week repeat-dose study.

Genotoxicity and Carcinogenicity

The omission of genotoxicity or carcinogenicity studies was acceptable according to ICH S6(R1) and S9, respectively.

Reproductive and developmental toxicity

No reproductive or developmental toxicity studies were conducted for tafasitamab. No changes were noted by histopathological examination of the male or female reproductive system in the 13-week repeat-dose study (MOR208P008).

Other toxicity studies

Tissue cross-reactivity studies were conducted in respectively a human (XC9-17208a) and a cynomolgus monkey tissue panel (XC9-17208b), in order to assess potential tissue cross-reactivity. In both studies, a positive staining pattern was noted in lymphocytes in the blood, hematopoietic B-cell precursors in the bone marrow and in several tissues, however, always in association to mononuclear leukocytes and lymphocytes. Positive mononuclear leukocytes and lymphocytes were confirmed to be B-cells based on their morphology and/or location (e.g. intravascular or perivascular migrating). Reduced staining intensity were noted in the cynomolgus tissue compared to the human tissue, which is reflected in the

more disseminated staining pattern of mononuclear leukocytes/lymphocytes observed in the human tissue panel.

In conclusion, a positive staining pattern were located to cells with B-lymphocyte morphology as expected and no unexpected tissue cross-reactivity were detected in any of the two studies.

2.3.5. Ecotoxicity/environmental risk assessment

A justification for not providing a full ERA was submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

Pharmacology

Tafasitamab was shown to provide full saturation of CD19 expressed in HEK cells at 14 µg/mL. Tafasitamab is selective for human and monkey CD19 as shown by flow cytometry of PBMCs from various species. Only weak or no binding was observed in dog, rabbit or mouse lymphocytes. Hence, the monkey is qualified as non-clinical testing species.

Tafasitamab is designed to elicit enhanced binding to Fc gamma receptors. Similar binding was shown for human and monkey, however increased binding compared to native IgG in mouse was also shown confirming the mouse as a valid model for in vivo pharmacology testing of tafasitamab treatment of human lymphomas.

Tafasitamab act in cell killing through several mechanisms, namely ADCC, ADCP and direct cytotoxicity, however not through CDC as is the case with e.g. rituximab.

Tafasitamab alone was shown to be efficient in several lymphoma model in the SCID mice. This effect could be increased when administered in combination with lenalidomide also in the SCID mice model.

Hence, non-clinical *in vitro* and in vivo proof of concept of tafasitamab in combination with lenalidomide for the treatment of lymphomas appear established.

The pharmacological effect was also characterised in vivo in the monkey in the single dose PK studies and the repeat-dose toxicology studies in monkeys. The duration of B-cell depletion was dose dependent, however doses down to 2 mg/kg provided immediate depletion of B-cells. It could have been of support of clinical dose setting, if the rich data sets on PK and PD endpoints were used for quantitative PKPD modelling. However, a dose-exposure-response analysis has been done post-hoc on clinical data.

As is acceptable for monoclonal antibodies, the safety pharmacology programme was included in the pivotal repeat-dose toxicity studies. No findings of concern were observed.

Pharmacokinetics

Pharmacokinetics in mice was evaluated in NMRI mice and can be used as surrogate for proof of exposure in the SCID mice models. However, only single dose data was presented, and no modelling of repeat-dose exposure was attempted. This could have provided some sort of reassurance of similarity to human exposure.

Three single dose studies were presented in monkeys. All in all, pharmacokinetic parameters fell out as expected for a monoclonal antibody in monkeys with half-lives in the range of 7.7 to 9.1 days.

Toxicokinetics were thoroughly evaluated in both the 8- and 13-weeks studies. The 8-week study suffered from several monkeys developing antidrug antibodies responsible for increased clearance of

tafasitamab. However, data were still sufficient for proper toxicokinetic evaluation and the results were overall in correlation with toxicokinetics in the 13-weeks study.

There was no evidence in the concentration-time profiles to suggest significant anti-tafasitamab antibody formation in the 13-weeks study, which was also supported by the anti-tafasitamab antibody assessments. It should however be mentioned that the higher concentrations of tafasitamab in this study may have interfered with the antidrug antibody assay. In this study both the level of the high dose and the frequency of dosing was doubled compared to the 8-weeks study. Nevertheless, there was no signs of increased clearance as a result of antidrug antibody development. The incidence of antidrug antibodies in patients was low. Safety margins of 7.9 and 9.4-fold based on steady state $AUC_{0\text{-}144h}$ and C_{max} was presented.

It should be noted that half-life is longer in the repeat-dose studies as compared to the single dose studies in monkeys. This was also observed in humans, however to even more extreme extent as clearance decreased from 0.41 to 0.19 L/day in patients over a period of two years (SmPC section 5.2).

Finally, a critical issue of deamidation of tafasitamab both as a degradant and a metabolite was investigated from a bioanalytical point of view. The deamidated tafasitamab is not biologically active, but was captured by the ECLA method, hence a bioactivity assay had to be developed. It was concluded that during the dosing phases, there were no difference between the two assays. The difference was however evident in the recovery phase. A PK model was developed based on the obtained data and used for simulating the impact on human PK. In the next round of assessment, a clear justification regarding the deamidation of tafasitamab and its potential impact on safety and efficacy was provided.

Toxicology

The toxicological profile of tafasitamab was characterised in three non-GLP single-dose studies (XC9-07907, XC9-08007, XC9-05707), in an 8-week repeat-dose study with biweekly i.v. infusions (XC9-14408) and in a 13-week repeat-dose study with weekly i.v. infusions (MOR208P008). The studies were all conducted in cynomolgus monkeys (*Macaca fascicularis*), due to lack of tafasitamab antibody binding to lymphocytes in other common laboratory animal species.

In general, tafasitamab was well tolerated in single-dose studies up to 10 mg/kg and in repeat-dose studies up to 100 mg/kg, supporting the NOAEL of 100 mg/kg determined based on the 13-week repeat-dose study. Except for an anticipated pharmacological effect on B-lymphocytes, no adverse effects were noted. Sufficient safety margins of 9.77 to 20.46-fold to clinical exposure were seen for the NOAELs from the repeat-dose toxicity studies, whereas, no safety margins existed for the single-dose studies. As single dose toxicity studies are not required (per guideline), the lack of any safety margins to the clinical dose is acceptable. However, the observed lack of toxicity cannot be reassuring for the clinical setting, as toxicologically relevant exposure has not been achieved in these studies.

B-cell depletion was seen at all doses tested, even at the lowest single-dose of 0.3 mg/kg. At higher doses, B-cell depletion was observed in peripheral blood, spleen, lymph nodes and bone marrow in both single-dose and repeat-dose toxicity studies. The findings correlated to histopathological evidence of reduced cellularity in the germinal centres and decreased immunohistochemical staining of B-cells. The findings of B-cell depletion were, however, reversible in most animals within the predefined recovery periods.

A concern was raised on the observations of slight tremor occurring occasionally in some animals of all treatment groups including controls in addition to severe body tremor detected in one animal in the high dose group. A justification concerning the potential mechanism of action of tafasitamab explaining the slight tremor was provided. Overall, the effect was judged to be related to infusion procedure and thus not tafasitamab-related.

Transient reduction in NK-cells were detected in both the single-dose and the repeat-dose studies and appeared to be linked to antibody-dependent cellular cytotoxicity (ADCC) mediated B-cell depletion due to degranulation and apoptosis of NK-cells or margination/re-localisation to tumour site. However, the effect of the transient reduction in NK-cells is considered to be limited, as B-cell counts in cynomolgus monkeys remain fully depleted under tafasitamab exposure and only recover upon withdrawal.

Additionally, a reduction in IgG concentration in serum and in primary and secondary antibody response to keyhole limpet haemocyanin (KLH) and tetanus toxoid (TT) respectively, were observed in the 13-week repeat-dose study and correlated with the above findings of B-lymphocyte depletion. Significant antidrug-antibody (ADA) formation were noted in the 8-week repeat-dose study, which was in contrast to findings in the 13-week repeat-dose study. A discussion of the issue was provided but no clear reason was identified. However, as no treatment-related or treatment boosted ADAs were noted following tafasitamab administration in humans, the issue will not be further pursued.

As tafasitamab is a monoclonal antibody, genotoxicity and carcinogenicity studies have not been conducted, since such tests are not relevant for this molecule in the proposed indication.

No studies were performed to evaluate the genotoxicity/carcinogenicity of tafasitamab, according to ICH S6(R1) and S9 guideline. However, a total of three cases of secondary primary malignancies were reported in L-MIND study and the applicant was asked to further discuss the mechanisms underlying the carcinogenic potential of the drug in relation to its pharmacological properties and a possible potentiation of lenalidomide effects. A comparison with rituximab was provided, which is considered acceptable due to the similar mode of action to deplete B-cells via ADCC and ADCP. Based on available rituximab data, no increased risk for SPMs induced by tafasitamab was expected.

Further, for lenalidomide an increased risk of secondary primary malignancies (SPMs) has been described and included in section 4.4 of the SmPC of lenalidomide. It is known that, patients with lymphoma which are treated by DNA damaging agents, genetic predisposed, exposed to environmental factors or stem cell transplantations are at high-risk for developing SPM.

Reproductive and developmental toxicity studies as well as specific studies to evaluate the effects on fertility have not been conducted with tafasitamab. Waiving stand-alone reproductive and developmental toxicity studies for the current indication of tafasitamab treatment in combination with the teratogenic drug Lenalidomide, was supported in accordance with the CHMP scientific advice.

This is considered acceptable for the present indication with treatment in combination with Lenalidomide, a drug known to be teratogenic or causing embryo-fetal lethality.

Moreover, no adverse effects on reproductive organs in males and females and no effects on menstrual cycle length in females were observed in the 13-week repeat-dose toxicity study in cynomolgus monkeys by histopathological examination of the male or female reproductive system (study MOR208P008).

The absence of reproductive and developmental toxicity studies was in accordance with a scientific advice given by CHMP in January 2017. For the present application, the absence of a developmental toxicity study in the pharmacologically-relevant non-human primates appears as reasonable taking into consideration notably the patient population being mostly beyond reproductive age (median age of 71-72 years in the supportive clinical studies), the co-administration with lenalidomide during the first 12 cycles, and measures proposed to avoid pregnancy in woman of childbearing potential (contraception during treatment and up to 3 months after cessation of treatment). This opinion will be revised in case of a future extension of indication inducing a significant increase in the proportion of women of childbearing potential elective to treatment with tafasitamab.

Based on its mechanism of action and on nonclinical and clinical data publicly available with other CD19- or CD20-targeting drugs, treatment-related immunotoxicity cannot be excluded in neonates after *in*

utero exposure to tafasitamab (namely B-cell depletion). This potential risk should be reported in the SPC to inform the prescriber and provide risk management measures. A statement in SPC 4.6 with cross-reference to SPC 4.4 is suggested, e.g.: "In case of exposure during pregnancy, depletion of B-cells may be expected in newborns due to the pharmacological properties of the product. Consequently, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered (see section 4.4)".

No unexpected tissue cross-reactivity of tafasitamab were observed and positive staining was noted in lymphocytes in the blood, hematopoietic B-cell precursors in the bone marrow and in several tissues, however, always in association to cells with B-lymphocyte morphology. Good compliance in the staining pattern were noted between human and monkey tissue.

Tafasitamab has shown to be highly specific to the CD19 antigen on B cells. Toxicity studies following intravenous administration to cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B-cells in peripheral blood and in lymphoid tissues. These changes reversed after cessation of treatment (see SmPC section 5.3).

The applicant has submitted an ERA, including a justification for not providing a full ERA which is acceptable on the basis of an exemption in line with EMEA/CHMP/SWP/4447/00 Rev. 1; Tafasitamab as a monoclonal antibody is readily biodegradable and therefore, it is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies performed were adequate for the type of product and intended use. All relevant information is included in section 5.3. of the SmPC. Data reveal no special hazards for humans.

As for the present indication treatment is in combination with Lenalidomide, a drug known to be teratogenic or causing embryo-fetal lethality, relevant warnings have been on prevention of pregnancy are included in the SmPC section 4.6.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

  An overview of the completed clinical trials with tafasitamab relevant for the evaluation of efficacy, safety, and PK/PD is presented below.

Table 4: Overview of completed studies with tafasitamab relevant to Clinical pharmacology

Overview of Completed Clinical Studies with Tafasitamab Relevant to Pharmacokinetics/Pharmacodynamics/Immunogenicity

Study	Disease	Subtypes*	Dose (mg/kg)	Dose regimen	No. of subjects	PK/PD Endpoints	PK Sampling	PD Sampling	ADA sampling	Status
MOR208C 203 L-MIND	R/R NHL	DLBCL	12	q1w for the first 3 28-day cycles (plus LD#); thereafter q2w; **tafasitamab in combination with LEN**	81	PK: quantification serum drug levels at baseline and after repeated IV administrations for up to 24 treatment cycles PD: Absolute and percentage change from baseline in measurements for B-, T-, and NK-cell populations	Cycle 1: Days 1, 4, 15 ± 1 (pre-dose and 1 h post infusion) Cycles 2 and 3: Days 1 ± 1, 15 ± 1 (pre-dose and 1h post infusion) Cycles 4-7, 9, 11, 13, 15, 17, 19, 21, 23: Day 1 ± 2 (pre-dose) EOT visit (PK sampling not to be performed from Cycle 25 onwards)	Cycle 1: Predose on Days 1, 8, and 22 Cycle 2: Predose on Days 1 Cycle 4: Predose on Day 22 Cycle 8: Predose on Day 15	Baseline; thereafter on Day 1 of every other cycle (i.e. Cycle 3, 5, 7…) until Cycle 23; at End of Treatment (EOT) visit (unless EOT occurred after Cycle 23).	Ongoing; Primary Results available from 30. Nov 2018 data cutoff (cutoff for clinical pharmacology data)
XmAb5574 -01	R/R CLL R/R SLL	--	0.3	q1w for 2 28-day cycles (plus LD#)	1	PK: C_{max}, T_{max}, t1/2 (alpha), t1/2 (beta), AUC∞, CL, V1, V2 PD: B lymphocyte depletion during therapy and degree of recovery at 12 weeks after the end of the final cycle	Cycle 1: Pre-dose and EOI on Days 1, 4, 8, 15, 22. In addition 1, 4, and 24 h post infusion on Day 1. Cycle 2: Pre-dose and EOI on Days 1, 8, 15, 22. In addition 1 and 4 h post infusion on Days 1 and 22. Post drug administration: on Days 23, 25, 28. Post Cycle 2 (FU): Post Cycle 2 on Weeks 2, 4, 6, 8 *For subjects in the extended therapy phase of the study^:* Cycle 3: Pre-dose on Day 15	Cycle 1: Pre-dose and 4 hours post infusion on Days 1, 2, 4, 8, and 15 Cycle 2: on Days 1, and 22 Cycles 4-6: on Day 1 Cycle 7: on Days 1, 15, and 28 Follow-Up: Weeks 4, 8, 12 (EOT)	Cycle 1: prior to study drug infusion on Days 1, and 15 Cycle 2: Days 1, 15, 22 and 28 For ext. therapy subjects only, additional ADA samples were collected on: Cycle 3: Day 15 Cycles 4-6: prior to infusion on Day 1 Cycle 7: Days 1 and 28	Completed; final CSR dated 19. Mar 2014; publication available Woyach et al. (2014)
			1		1					
			3		3					
			6		3					
			9		3					
			12		16~					
		MCL	12		12					

Study	Disease	Subtypes*	Dose (mg/kg)	Dose regimen	No. of subjects	PK/PD Endpoints	PK Sampling	PD Sampling	ADA sampling	Status
							Cycle 4, Day 1: Pre-dose, EOI, 1 and 4 h post infusion. Cycle 5, Day 1: Pre-dose and EOI Cycle 6, Day 1: Pre-dose, EOI, 1 and 4 h post infusion. Cycle 7: Pre-dose on Days 1, 15, 28. End of infusion on Day 1. Post Cycle 7 (FU): Weeks 2, 4, 6, 8, 12 (EOT)		For subject in either part of the study ADA samples were also taken at the 4, 8, and 12 week Follow-Up visits.	
MOR208C 201	R/R NHL	DLBCL	12 mg/kg	q1w for up to 3 28-day cycles; thereafter q2w or q4w	35	PK: C_{max}, C_{last}, Cpd, Tmax, AUC_{0-t}, t1/2, λ_z PD: Absolute and percentage change from baseline in measurements for B-, T-, and NK-cell populations	Cycle 1: Day 1 (Pre-dose, EOI, 1h, 4 h, 24h post infusion); Days 8 ± 1, 15 ± 1, 22 ± 1 (Pre-dose, 1h post infusion) Cycles 2 and 3: Days 8 ± 1, 22 ± 1 (Pre-dose, 1h post infusion); Day 28 ± 4 First, second and third follow-up visit	Cycle1: Predose on Days 1, 2, 8, and 15 Cycle 2: Predose on Days 1, 15, and 28 Cycle 3: Predose on Days 1, 15, and 28 (only if SD observed after Cycle 2, Day 22) End of study visit	Baseline; Day 1 of Cycle 2 and 3; Follow up visits 1 and 3 (~4 and ~16 weeks after end of Cycle 3, respectively); at the End of Study visit (EOS; up to 4 weeks after last tafasitamab infusion)	Ongoing; Primary Results available from 28. Sep 2018 data cutoff (cutoff for clinical pharmacology data)
		FL			34					
		other iNHL			11					

Study	Disease	Subtypes*	Dose (mg/kg)	Dose regimen	No. of subjects	PK/PD Endpoints	PK Sampling	PD Sampling	ADA sampling	Status
MOR208C 202	R/R ALL	-	12 mg/kg	q1w for up to 4 28-day cycles (plus LD#); thereafter q2w	22	PK: C_{max}, T_{max}, $AUC_{0\text{-last}}$, Cpd PD: Absolute and percent change from baseline in measurements of B, T, and natural killer (NK) cell populations	Cycle 1: Day 1 (Pre-dose, EOI, 1h, 4h, 24h post infusion); Days 4 ± 1, 8 ± 1, 15 ± 1, 22 ± 1 (Pre-dose, 1h post infusion) Cycles 2, 3, 4: Day 8 ± 1, Day 22 ± 1 (Pre-dose, 1h post infusion) Extension treatment: first, third, and fifth extended dose of tafasitamab (Pre-dose, 1h post infusion) End of study visit	Cycle 1: Predose on Days 1, 8, 15 and 22 Cycle 2: Predose on Days 1 and 15 Cycle 3: Predose on Days 1 and 15 Cycle 4: Predose on Days 1 and 15 During Extended Treatment: Predose every fourth week (1st 3rd and 5th dose)	Baseline; Day 1 of Cycle 2 and 4; during extension treatment at the 1st, 3rd and 5th dose (i.e., ~ 2 / 6 / 10 weeks after start of extension treatment); EOS visit (~1 week after last tafasitamab infusion)	Study Terminated Early; final CSR dated 7. Oct 2016
MOR208C 205 COSMOS	R/R CLL R/R SLL	--	12 mg/kg	q1w for the first 3 28-day cycles (plus LD#); thereafter q2w; **tafasitamab in combination with venetoclax or idelalisib**	24	PK: quantification serum drug levels at baseline and after repeated IV administrations. PD: Absolute and percentage change from baseline in measurements for B-, T-, and NK-cell populations	Cycle 1: Day 1, 4, 15 (Pre-dose, 1h post infusion) Cycles 2 and 3: Day 1, 15 (Pre-dose, 1h post infusion) Cycle 4 onwards: Day 1 (Pre-dose) in odd-numbered cycles only (i.e. Cycles 5, 7, 9,…) End of Treatment (EOT) visit	Cycle 1: Day 1 and 8 (predose) Cycle 2: Days 1 and 15 (predose) Cycle 4: Day 15 (predose) End of treatment visit	Baseline; Day 1 of Cycles 2 and 3; thereafter on Day 1 of every other cycle (i.e. Cycle 5, 7, 9…); EOT visit (up to 30 days after last dose of study medication)	Ongoing; Primary Study Completion Results available from 9. Nov 2018 data cutoff (cutoff for clinical pharmacology data)

R/R= relapsed or refractory, CLL= chronic lymphocytic leukemia, SLL= small lymphocytic lymphoma, PLL= prolymphocytic leukemia, MCL= mantle cell lymphoma, NHL= non-Hodgkin's lymphoma, iNHL= indolent non-Hodgkin's lymphoma, B-ALL= B-cell acute lymphoblastic leukemia, DLBCL= diffuse large B-cell lymphoma, EOI= End of infusion, q1w= once a week, q2w= every other week, q4w= every 4 weeks, LD= loading dose, PK= pharmacokinetics, PD= pharmacodynamics, LEN= lenalidomide, nt NK= natural killer cells, N/A= not applicable

* NHL subtypes: DLBCL, FL, iNHL, MCL

LD = loading dose, administered on Day 4 of Cycle 1.

+ 8 subjects enrolled in the expansion phase of Cohort 6 (12 mg/kg) received an additional 4 monthly doses of tafasitamab in Cycles 3-7 (extended therapy phase of the study) after completing the initial two 28-day cycles

Table 5: Ongoing studies that are not part of the present MAA

Additional Tafasitamab Clinical Studies (Planned/Ongoing), not Part of the MAA

Study Number [CMC material used]	Study Status	Phase / Type of Study	Indication/ number of patients
MOR208C107 (First-MIND) [CMC4]	Ongoing As of Mar 2020, 8 patients enrolled.	Phase 1b Safety, PK and efficacy of tafasitamab or tafasitamab + LEN plus R-CHOP	Treatment-naïve DLBCL N=60 planned
MOR208C310 [CMC4]	Planned	Phase 3 Efficacy and safety of tafasitamab and LEN plus R-CHOP versus R-CHOP	Treatment-naïve DLBCL N=850
MOR208C311 [CMC4]	Planned	Phase 3 Efficacy and safety of tafasitamab plus LEN and rituximab versus LEN and rituximab	R/R FL and R/R MZL N=618

DLBCL=diffuse large cell B-cell lymphoma, FL=follicular lymphoma, LEN=lenalidomide, MAA=Marketing Authorization Application, MZL=marginal zone lymphoma, N=number of patients, PK=pharmacokinetics, R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R/R=relapsed/refractory.

2.4.2. Pharmacokinetics

The pharmacology of tafasitamab (PK and PD) was investigated in 5 clinical studies in patients diagnosed with different B-cell malignancies. Based on multiple dosing and sparse PK sampling, an integrated population PK analysis was performed with results from clinical studies XmAb5574-01 (n=27 subjects), MOR208C201 (n=91), MOR208C202 (n=22) and MOR208C203 (L-MIND, n=81). Accordingly, data from 221 subjects with either R/R CLL/SLL, R/R NHL (including DLBCL), or R/R ALL were included in the pop PK analysis. The analysis was conducted on a data base containing 3972 measurable PK observations.

No dedicated human PK studies were performed for tafasitamab.

During the development programme, weekly (or q2w or q4w) doses of tafasitamab from 0.3 mg/kg to 12 mg/kg have been administered to patients with varying age, body weight, sex, disease type, tumour size, B-cell counts etc. The effect of renal or hepatic impairment was not formally tested in dedicated clinical trials.

Methods

Assays and bioanalysis

Three types of immune assays were employed throughout the clinical development for quantification of tafasitamab. The first-generation PK assay (used in Phase I trial XmAb5574-01) was an enzyme-linked immunosorbent assay. The second-generation assay was based on electrochemiluminescence technology and more specific (use in studies L-MIND; COSMOS, MOR208C201 and MOR208C202). The third assay was used in COSMOS and could detect "bioactive" tafasitamab capable of binding to CD19.

Deamidation of asparagine to aspartate and to a lower extent glutamine are common post translation protein modifications. Non-enzymatic deamidation at Asp33 hinders binding of tafasitamab to its target CD19. Re-analysis of samples indicated that serum values of "bioactive" tafasitamab were lower with up to 40% (see below figure).

Figure 12: Mean tafasitamab concentration vs time profiles in COSMOS

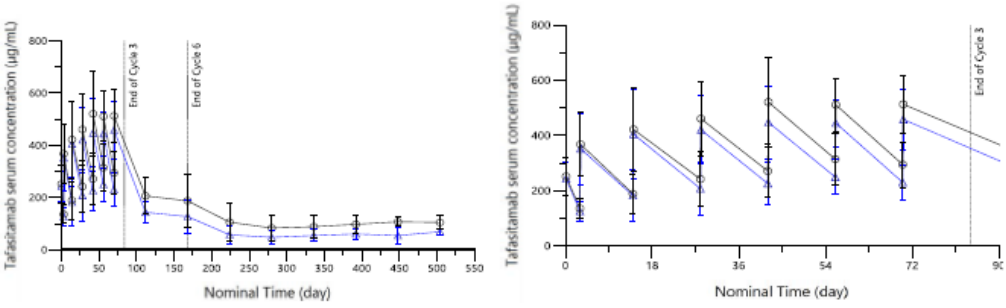


Figure 1 Mean (±SD) tafasitamab serum concentration vs time profiles in MOR208C205 (COSMOS), determined with the Standard PK assay or the bioactive drug PK assay

Tafasitamab serum concentration vs time profiles as determined with the bioactive drug assay (blue triangles and blue dashed line); and as determined with the Standard PK assay (black circles black solid line). Left: complete observation period; right: Cycles 1-3 only (i.e. weekly dosing scheme incl. a loading dose on Cycle 1 Day 4). Dashed vertical lines represent end of Cycle 3 (84 days, change from weekly to bi-weekly dosing) and end of Cycle 6 (168 days, change from bi-weekly to four-weekly dosing).

None of the validation stability studies accounted for deamidation which for tafasitamab leads to deactivation. The process is favoured by elevated temperatures as well as by pH shifts to alkaline and is a function of time. From a drug quality perspective, the deamidation process is considered adequately controlled. A forced biodegradation study suggests that at least 20% deamidation occur ex vivo during sample preparation and analysis. Interference caused by deamidation of tafasitamab on evaluation of ADAs is expected to be minor. The exact exposure level of tafasitamab is not critical for clinical efficacy.

Several tafasitamab formulation/process versions were tested in the clinical trials (CMC1 to CMC4). The pivotal study L-MIND (or MOR208C203) was conducted using CMC2 and CMC4 tafasitamab material. Physico-chemical comparability of CMC2 and CMC4 drug product have been demonstrated and deamidation degradation kinetics were similar for CMC2 and CMC4.

Three generation ADA assays were used for detection of anti-bodies to tafasitamab. The 1st generation assay was used for Study XmAb5574-01. The 2nd generation assay based on electrochemiluminescence was used for studies COSMOS, MOR208C201 and MOR208C202. Drug interference testing showed that 2500 ng/mL ADA could be detected in presence of 100 µg/mL drug, and 40 ng/mL ADA could be detected in presence of 5 µg/mL drug. In a later validation, 5000 ng/mL ADA could be detected in presence of 100 µg/mL drug. The 3rd generation assay used in L-MIND had drug tolerance determined using 2 different positive controls (i.e. a monoclonal and a polyclonal positive control) where ≥ 1000 µg/mL tafasitamab did not interfere to detect 100 ng/mL of an idiotypic monoclonal mouse anti-tafasitamab control antibody. Presence of more than 120 µg/mL tafasitamab interfered with detecting 100 ng /mL of polyclonal cynomolgus monkey-derived anti-tafasitamab antibodies. In general, the level of drug tolerance in the ADA assays might not be sufficient to cover the expected drug concentrations in the

ADA samples for detection of at least 100 ng/mL ADA. In L-MIND, ADA samples were collected with tafasitamab trough levels up to 394 µg/mL. In combination with idelalisib (COSMOS), tafasitamab trough concentrations have been observed up to 450 µg/mL.

Population PK analysis

The PK of tafasitamab was described by non-compartmental analysis and by population PK analysis. The Pop PK model for tafasitamab was a 2-compartment linear disposition model with time-dependent clearance and with inter-individual variability on CL, V, CL2 and V2 described by exponential error models and a mix ratio error model for the residuals. The final Pop PK model included data from 4 clinical trials, XmAb5574-01 (Phase 1 dose escalation trial in subjects with CLL/SLL, N=27 subjects), MOR208C201 (Phase II trial in subjects with NHL, N=92 subjects [N=91 in the PK population]), MOR208C202 (Phase II trial in subjects with ALL, N=22 subjects), and MOR208C203/L-MIND (Phase II trial in subjects with DLBCL, N=81 subjects). Statistically significant covariates were body weight, serum albumin, sex, and indication. The estimated typical value for the initial terminal elimination half-life was 16.9 days. The final model was qualified using prediction-corrected VPCs, GoF plots and bootstrap analysis.

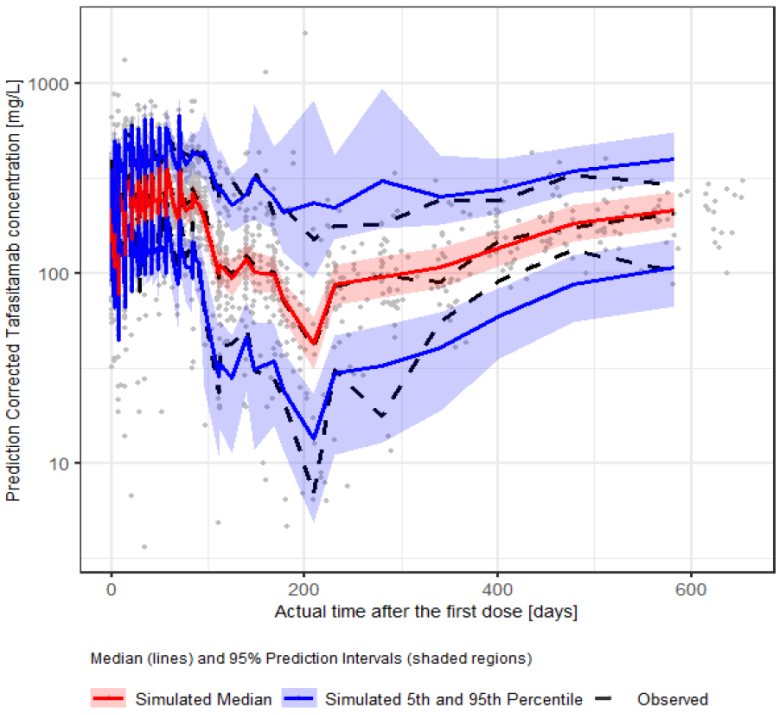
Table 6: Final model parameter estimates for tafasitamab

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.
Run: run030

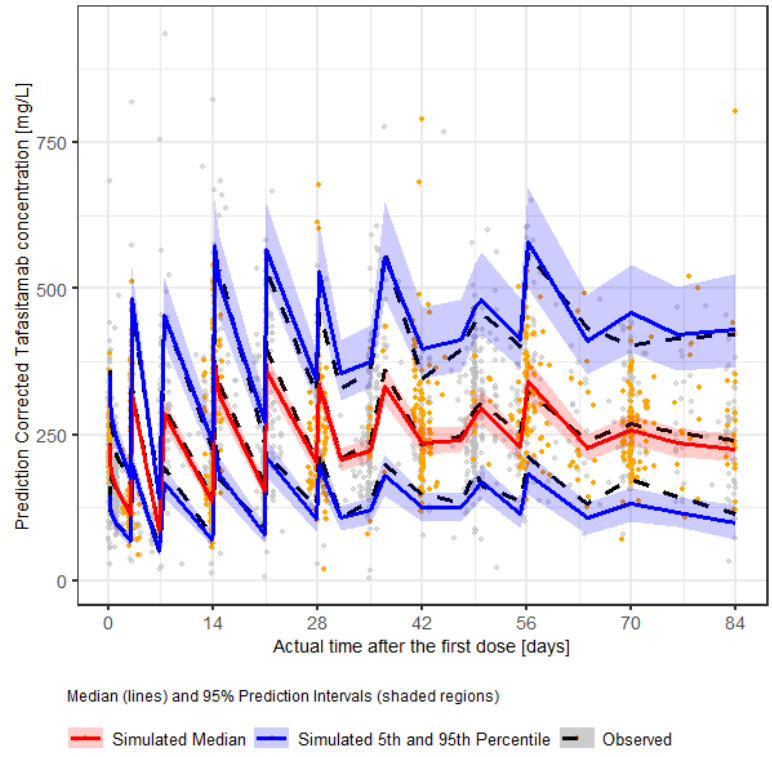
Figure 13 and Figure 14: Prediction – corrected visual predictive check plots

Figure 18. Prediction-corrected VPC for trials XmAb5574-01, MOR208C201, MOR208C202 and MOR208C203/L-MIND



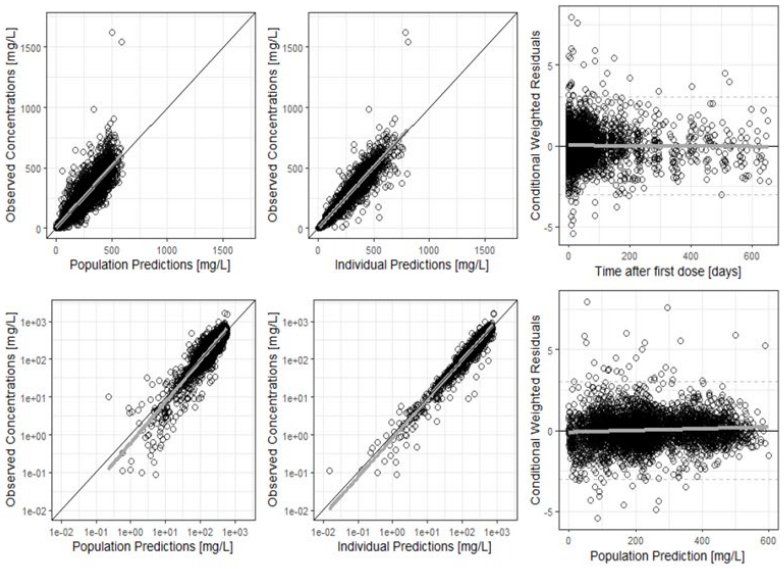
Item 42. *Note*: grey dots are observed data points; the black dashed lines are the observed p5, median and p95. The pink area is the 95% PI of the simulated median, purple areas are the 95% PI of the simulated p5 and p95. *Abbreviations*: p5 = 5th percentile, p95 = 95th percentile, PI = prediction interval.

Figure 15 Prediction-corrected visual predictive check plot - Cycles 1 to 3



Orange and grey dots display prediction corrected Tafasitamab with or without co-administration of Lenalidomide, respectively.

Figure 15: Goodness-of-fit plots for tafasitamab final pop PK model



Item 37. *Note*: Dots are individual data points and grey lines are smoothed LOESS lines. Predictions vs. observations are shown on linear (top row) and log/log scales (bottom row). In the plots in the left and middle columns, solid black lines are lines of identity; in the 2 plots in the right column, a black horizontal line denotes CWRES = 0, and dashed black lines show the boundaries of the CWRES ± 3 interval.

Individual estimates of exposure parameters (e.g. AUC, C_{max} and $MaxC_{min}$) were derived by simulation.

Table 7 : Summary of simulated exposure metrics across studies at 12 mg/kg

Statistic	AUC_{0-28} day·mg/L	AUC_{0-56} day·mg/L	$Cmin_{0-84}$ mg/L	$Cmin_{ext}$ mg/L	$Cmax_1$ mg/L	DCMIN mg/L	MaxCmax mg/L	MaxCmin mg/L	NDOSE
All studies (N=210 at 12 mg/kg)									
n	210	210	208	65	210	65	210	208	210
Mean	5824	12609	171	139	243	51.9	467	227	16.5
sd	1760	4580	60.8	75.2	59.1	60.5	124	90.1	16.4
Median	5868	12801	172	130	238	51.5	459	222	12
CV%	30.2	36.3	35.5	54	24.4	117	26.7	39.7	99.3
Min	834	924	30	21.1	117	-128	136	40.3	1
Max	11582	23971	351	394	463	181	836	607	75
geo mean	5509	11509	159	116	236	58.2	450	209	11.4
geo CV%	37.5	51.6	42.2	75.7	24.7	101.1	28.6	45.9	101.4

Item 6. *Abbreviations*: AUC_{0-28} = area under the serum concentration-time curve for the first treatment cycle (28 days), AUC_{0-56} = area under the serum concentration-time curve for the first 2 treatment cycles (56 days), $Cmin_{0-84}$ = average trough level up to Day 84 (induction period), $Cmin_{ext}$ = average trough level from Day 85 onwards (extension period), $Cmax_1$ = maximum concentration after the first dose, DCMIN = difference in simulated average trough levels ($Cmin_{ext}$ - $Cmin_{0-84}$), MaxCmax = maximum concentration, MaxCmin = maximal trough concentration, NDOSE = number of doses administered.
CV = coefficient of variation in %, geo CV% = geometric CV in %, geo mean = geometric mean, Max = maximum, Min = minimum, sd = standard deviation, n = number of subjects.

1000 bootstrap runs were used to display covariate-induced changes of the PK parameters or of relevant exposure metrics. Covariate effects were moderate in size for exposure (p5-p95 of the respective covariate range caused a change of < ±50% of the derived exposure parameter).

Table 8: Impact of continuous covariate effects on tafasitamab CL and V

	min	p5	med	p95	max
WT range (kg)	**40.4**	**51.7**	**76.6**	**117**	**163**
CL variation with WT (L/day)	0.238	0.294	0.413	0.595	0.788
CL variation with WT (%)	-42	-29	0	44	91
V variation with WT (L/day)	4.23	4.67	5.47	6.49	7.41
V variation with WT (%)	-23	-15	0	19	35
Albumin range (g/L)	**23**	**30**	**40**	**47**	**51**
CL variation with albumin (L/day)	0.751	0.564	0.413	0.350	0.318
CL variation with albumin (%)	82	37	0	-15	-23

Item 33. *Abbreviations*: CL = clearance, max = maximum, med = median, min = minimum, p5 = 5th percentile, p95 = 95th percentile, V = central volume of distribution, WT = body weight.

An exploratory Pop PK analysis of the sparse preliminary PK data available from 21 subjects from ongoing trial MOR208C205/COSMOS indicated that the final Pop PK model for tafasitamab underpredicted the observed concentrations in both treatment arms.

Figure 16: Exploratory Pop PK analysis – preliminary data COSMOS

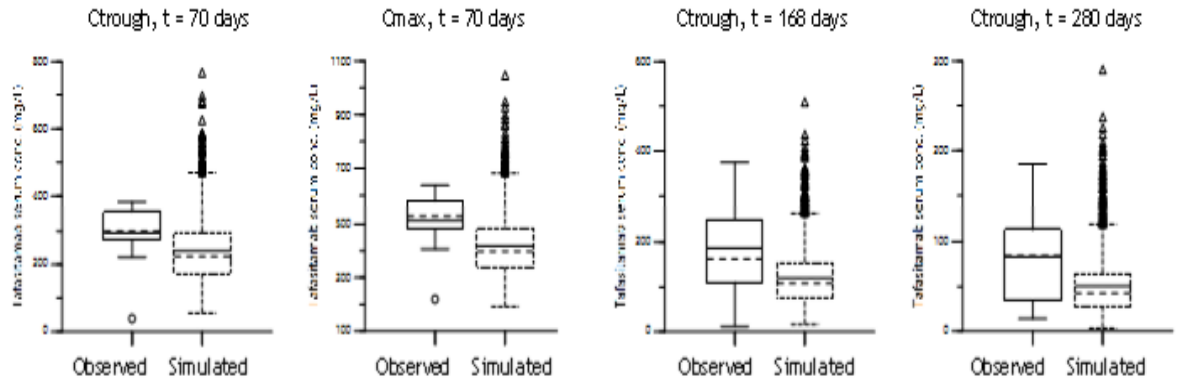


Figure 21: Comparison of observed tafasitamab serum levels in MOR28C205 vs simulated levels as per Pop-PK model MOR208L032
Comparison of simulated tafasitamab serum levels of the virtual CLL patient population dataset (N=2000) with the observed tafasitamab serum levels in trial MOR208C205 (N≤16). Source: Figure 9 Report MOR208L049

Figure 17: External Pc-VPC plots of tafasitamab PK data from MOR208C205 using popPK model MOR208L032

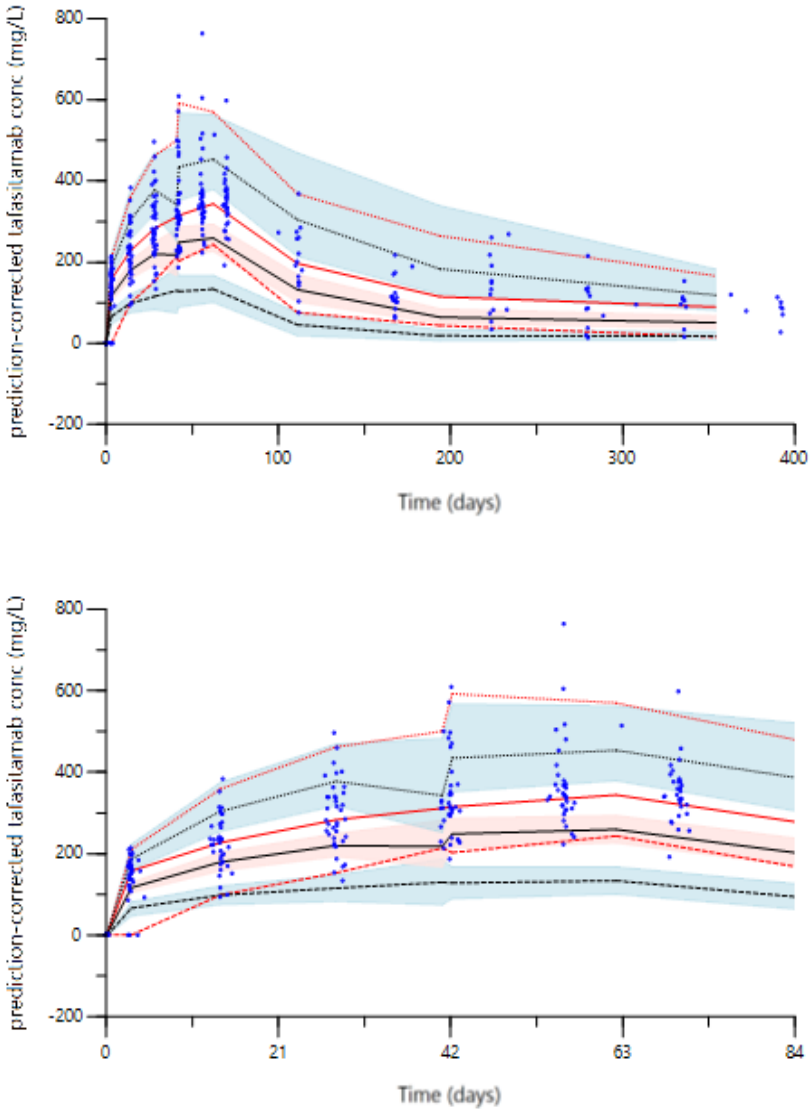


Figure 18: External pcVPC of tafasitamab PK data from MOR208C205 using Pop-PK model MOR208L032
Top panel: full time scale; bottom panel: zoom-in for Cycles 1-3 (until Day 84) only. Red dashed line, red solid line, and red dotted line represent observed 5th percentile, median, and 95th percentile of observed data, respectively. Black dashed line, black solid line, and black dotted line represent 5th percentile, median, and 95th percentile of predicted data, respectively, along with the respective 90% confidence intervals (blue and red shaded areas). Note that the pcVPC was not available beyond 350 days due to limited data, and that 1 observation was removed to increase visibility of the pcVPC as this observation was the only one within the particular bin (subject 95019-03, t=22.927 days).
Source: Figure 7 Report MOR208L049

Absorption

No clinical studies were conducted to evaluate the bioavailability (BA) or bioequivalence (BE) of tafasitamab as the product is administered intravenously which is 100% bioavailable.

Based on the population PK analysis, tafasitamab average serum trough concentrations (±standard deviation) were determined at 179 (±53) µg/mL during weekly IV administrations at 12 mg/kg including

an additional dose at Day 4 of Cycle 1 in combination with LEN (MOR208C203/L-MIND). During bi-weekly administrations from Cycle 4 onwards average trough serum concentrations of 153 (±68) µg/mL were determined. The simulated mean Cmax of tafasitamab in trial L-MIND was determined at 483 (±109) mg/L. The simulated mean Cmax at 12 mg/kg across studies was 467 mg/L.

Distribution

Volume of distribution was examined in study XmAb5574-01 in patients with R/R CLL or SLL. Mean central Vd was 121.8 mL/kg at steady state (Vss) corresponding to approximately 8 L in a 70 kg subject. In the pop PK analysis, the estimated typical Vd was 9.32 L, very much like the result in XmAb5574-01.

No study on protein binding has been conducted.

Elimination

The terminal half-life ($t_{1/2}$) was determined to be 16.9 days in the pop PK analysis. Initial drug clearance (CL) was 0.41 L/day whereas the calculated clearance after 700 days (i.e. ~2 years, the approximate maximum PK observation period in clinical trial MOR208C203/L-MIND) was 0.19 L/day.

Metabolism

As tafasitamab is a monoclonal antibody, no dedicated *in vitro* drug metabolism study was performed. The primary elimination pathways for mAbs like tafasitamab are degradation by the reticulo-endothelial system (like endogenous IgG) or by target-mediated elimination. Metabolites are amino acids and small peptides that are recycled into the protein metabolism.

Excretion

The routes of excretion have not been investigated in detail. It is not expected that this protein should be eliminated differently than other proteins.

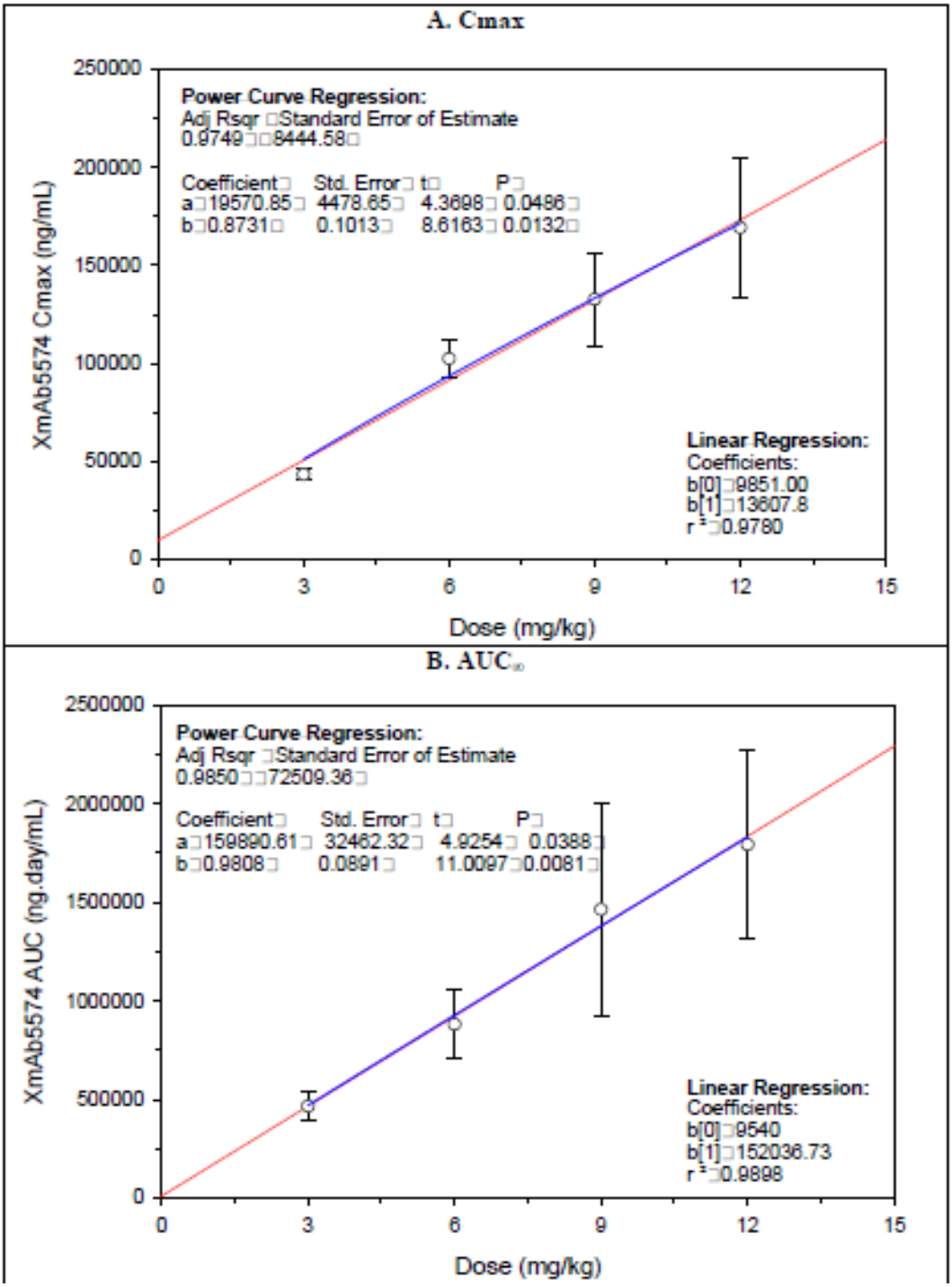
Bioavailability and Bioequivalence

No clinical studies were conducted to evaluate the bioavailability (BA) or bioequivalence (BE) of tafasitamab as the product is administered intravenously which is 100% bioavailable.

Dose proportionality and time dependencies

The PK of tafasitamab in the therapeutic dose range is linear in the dose range from 3 to 12 mg/kg. The correlation between dose and exposure is depicted below.

Figure 18: Dose-proportionality assessment of tafasitamab (XmAb5574): Mean (+/- SD) C_{max} and AUC_{inf} values vs. dose in clinical study XmAb5574-01



Time dependency

In the pop PK analysis, the calculated clearance after 700 days (i.e. ~2 years, the approximate maximum PK observation period in clinical trial MOR208C203/L-MIND) was 0.19 L/day. This is half the value of the calculated initial clearance suggesting a time dependent change in the clearance beyond 300 days of treatment. A decrease in clearance over time has been reported for several other monoclonal antibodies as well.

Intra- and inter-individual variability

Inter-individual variability was estimated for Cl, inter-compartmental clearance (Cl2), central Vd, and peripheral Vd in the final pop PK model. The interindividual variability in the selected PK parameters estimated in the final pop PK model varied between 19% and 70%.

Special populations

Impaired renal and hepatic function

No dedicated studies on the impact of renal or hepatic impairment have been conducted. The pop PK analysis did not indicate any impact of creatinine clearance in the interval 34 to 299 mL/min or of hepatic function (AST (10-472 U/L), ALT (6-336 U/L), ALKP (42-773 U/L), GGT (7-936 U/L)) on the systemic exposure of tafasitamab.

Gender

As expected, the volume of distribution was slightly lower in women; however, this was not translated into an overall difference in clearance based on gender.

Race

Race and ethnicity could not be formally tested as covariates. For race, the large majority of data was derived from "White" (91.4%) subjects; for ethnicity the large majority of data was "Not Hispanic/Latino" (52.0%) or "Missing" (46.6%). Since the route of administration of tafasitamab is IV and the metabolism is expected to be like other proteins, race or ethnicity is not expected to influence the PK of the drug product.

Weight

As determined by stepwise covariate model building, body weight at baseline (WTB) was found to have a significant effect on CL and V. Extremes of WT (range: 40.4-163 kg, as observed in the dataset) were associated with a change in clearance from -42% to +91% compared to a subject with median WTB. However, body weight had no clinically relevant effect on the systemic exposure of tafasitamab.

Figure 19: Univariate impact of covariates on tafasitamab exposure metrics

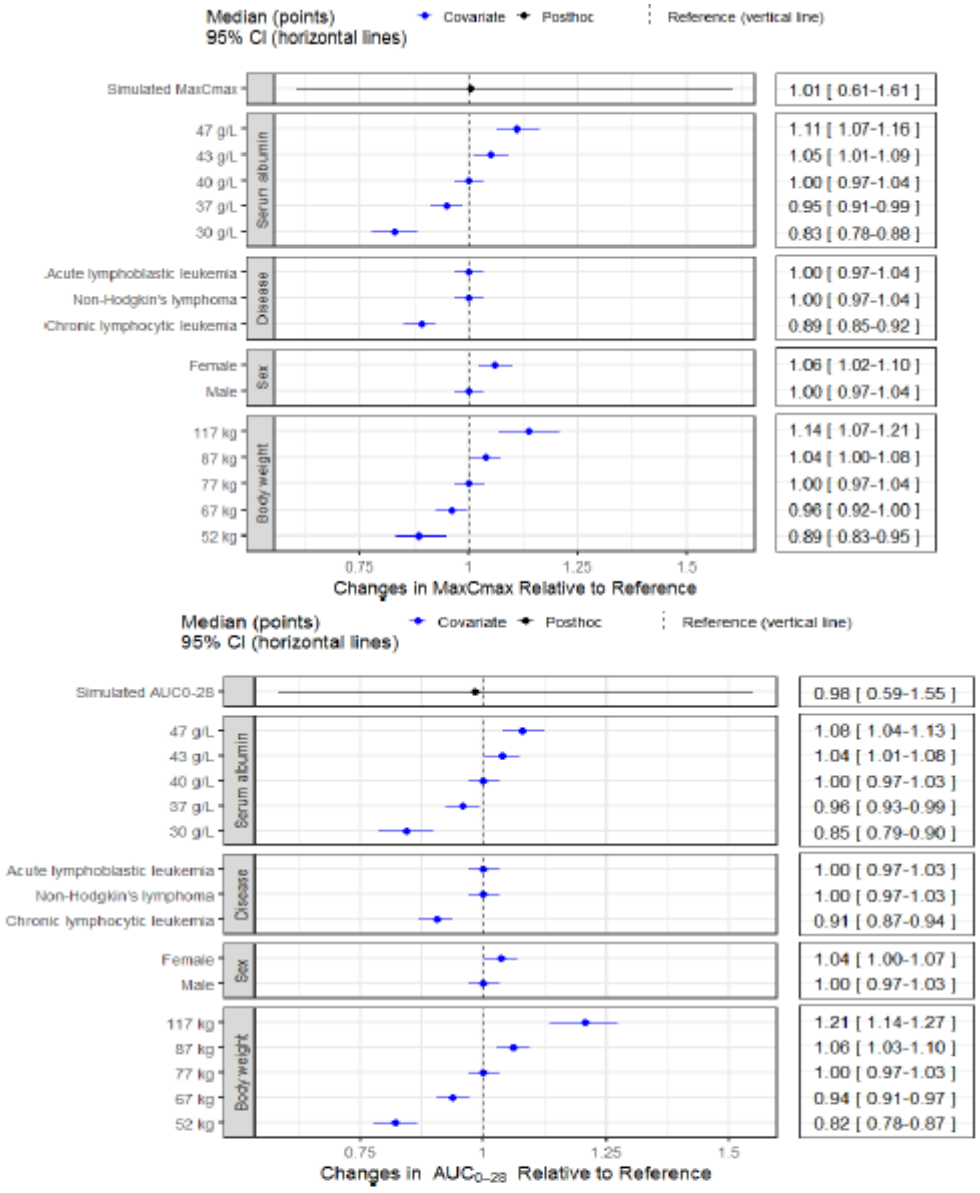


Figure 16: Univariate Impact of Covariates on Tafasitamab Exposure Metrics

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

Age

Age (16 to 90 years) had no clinically relevant effect on the systemic exposure of tafasitamab.

Information on patients in different age groups above the age of 65 years who were enrolled in the clinical studies with tafasitamab, that were a part of the MAA submission is provided below.

Table 9: Number of patients in different age categories

	Study N (%)	Treatment	Age <65 N (%)	Age 65-74 N (%)	Age 75-84 N (%)	Age 85+ N (%)
Controlled Trials	Not applicable					
Non-Controlled Trials	MOR208C201, N=92 (100) R/R NHL	Tafasitamab	43 (46.7)	28 (30.4)	17 (18.5)	4 (4.4)
	MOR208C203 (L-MIND), N=81 (100) R/R DLBCL	Tafasitamab + lenalidomide	23 (28.4)	27 (33.3)	30 (37.0)	1 (1.2)
	MOR208C202, N=22 (100) R/R ALL	Tafasitamab	20 (90.9)	1 (4.6)	1 (4.6)	0
	MOR208C205, N=24 (100) R/R CLL	Tafasitamab + idelalisib/ venetoclax	11 (45.8)	9 (37.5)	4 (16.7)	0
	XmAb5574-01*, N=27 (100) R/R CLL	Tafasitamab	11 (40.7)	11 (40.7)	5 (18.5)	0
Sum	**Tafasitamab monotherapy or in combination, N=246 (100%)**		**108 (43.9)**	**76 (30.9)**	**57 (23.2)**	**5 (2.0)**

Effect of albumin

Baseline albumin (ALB) was found to be a statistically significant covariate (inverse correlation with CL) and was incorporated in the final pop PK model. Extremes of ALB (range: 23-51 g/L, as observed in the dataset) were associated with a change in CL from +82% to -23% compared to a subject with median ALB levels. However, albumin had no clinically relevant effect on the systemic exposure of tafasitamab.

Immunogenicity

A formal assessment of ADA-positive vs ADA-negative subjects as covariate within the Population PK study was not feasible due to the low number of ADA-positive subjects. Thus, to test for a possible influence of ADA on tafasitamab PK, individual concentration-time profiles of ADA positive subjects were graphically compared to the range of individual concentrations of all subjects by study and dose level. No neutralising Abs were detected in the L-MIND study.

Figure 20: PK profiles for ADA positive vs ADA negative for the L-MIND study (12 mg/kg dose)

Note:

Individual subjects are plotted in black font, the two subjects with positive ADA results at baseline (subjects 3600207 and 9400406) are shown in red font.
Source: Population PK Report MOR208L032, Figure 13.

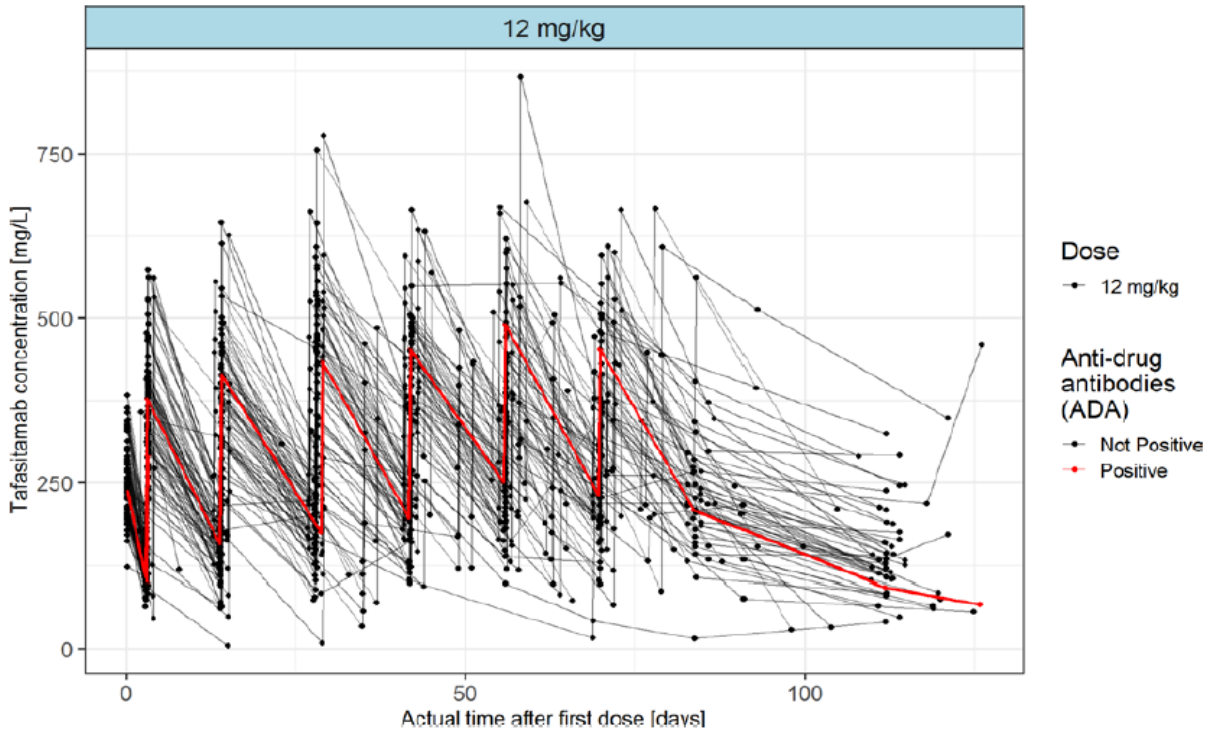


Table 10: Summary of Immunogenicity results of each clinical trial

Clinical Trial	L-MIND (MOR208C203)	COSMOS (MOR208C205)	MOR208C201	MOR208C202	XmAb5574-01
Subject Population	R/R DLBCL	R/R CLL/SLL	R/R NHL	R/R ALL	R/R CLL/SLL
Therapy	Tafasitamab in combination with lenalidomide	Tafasitamab in combination with idelalisib or venetoclax	Tafasitamab monotherapy	Tafasitamab monotherapy	Tafasitamab monotherapy
Tafasitamab dose level	12 mg/kg	12 mg/kg	12 mg/kg	12 mg/kg	0.3 / 1 / 3 / 6 / 9 / 12 mg/kg
ADA assay	3rd generation (SPEAD)	2nd generation	2nd generation	2nd generation	1st generation
NAb assay	Yes	No	No	No	No
ADA results available	81/81 (100 %)	23/24 (95.8 %)	92/92 (100 %)	22/22 (100 %)	27/27 (100 %)
ADA negative at baseline	79/81 (97.5 %)	21/23 (91.3 %)	87/92 (94.6%)	22/22 (100 %)	19/27 (70.4%)
ADA positive at baseline	2/81 (2.5 %)	2/23 (8.7 %)	5/92 (5.4%)	0/22 (0 %)	8/27 (29.6 %)
Median Titer (Min, Max)	18 (4, 32)	20 (20, 20)	20 (20, 320)	--	20 (20, 1280)
Neutralizing	0/81 (0 %)	not done	not done	not done	not done

Clinical Trial	L-MIND (MOR208C203)	COSMOS (MOR208C205)	MOR208C201	MOR208C202	XmAb5574-01
Non-Neutralizing	2/81 (2.5 %)	not done	not done	not done	not done
ADA negative during treatment	73/73 (100%)	23/23 (100 %)	85/86 (98.8 %)	18/18 (100%)	22/27 (81.5 %)
ADA positive during treatment	0/73 (0 %)	0/23 (0 %)	1/86 (1.2 %)	0/18 (0 %)	5/27 (18.5 %)
Treatment-boosted	0/73 (0 %)	0/23 (0 %)	0/86 (0%)	0/18 (0 %)	0/27 (0%)
Treatment-emergent	0/73 (0 %)	0/23 (0 %)	0/86 (0%)	0/18 (0 %)	0/27 (0%)
Median Titer (Min, Max)	--	--	40 (40, 40) #	--	20 (20, 640)
Neutralizing	0/73 (0 %)	not done	not done	not done	not done
Non-Neutralizing	0/73 (0 %)	not done	not done	not done	not done

Notes: All number and percentages refer to numbers of subjects. Drug interference in 1st and 2nd generation ADA assay and in the NAb assay possible. NAb assay (neutralizing / non-neutralizing) was only performed for ADA-positive samples in L-MIND. L-MIND and COSMOS studies are ongoing; data presented is from data cut-off 30-NOV-2018 and 09-NOV-2018, respectively. Treatment-boosted: ADA-positive at baseline, increasing titer during treatment; treatment-emergent: ADA-negative at baseline, ADA-positive during treatment. Note that lowest titer in the 1st and 2nd generation ADA assay was reported as 20 (i.e. at MRD); lowest titer in the 3rd generation ADA assay (SPEAD) as 1. R/R = Relapsed or refractory; ALL=Acute lymphoblastic leukemia; DLBCL = Diffuse large B-cell lymphoma; NHL = Non-Hodgkin-Lymphoma; CLL = Chronic lymphocytic leukemia; SLL = Small lymphocytic lymphoma; SPEAD = solid-phase extraction followed by acid dissociation.
#: only 1 sample was ADA-positive
Source: Integrated Summary of Immunogenicity Table 1

Pharmacokinetic interaction studies

As tafasitamab does not undergo extensive hepatic metabolism or renal excretion, no dedicated *in vitro* and clinical drug-drug interaction studies were performed. However, the potential impact of lenalidomide on the PK of tafasitamab was evaluated during covariate analysis of the population PK analysis and no effect of concomitant administration of lenalidomide on tafasitamab PK was detected.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Tafasitamab is an Fc-enhanced humanised monoclonal antibody (mAb) that binds to the human B-cell specific cell surface antigen of the B-cell receptor, CD19. The major pharmacological effect of tafasitamab is B-cell depletion. CD19 is expressed throughout normal and malignant B-cell development up to terminal plasma cell differentiation and is present on the surface of malignant hematopoietic cells. Thus, CD19 represents an important therapeutic target for the treatment of B-cell malignancies. Alteration of

two amino acid residues in the constant region of tafasitamab significantly increases binding to Fc gamma receptors (FcγR), including FcγRIIIa (CD16) and FcγRII (CD32), leading to enhanced *in vitro* antibody-dependent cell-mediated cytotoxicity ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and direct cytotoxic effects (apoptosis) on tumour cells relative to the unmodified antibody.

Primary and Secondary pharmacology

The primary pharmacodynamic endpoint was change from baseline in B-cell count. Assessment of an exposure-efficacy relationship was conducted using PFS or ORR as efficacy parameters, while treatment emergent adverse events of special interest (AESIs) were used for the assessment of an exposure-safety relationship.

B-lymphocyte depletion

Results for pharmacodynamic B-cell depletion during tafasitamab treatment for five clinical studies, XmAb5574-01, MOR208C201, MOR208C202, MOR208C203/L-MIND, and MOR208C205, were analysed and the data presented in MOR208L038. In all studies, tafasitamab treatment led to a strong reduction in peripheral B-cells. An overview on onset of depletion and time to reach the nadir of the relative reduction is given below.

Table 11: Summary of peripheral B-cell counts of clinical studies analysed

Study	Indication	Cohort	Median number of B-cells at baseline	Median relative change to baseline [%]		Timepoint when median nadir was reached
				at cycle 1 day 8	at nadir	
MOR208C203/L-MIND	DLBCL (lymphoma)	All subjects	12	-96.91	-100.00	Cycle* 5 day 1
MOR208C201	NHL (lymphoma)	All subjects	59	-42.07	-80.00	Cycle* 3 day 1
XmAb5574-01	CLL (leukemia)	cohort 6	12607	-72.18	-95.54	4 week follow up visit (after 3* cycles)
		cohort 6 ext.	9234	-66.61	-98.06	4 week follow up visit (after 7* cycles)
MOR208C202	ALL (leukemia)	All subjects	320	-91.74	-98.23	Cycle 2* day 15
MOR208C205 (COSMOS)	CLL (leukemia)	+ Idelalisib	11453	6.57	-98.2	Cycle 4* day 15
		+ Venetoclax	4065	-36.51	-99.65	Cycle 4* day 15

* one cycle = 28 days

Based on an evaluation of eight patients who achieved a response but relapsed early, there is no indication that monitoring of peripheral B-cell counts (or NK cell counts) could be used to detect an early relapse.

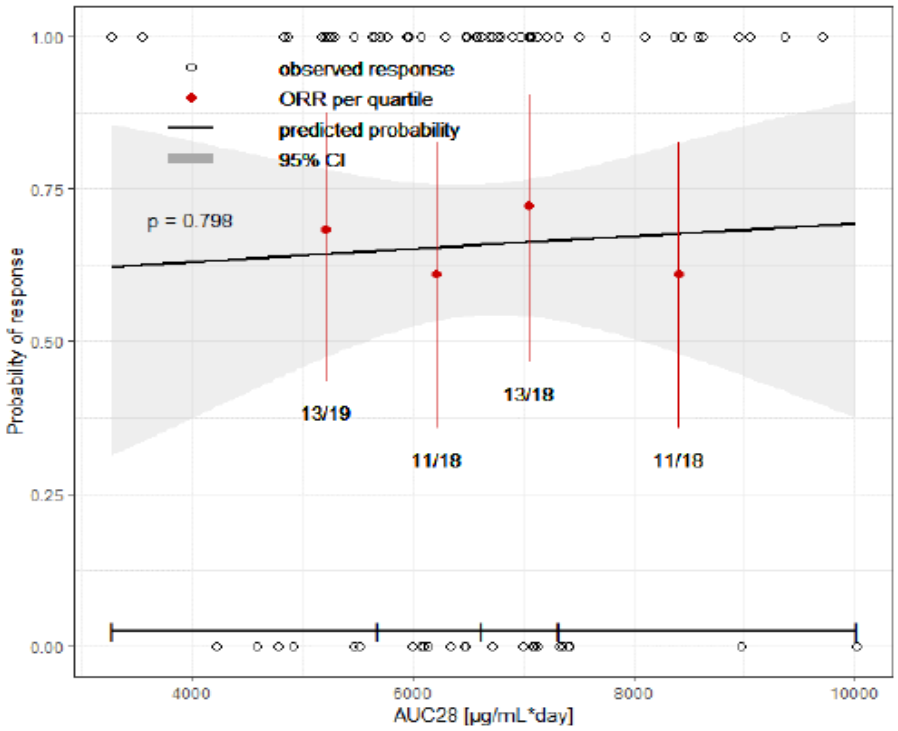
Relationship between plasma concentration and effect

Exposure-response relationship for clinical efficacy

In order to evaluate a potential exposure-response relationship for clinical efficacy of tafasitamab, data from three different clinical studies were analysed independently (XmAb5574-01, MOR208C201 and MOR208C203/L-MIND) (MOR208L035). The studies included subjects with R/R DLBCL (i.e. the target indication – studies MOR208C201, N=28 and MOR208C203/L-MIND, N=81) but also with other NHL subtypes (MOR208C201, total N=64) or R/R CLL/ SLL (study XmAb5574-01, N=27).

An exposure-response relationship for clinical efficacy was observed for tafasitamab monotherapy clinical studies XmAb5574-01 (subjects with R/R CLL/SLL) and MOR208C201 (subjects with R/R NHL/DLBCL). Within these monotherapy studies, higher exposure to tafasitamab resulted in increased best ORRs and prolonged median PFS. However, in combination with LEN (MOR208C203/L-MIND), tafasitamab exhibited a flat exposure-response relationship for ORR and PFS, whereas ORRs increased almost two-fold compared to tafasitamab in monotherapy (XmAb5574-01 and MOR208C201). Based on these results, increasing exposure to tafasitamab is unlikely to result in higher response rates when used in combination with LEN.

Figure 21: Analysis of objective response versus AUC28 for clinical study MOR208C203/L-MIND



Black solid line and grey shaded areas represent logistic model-predicted relationship and 95% confidence interval based on the sensitivity analysis population (N=73). 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 bottom of 95% CIs. Black circles on top and bottom represent actual observations used for regression. Note that only subjects receiving all planned 5 doses during Cycle 1 were included in this analysis in order to avoid bias of an early drop-out leading to low AUC28.
ORR = objective response rate; AUC28 = AUC from 0-28 days (i.e the 1st treatment cycle, as obtained from the Population PK report MOR208L032).
Source: Report MOR208L035 Figure 11

In order to investigate the effect of lowering the administration frequency from once weekly dosing (Q1W) to every other week dosing (Q2W) in study MOR208C203/L-MIND, the exposure parameter Ctrough was selected to quantify the decrease in exposure and tested as predictor for PFS. Switching the dosing frequency of tafasitamab in combination with LEN from initially Q1W to Q2W, after three treatment cycles, as implemented in MOR208C203/L-MIND, had no pronounced effect on PFS.

Exposure-response relationship for clinical safety

In order to evaluate a potential exposure-response relationship for safety, AEs were analysed against tafasitamab exposure for R/R NHL patients (study MOR208C201, including R/R DLBCL patients) and R/R DLBCL patients (MOR208C203, L-MIND). In both studies, all patients were treated at the dose level of 12 mg/kg tafasitamab (monotherapy in MOR208C201 and in combination with LEN in MOR208C203). The tafasitamab exposure metrics $AUC_{0\text{-}28}$ and Cmax were derived by simulation for each patient from a pop PK model. The individual exposure metrics were separated into exposure quartiles and analysed against TEAEs, each AESI and neutropenia ≥Grade 3.

Adverse Events of Special Interest (AESI)

For most TEAEs of special interest, there was no evidence of increasing risk with increasing exposure. For MOR208C201 (tafasitamab monotherapy in subjects with R/R NHL/DLBCL), there was an apparent exposure-response relationship for non-allergic rash/skin reactions leading to increased numbers for increasing AUC28 values; however, this was not observed for patients with DLBCL. For MOR208C203 (L-MIND, tafasitamab in combination with LEN in subjects with R/R DLBCL), an apparent exposure-response relationship was observed for anaphylactic reaction, tumour flare reaction, non-allergic rash/skin reactions, diarrhoea, and neutropenia. However, the increase in OR with increasing exposure quartiles for these TEAEs was moderate, and numbers of patients per exposure quartiles were low. For several TEAEs, also an apparent *lower* risk was observed with increasing exposure. In summary, there was no obvious increase in TEAEs with increasing tafasitamab exposure as determined by AUC_{0-28} and C_{max}.

Table 12: Summary of TEAEs of special interest by AUC_{28} and C_{max} – Safety analysis set

Any TEAE of Special Interest	MOR208C201[a]		L-MIND[a,b]	
	All Patients N = 92 n (%)	DLBCL Patients N = 35 n (%)	All Patients N = 81 n (%)	Extended Monotherapy N = 40 n (%)
Any TEAE of Special Interest	60 (65.2)	26 (74.3)	78 (96.3)	27 (67.5)
AUC28 Quartile 1	17 (18.5)	8 (22.9)	20 (24.7)	7 (17.5)
AUC28 Quartile 2	18 (19.6)	9 (25.7)	20 (24.7)	6 (15.0)
AUC28 Quartile 3	15 (16.3)	7 (20.0)	19 (23.5)	7 (17.5)
AUC28 Quartile 4	10 (10.9)	2 (5.7)	19 (23.5)	7 (17.5)

Any TEAE of Special Interest	MOR208C201[a]		L-MIND[a,b]	
	All Patients N = 92 n (%)	DLBCL Patients N = 35 n (%)	All Patients N = 81 n (%)	Extended Monotherapy N = 40 n (%)
Any TEAE of Special Interest	60 (65.2)	26 (74.3)	78 (96.3)	27 (67.5)
Cmax Quartile 1	18 (19.6)	10 (28.6)	21 (25.9)	4 (10.0)
Cmax Quartile 2	18 (19.6)	9 (25.7)	19 (23.5)	4 (10.0)
Cmax Quartile 3	13 (14.1)	5 (14.3)	19 (23.5)	7 (17.5)
Cmax Quartile 4	11 (12.0)	2 (5.7)	19 (23.5)	12 (30.0)

2.4.4. Discussion on clinical pharmacology

The present MAA concerns tafasitamab, a humanised monoclonal antibody of the immunoglobulin (Ig) G1 subclass directed against the CD19 receptor which is expressed throughout normal and malignant B-cell development up to terminal plasma cells. Tafasitamab is developed for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), first in combination with lenalidomide, then followed by monotherapy.

The pharmacology of tafasitamab (PK and PD) was investigated in 5 clinical studies in patients suffering from different B-cell malignancies. Due to the PD effect of the substance no dedicated human PK studies in healthy subjects were performed. The effect of renal or hepatic impairment was not formally tested in dedicated clinical trials, and no interaction studies has been undertaken. Based on data from four studies, an integrated population PK analysis on 3972 PK observations from 221 subjects with either R/R CLL/SLL, R/R NHL (including DLBCL), or R/R ALL was performed.

Quantification of tafasitamab was conducted using 3 different validated immunoassays. The validations and bioanalysis were overall acceptable with some exceptions: Two analytical methods were used for quantification without cross-validation. Several formulations were applied during clinical development (CMC1 to CMC4). The bioanalytical reports for COSMOS will be provided when finalised as recommended by the CHMP.

The absorption, distribution, biotransformation and elimination were documented based on a population pharmacokinetic analysis (see SmPC section 5.2).

Based on an analysis of tafasitamab in combination with lenalidomide, tafasitamab average serum trough concentrations (± standard deviation) were 179 (± 53) µg/mL during weekly (plus an additional dose on day 4 of cycle 1) intravenous administrations of 12 mg/kg. During administration every 14 days from cycle 4 onwards, average trough serum concentrations were 153 (± 68) µg/mL. Overall maximum tafasitamab serum concentrations were 483 (± 109) µg/mL.

The total volume of distribution for tafasitamab was 9.3 L.

The exact pathway through which tafasitamab is metabolised has not been characterised. As a human 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.

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

In order to evaluate the influence of ADAs on tafasitamab PK, individual concentration-time profiles of ADA positive subjects were graphically compared with ADA negative subjects (all data from the 12 mg/kg cohorts). This evaluation did not indicate any clinically meaningful difference in exposure between ADA positive and negative subjects. Anti-drug-antibodies were evaluated using 3 different ADA assays for screening. The applicant will further develop the drug tolerance of the 3rd generation ADA assay with the objective to improve the method by excluding drug interference at trough levels observed in COSMOS - recommended by the CHMP. Further, the applicant will provide the final bioanalytical reports for pharmacokinetic (PK) and anti-drug antibody (ADA) sample analysis of COSMOS after trial completion.

The Pop PK of tafasitamab could be described by a 2-compartment linear disposition model with time-dependent clearance and inter-individual variability on CL, V, CL2 and V2. Significant covariates were body weight on both clearance and central volume, serum albumin (inverse correlation with CL), sex (lower V in females), and indication (subjects with NHL or ALL had a lower V than subjects with CLL/SLL). However, the magnitude of the effects caused by these covariates is not considered clinically relevant. The applicant will update the Pop PK model post-approval to include final data from COSMOS and submit the results as per the recommendation of the CHMP.

The PK of tafasitamab in the therapeutic dose range is linear.

Weight and s-albumin were found to have a significant effect on Vd and/or CL but no clinically relevant effects on the systemic exposure of tafasitamab was demonstrated.

The ADA incidence was highest in study XmAb5574-01. The applicant has no plausible explanation for the relatively high incidence of pre-existing ADAs in this study (not further pursued).

Based on the available data, no dose adjustment is required in the special populations included in the pharmacology programme.

B-cell depletion was used as a PD marker of biological effect of tafasitamab. In all five studies in the clinical pharmacology programme, tafasitamab treatment led to a major reduction in peripheral B-cell counts.

AUC_{0-28} was the main exposure parameter for the exposure-efficacy analyses in the L-MIND study. The study demonstrated a flat exposure-response relationship and therefore increasing exposure to tafasitamab is unlikely to result in higher response rates when used in combination with LEN.

No indication of an overall exposure-safety relationship has been observed for AUC_{0-28} and Cmax. For some TEAEs, an exposure relationship could be suspected but the subject numbers are small and therefore firm conclusions cannot be drawn.

Age, body weight, sex, tumour size, disease type, B-cell or absolute lymphocyte counts, anti-drug antibodies, lactate dehydrogenase and serum albumin levels had no relevant effect on the pharmacokinetics of tafasitamab. The influence of race and ethnicity on the pharmacokinetics of tafasitamab is unknown (see SmPC section 5.2).

Renal impairment

The effect of renal impairment was not formally tested in dedicated clinical trials; however, no clinically meaningful differences in the pharmacokinetics of tafasitamab were observed for mild to moderate renal impairment (creatinine clearance (CrCL) ≥ 30 and < 90 mL/min estimated by the Cockcroft-Gault equation). The effect of severe renal impairment to end-stage renal disease (CrCL < 30 mL/min) is unknown (see SmPC section 5.2).

Hepatic impairment

The effect of hepatic impairment was not formally tested in dedicated clinical trials; however no clinically meaningful differences in the pharmacokinetics of tafasitamab were observed for mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or total bilirubin 1 to 1.5 times ULN and any AST). The effect of moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) is unknown.

Non-enzymatic deamidation at asparagine 33 in the light chain of tafasitamab hinders binding of tafasitamab to its target CD19. Non-clinical mechanistic studies have indicated this process occur in the drug material and *in vivo* and *in vitro*. Physico-chemical comparability of CMC2 and CMC4 drug product have been demonstrated and deamidation degradation kinetics were similar for CMC2 and CMC4 (see SmPC section 5.2).

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programme package is considered adequate and the proposed dosing of tafasitamab appears appropriate.

The applicant accepted a recommendation from the CHMP to submit additional results post-approval when COSMOS is finalised. The applicant is asked to improve drug tolerance of the 3rd generation ADA assay.

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The final bioanalytical reports for pharmacokinetic (PK) and anti-drug antibody (ADA) sample analysis of COSMOS after trial completion.
- The current tafasitamab population PK model by including COSMOS PK data after finalisation of the clinical trial. The applicant will submit all COSMOS reports (including the updated

Population-PK report as well as the corresponding bioanalytical reports for PK and ADA sample analysis.

- further develop the drug tolerance of the 3rd generation ADA assay with the objective to improve the method by excluding drug interference at trough levels observed in COSMOS.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

One phase 1 dose escalation study has been performed in 27 patients with R/R CLL/SLL (XmAB5574-01). This was the first-in-human (FIH) trial with tafasitamab which was administered intravenously (IV) as monotherapy at doses ranging from 0.3 to 12 mg/kg for up to seven 28-day cycles.

A total of 27 male and female subjects aged 40 to 84 years old were enrolled in six cohorts of tafasitamab: 0.3 mg/kg (n=1), 1 mg/kg (n=1), 3 mg/kg (n=3), 6 mg/kg (n=3), 9 mg/kg (n=3) and 12 mg/kg (n=16).

Tafasitamab was administered as a 2-hour intravenous (IV) infusion in Cycle 1 on Day 1, 4, 8, 15, and 22, and in Cycle 2 on Day 1, 8, 15, and 22, with a total of 9 doses of tafasitamab over two 28-day cycles of therapy. In the optional extended therapy phase for subjects in the 12 mg/kg cohort, 8 subjects could receive an additional 4 administrations as a single infusion every 28 days (Day 1 of Cycles 4, 5, 6, and 7) for an additional 20 weeks at the same dose level. The primary objectives were to identify the maximum tolerated dose (MTD) and/or recommended dose(s) (RD) of tafasitamab for further clinical studies; to characterize the safety and tolerability profile of IV dosing of tafasitamab; and to characterize the PK, PD, and immunogenicity of IV dosing of tafasitamab.

The dose-response study showed no benefit at the 3 mg/kg or below, objective responses were seen in the 6, 9, and 12 mg/kg cohorts. PR was noted in 1 patient in each of the 6 and 9 mg/kg cohort. Due to the acceptable safety profile of the highest administered dose, 12 mg/kg, this cohort was expanded to a total of 16 patients. In the 12 mg/kg cohort, tafasitamab showed preliminary antitumour efficacy with an ORR of 37.5%, the best response was PR, and no patients experienced CR in any of the dose groups. Disease progression rate was lower in the 12 mg/kg cohort. The longest TTP and PFS were seen for the 12 mg/kg cohort. (Please see PK section for further details.) The 12 mg/kg dose level was considered the optimal dose and was used in future studies. From an overall view, the selected dose is acceptable. The applicant acquired the rights to tafasitamab in 2010 and initiated two Phase 2 open-label studies investigating tafasitamab monotherapy in R/R B-cell NHL (MOR208C201) and in R/R B-cell ALL (MOR208C202).

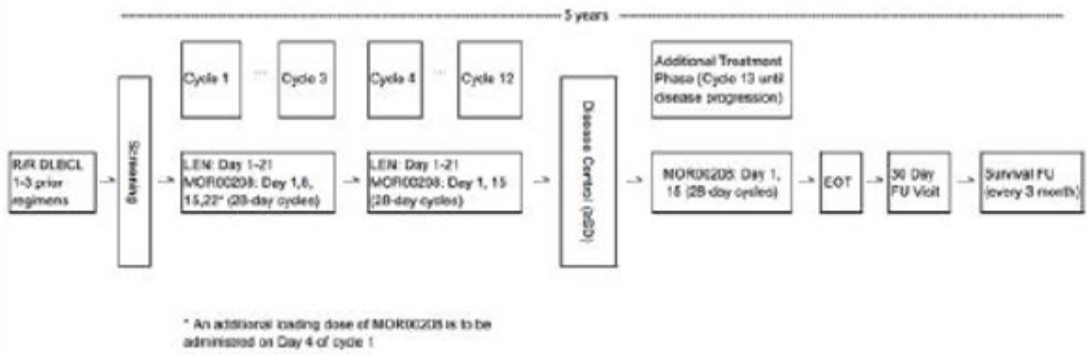
2.5.2. Main study(ies)

Main study: Pivotal study MOR208C203, L-MIND

Study MOR208C203 (L-MIND) is a phase 2 single-arm, open-label study of the efficacy of tafasitamab when combined with lenalidomide followed by tafasitamab monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from low grade lymphoma, and who are ineligible for or refuse autologous stem cell transplant (ASCT).

Methods

Figure 22: Schematic design of Study MOR208c203



Abbreviations: Abbreviations: EOT = End of treatment; FU = Follow-up; LEN = Lenalidomide; R-R DLBCL = Relapsed or refractory diffuse large B-cell lymphoma; SD = Stable disease.

Study Participants

Main inclusion criteria:

- Age ≥18 years old
- Histologically confirmed DLBCL NOS; T cell/histiocyte rich large B-cell lymphoma; EBV-positive DLBCL of the elderly, Grade 3b Follicular Lymphoma, Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, histological transformation to DLBCL from an earlier diagnosis of lowgrade lymphoma (such as follicular lymphoma, marginal zone lymphoma, CLL) with a subsequent DLBCL relapse. Diagnoses according to the REAL /WHO classification
- Relapsed and/or refractory disease. The primary refractory disease was defined as a disease progressing in the course of the first-line treatment as per International Working Group (IWG) response criteria (Cheson et al., 2007), and/or, showing a response of less than a PR to first-line treatment or disease recurrence/progression within < 6 months from the completion of first-line therapy. Disease refractory to last treatment was defined as having had less than a PR to the most recently administered systemic therapy. Relapsed//progressive/recurrent disease was defined as the appearance of any new lesions or increase by ≥ 50% of previously involved sites from nadir according to the IWG response criteria (Cheson et al., 2007) after the most recent systemic therapy
- Received at least one, but no more than three previous systemic regimens for the treatment of DLBCL and one therapy line had to include a CD20-targeted therapy (eg. RTX)
- ECOG status of 0-2
- Patients not considered eligible in the opinion of the investigator, or patients unwilling to undergo intensive salvage therapy including ASCT. Documentation of the reason had to be provided in the patient's source data

Main exclusion criteria:

- Other histological type of lymphoma incl. Primary mediastinal (thymic) large B-cell or Burkitt lymphoma, primary refractory DLBCL, a history of "double/triple-hit" genetics DLBCL (simultaneous MYC with BCL-2 and/or BCL-6 translocation(s). MYC, BCL-2, BCL-6 testing prior to study enrolment was not required

- Not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anti-cancer therapy or other lymphoma-specific therapy, within 14 days prior to Day 1 dosing, or required parenteral antimicrobial therapy for active, intercurrent infections
- Previously treated with CD19-targeted therapy or IMiDs® (e.g., thalidomide, LEN)
- History of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs® and/or the excipients contained in the study drug formulations
- Undergone ASCT within the period ≤ 3 months prior to the signing of the ICF
- Prior allogenic stem cell transplantation
- History of deep venous thrombosis/embolism, threatening thromboembolism, known thrombophilia or at a high risk for a thromboembolic event
- Ongoing other anti-cancer or experimental treatments
- Prior history of malignancies other than DLBCL, unless the patient had been free of the disease for ≥ 5 years prior to screening, with the exceptions of: basal – or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, breast, bladder or incidental histological finding of prostate cancer (TNM stage T1a or T1b).
- Positive hep. B and/or C serology, seropositivity for or history of active viral infection with human immunodeficiency virus history
- CNS lymphoma, clinically significant cardiovascular, CNS and/or other systemic disease

Treatments

The study period consisted of a screening period followed by a maximum of 12 cycles for LEN plus tafasitamab followed by tafasitamab monotherapy thereafter, until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever came first. 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.

Tafasitamab: 12.0 mg/kg administered by IV infusion on Day 1, 8, 15 and 22 of each 28-day cycle, Cycles 1-3. On Day 4, Cycle 1, an additional loading dose of tafasitamab was administered. Thereafter, q 14 days, Day 1 and 15 of each 28-day cycle.

Lenalidomide: 25 mg orally, Days 1 to 21 of each 28-day cycle. The dose could be modified if not tolerated according to Lenalidomide SmPC.

Objectives

Primary Objective

To determine the activity of a combination of LEN with Tafasitamab in terms of ORR (ORR = CR + PR) in adult patients with R-R DLBCL.

Secondary Objectives

To determine the activity of a combination of LEN with Tafasitamab with respect to:

1. Disease control rate (DCR = CR + PR + SD)
2. Duration of response (DoR)
3. Progression-free survival (PFS)

4. OS, TTP and the time to next treatment (TTNT)
5. Safety of LEN combined with Tafasitamab.
6. The immunogenicity of Tafasitamab treatment
7. To assess the PK of Tafasitamab
8. To make a preliminary evaluation of ORR, DCR, DoR, PFS, OS, TTP and TTNT in patients treated with a combination of LEN plus Tafasitamab in cohorts with a "low risk", "low-intermediate", "high-intermediate" and "high" International Prognostic Index (IPI)
9. To compare each patient's TTP on LEN plus Tafasitamab with the TTP of their most recent prior therapy
10. To correlate efficacy parameters with certain biomarkers (e.g., baseline tumour CD19 expression level, peripheral NK cell count, constitutional FcγRIIIa and FcγRIIa polymorphism status)

Outcomes/endpoints

Primary Endpoint

The primary efficacy endpoint of this study was ORR, defined as the proportion of complete and partial responders (ORR = CR + PR), as assessed by Independent Radiology/Clinical Review Committee (IRC).

Secondary Endpoints:

- Disease control rate, 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 tumour response and the first time point where a change in response was detailed (specifically, the duration of CRs or PRs until progression or relapse was evaluated);
- Progression-free survival (PFS), defined as the time between first study drug dosing and tumour 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 (the only events of interest are limited to disease progression and death from lymphoma - death from other causes were not considered in relation to the TTP evaluation);
- Overall survival (OS), defined as time from first study drug dosing to the date of death;
- Time to next treatment (TTNT).
- Incidence and severity of AEs
- Determination and characterisation of a potential anti-MOR00208 antibody formation
- Pharmacokinetic analysis of MOR00208
- Absolute and percentage change from baseline in measurements of B-, T- and NK cell populations
- Analysis of exploratory and diagnostic biomarkers from blood and tumour tissue (e.g., CD19, CD20, B-cell lymphoma-2 (BCL-2), and B-cell lymphoma-6 (BCL-6) expression, CD16 expression on NK cells, ADCC capacity), GEP for cell of origin subtyping and evaluation of AEs and ORR by FcγRIIIa and FcγRIIa polymorphism.

Disease response assessments were made according to the revised response criteria based on the guidelines of the International Working Group (IWG) reported by Cheson et al. 2007.

Sample size

The protocol states that "for the determination of a suitable sample size, it is assumed that the combination treatment could improve the ORR from a value of 20% (under monotherapy) to 35% (under combination therapy)." A sample size of 80 subjects would be sufficient to show with 85 % power that the combination treatment could improve the ORR from a value of 20% (under monotherapy) to 35% (under combination therapy). A dropout rate of 10 % was included.

Randomisation

Not applicable; this was a single arm study

Blinding (masking)

Not applicable; This was a single arm study.

Statistical methods

For the analysis of efficacy and baseline characteristics, the full analysis set (FAS) was the primary population. The FAS included all patients who received at least one dose of tafasitamab and at least one dose of LEN.

The Per protocol set (PPS) included all patients in the FAS who did not have any major protocol deviations that could confound the interpretation of the primary analyses conducted on the FAS. The PPS included all patients in the FAS who had received at least one dose of tafasitamab and LEN, and underwent at least one post-baseline response assessment.

The primary efficacy variable, ORR, CR + PR: The number and percentage of patients classified as having best objective response of CR or PR as well as 95% confidence limits (using the Clopper-Pearson exact method) were presented. Patients with no post-baseline assessment of response or not evaluable were included as non-responders. No formal hypothesis testing was conducted.

Sensitivity Analyses of the Primary Endpoint was analysed using best ORR based on the INV assessment (FAS), best ORR based on the PPS (based on INV and IRC assessment) and best ORR excluding patients with no post-baseline assessment of response or with all post-baseline assessments categorised as "Unknown". The analysis was performed using the FAS based on both IRC and INV assessment.

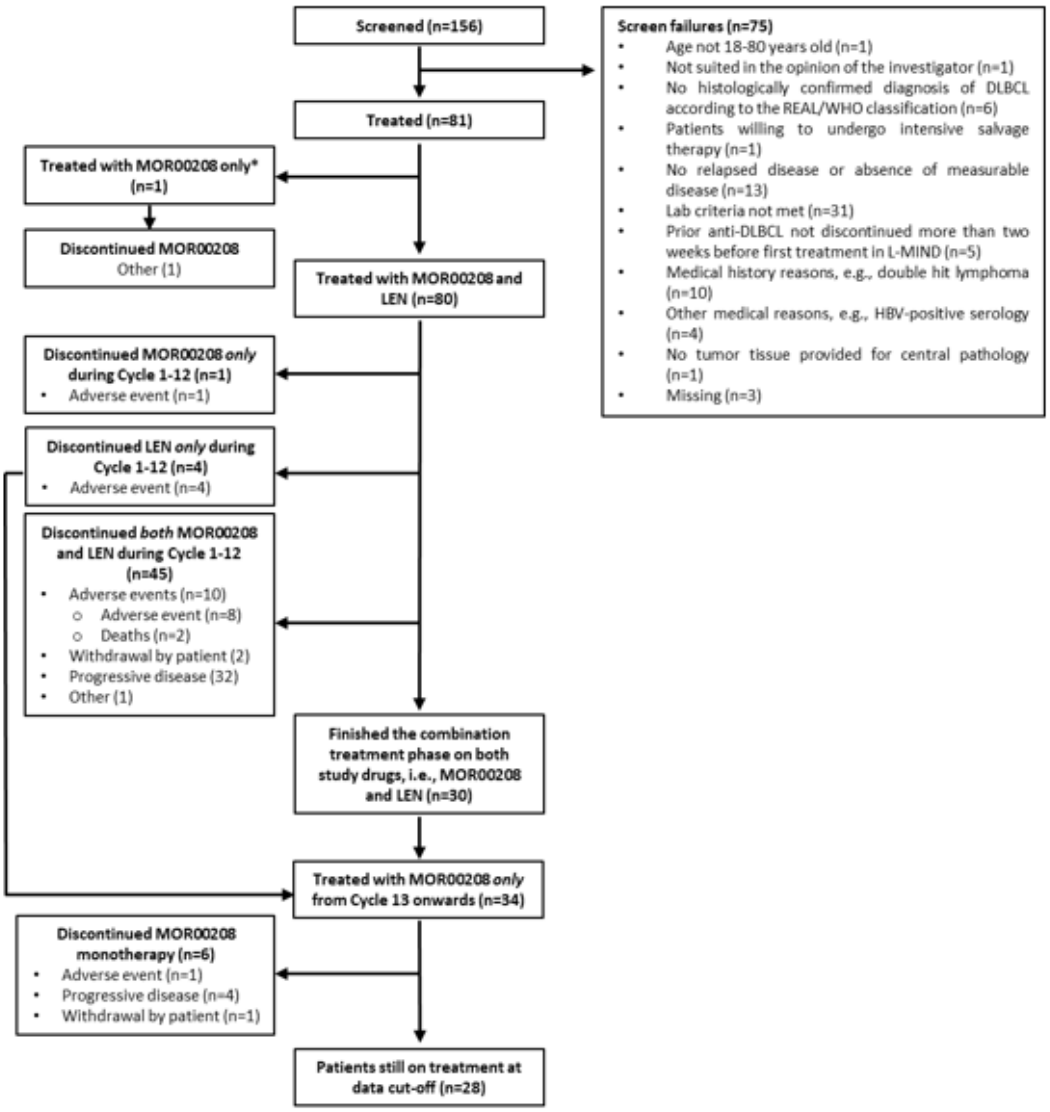
Secondary endpoints: The same statistical methods as for the primary endpoint were used. The distribution of PFS was estimated using the Kaplan-Meier (K-M) method. The median PFS time along with 95% confidence intervals, the 25th and 75th percentiles is presented (Brookmeyer and Crowley 1982).

Sensitivity analyses: The main analysis will be conducted on the PPS, based on the INV response assessment as entered on the 'Lymphoma Tumour Assessment' eCRF page. The analysis will be conducted using both the FAS and the PPS. Patients having more than one missed visit, but having an available death date, will be included in the time-to-event analysis and considered as having a PFS event. The analysis will be performed on the FAS for both IRC and INV response assessment.

Results

Participant flow

Figure 2-1 Patient Disposition at Primary Data Cut-off of 30 Nov 2018 (All Enrolled Patients) (MOR208C203)



DLBC = Diffuse large B-cell lymphoma; LEN = Lenalidomide; n = Number of patients; REAL = Revised European American Lymphoma; WHO = World Health Organization.

The enrolled patient population consisted of all patients who received at least 1 dose of any study drug (tafasitamab or LEN).

These summaries include discontinuations of tafasitamab and LEN at the same time as well as sequential discontinuations. If study drugs were discontinued sequentially for different reasons, only the reason for the later discontinuation was summarized.

These summaries include patients who discontinued the other study drug before completing 12 cycles (discontinuations at the same time as well as sequential discontinuations).

More than one reason for screen failure could be given.

Percentage is based on the number of enrolled patients and for screen failures was based on the number of screened patients.

Source: m5.3.5.1/MOR208C203/Fig10-1, Data cut-off 30 Nov 2018

Table 13: Patient disposition at primary data cut-off of 30 Nov 2018 (All patients enrolled) (MORR208C203)

	Tafasitamab + LEN (N = 81) n (%)
Patients enrolled (a)	81
Patients treated with both study drugs	80 (98.8)
Patients treated with only 1 study drug	1 (1.2)
LEN only	0
Tafasitamab only	1 (1.2)
Patients who reached Cycle 13 Day 1 on at least 1 study drug	34 (42.0)
Patients still on treatment with Tafasitamab + LEN combination therapy (Cycles 1-12)	0*
Patients still on treatment with Tafasitamab monotherapy after combination treatment phase (Cycle 13 onwards)	28 (34.6)
Patients who successfully finished the combination treatment phase on both study drugs (12 cycles)	30 (37.0)
Patients who discontinued tafasitamab after successful completion of combination treatment (12 cycles)	5 (6.2)
Patients who discontinued LEN after completion of combination treatment (12 cycles)	30 (37.0)*
Patients who discontinued Tafasitamab after Cycle 12 regardless of successful or unsuccessful completion of combination treatment	6 (7.4)
Patients who did not successfully finish the combination treatment phase (b)	51 (63.0)
Patients who discontinued both tafasitamab and LEN before completing 12 cycles (b),(c)	46 (56.8)
Patients who discontinued only LEN before completion of combination treatment (12 cycles)	4 (4.9)
Patients who discontinued only Tafasitamab before completion of combination treatment (12 cycles)	0
Patients who discontinued LEN before completion of combination treatment (12 cycles) (d)	49 (60.5)
Patients who discontinued Tafasitamab before completion of combination treatment (12 cycles)	47 (58.0)
Patients who discontinued LEN at any time during the study	80 (98.8)*
Patients who discontinued LEN at any time during the study without discontinuation of Tafasitamab at the same time	74 (91.4)
Patients who discontinued Tafasitamab at any time during the study	53 (65.4)
Patients who discontinued Tafasitamab at any time during the study without discontinuing LEN at the same time	47 (58.0)

LEN = lenalidomide; N/n = number of patients

(a) The enrolled patient population consisted of all patients who received at least 1 dose of any study drug (Tafasitamab or LEN).

(b) These summaries include patient 94004-06 who received tafasitamab but was never treated with LEN.

(c) These summaries included discontinuations of tafasitamab and LEN at the same time as well as sequential discontinuations.

Successful completion of combination therapy means patients completed 12 cycles on both drugs.

* Expected based on study design

Percentage is based on the number of enrolled patients.

Source: m5.3.5.1/MOR208C203/Tab10-1, Data cut-off 30 Nov 2018

Recruitment

Study Initiation Date: 29 March 2016

Initial data cut-off was 30 Nov 2018. The applicant also provided an addendum with data cut-off as of 30 November 2019.

In total, 56 sites in 10 countries (Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, United Kingdom and United States) were activated for enrolment, out of which 14 sites did not screen any patients; 42 sites screened patients; 35 sites enrolled patients.

Conduct of the study

Changes in the Protocol

The original protocol submitted to the Ethics Committee/Health Authorities was protocol version 3.0 (dated 18 Mar 2015). As of 30 Nov 2018, protocol version 3.0 had been amended three times. A summary of main changes for each amendment is shown below.

In Amendment # 1 dated 27 May 2015 the dosing schedule was changed to bi-weekly tafasitamab administration from Cycle 4. Patient inclusion /exclusion criteria were updated as follows: patients with evidence of histological transformation to DLBCL from indolent NHL were included. Biopsied material which was ≤ 3 years old was accepted for the purpose of the study. Exclusion criterion was re-worded allowing DLBCL transformed from indolent NHL into the study. The duration time free from disease (of prior malignancies) was increased from ≥ 3 years to ≥ 5 years prior to screening. The collection of ECG RR intervals was added as were needed for QTc calculations.

In Amendment # 2 dated 27 Jun 2016 The target patient population/inclusion criteria were updated. This amendment allowed up to three prior lines for DLBCL treatment (previously two prior lines). Detailed description of DLBCL histologies that could qualify for the study was added. Upper age limit for study entry (80 years) was removed based on feedback from several initiated sites. Fresh tumour tissues for central pathology review was specified. The lesion must be positive on PET scan (based on Juweid et al., 2007). The definition of primary refractory DLBCL was revised, (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.

In Amendment # 3 dated 23 Oct 2017 the treatment with tafasitamab was extended beyond Cycle 24 until progression because the previous version of the protocol allowed an extended treatment with tafasitamab for patients with an ongoing response of CR or PR for 24 cycles. In view of limited treatment options available for treatment of relapsed/refractory DLBCL, an option of continuing with tafasitamab treatment beyond Cycle 24 and until disease progression (or unacceptable toxicity) was provided in this protocol amendment, based on the decision of the treating investigator. The imaging frequency after Cycle 24 while on treatment with tafasitamab was changed to once per year, either CT or MRI, followed by PET at the investigator's discretion. More frequent scans were not recommended as per standard of care. Disease assessment by CT/MRI during additional treatment phase.

The CSR was addended 13 Mar 2020, to provide efficacy analyses based on the data cut-off 30 Nov 2019 as well as additional statistical analyses, please refer to the statistical section.

Protocol deviations

A summary of key protocol deviations is presented.

Table 14: Key protocol deviations

Protocol Deviation	MOR00208 + LEN (N = 81) n (%)
Overall	
Prohibited concomitant medication	5 (6.2)
Informed consent form	21 (25.9)
Eligibility criteria	16 (19.8)
Laboratory assessment	29 (35.8)
Procedure or test	62 (76.5)
Study drug and treatment	31 (38.3)
Visit schedule and assessment	1 (1.2)
Other	22 (27.2)

Abbreviations: LEN = Lenalidomide; N/n = Number of patients; SAF = Safety analysis set.
Percentages were based on the number of patients in SAF, N.
A patient can have more than one protocol deviation.
Only patient-related protocol deviations are included in this table.

Table 15: Protocol deviations in the FAS that led to exclusion from the PPS

Protocol Deviation Leading to Exclusion from PPS	MOR00208 + LEN (N = 80) n (%)
Prohibited concomitant medication	2 (2.5)
Eligibility criteria	1 (1.3)

Abbreviations: FAS = Full analysis set; LEN = Lenalidomide; N/n = Number of patients; PPS = Per protocol set.
Percentages were based on the number of patients in FAS, N.

Two (2.5%) patients were excluded from the PPS due to prohibited concomitant medication or radiotherapy. One (1.3%) patient was excluded due to inclusion criterion 4b (a PET-positive measurable disease could not be confirmed as a part of screening assessments).

Baseline data

Table 16: Demographics characteristics (FAS) in MOR208C203

Demographic Characteristics	Tafasitamab + LEN (N = 81)
Age (years)	
n	81
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 (79.0)
< 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)*
Weight (kg)	
n	80
Mean (StD)	78.09 (18.265)
Median	75.25
Q1, Q3	66.50, 87.95
Min, max	43.3, 144.8

SAF = safety analysis set; LEN = lenalidomide; StD = standard deviation; Q1 = lower quartile; Q3 = upper quartile
Percentages were based on the number of patients in the SAF, N.
Race was collected including before entry into the study, as applicable.
Age collected at study entry included.
*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).
Source: m5.3.5.1/MOR208C203 Amended Sep20/Tab14.1.5.2, Data cut-off 30 Nov 2018

Table 17: Baseline characteristics in study L-MIND

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)	39.584 (34.8392)
Median	26.870
Q1, Q3	16.890, 50.500
Min, max	7.75, 189.27
Time since discontinuation of last prior anti-DLBCL medication or ASCT (months)	
n	81
Mean (StD)	16.994 (21.8378)
Median	9.200
Q1, Q3	4.860, 20.240
Min, max	0.62, 121.92
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 (55.6)
2	7 (8.6)
Ann Arbor Disease Staging dichotomised 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 (elevated)	45 (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)
Cell of origin based on gene expression profiling n (%)	
GCB	7 (8.6)
ABC	19 (23.5)
Unclassified	6 (7.4)
Not evaluable	5 (6.2)
Missing	44 (54.3)
Rituximab refractoriness n (%)	
Yes	34 (42.0)
No	46 (56.8)
Unknown	1 (1.2)
Refractoriness to last prior therapy n (%)	
Yes	36 (44.4)
No	45 (55.6)

Baseline Characteristics	Tafasitamab + LEN (N = 81)
Primary refractoriness n (%)	
Yes	15 (18.5)
No	66 (81.5)
Prior ASCT n (%)	
Yes	9 (11.1)
No	72 (88.9)
FcγRIIIa affinity n (%)	
High affinity: FCγRIIIa-158 V homozygosity	15 (18.5)
Low affinity: FCγRIIIa-158 F homozygosity or FCγRIIIa-158 F/V heterozygosity	47 (58.0)
Missing	19 (23.5)
FcγRIIa affinity n (%)	
High affinity: FCγRIIa-131 H homozygosity	26 (32.1)
Low affinity: FCγRIIa-131 R homozygosity or FCγRIIaA-131 H/R heterozygosity	34 (42.0)
Missing	21 (25.9)
NHL subtype per central pathology n (%)	
Composite lymphoma with DLBCL component	9 (11.1)
DLBCL	54 (66.7)
DLBCL (double-hit lymphoma)	1 (1.2)
DLBCL (triple-hit lymphoma)	1 (1.2)
EBV-positive DLBCL	2 (2.5)
Follicular lymphoma (Grade 2 + 3a)	1 (1.2)
Follicular lymphoma Grade 2	2 (2.5)
Mantle cell lymphoma	1 (1.2)
Marginal zone lymphoma	5 (6.2)
T Cell/histiocyte rich large B cell lymphoma	2 (2.5)
Unknown	2 (2.5)
Missing	1 (1.2)

ABC = activated B-cell; ASCT = autologous stem cell transplantation; BMI = body mass Index; DLBCL = diffuse large B-cell lymphoma; EBV=Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; SAF = safety analysis set; GCB = germinal centre B-cell; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LEN = lenalidomide; N = number of patients in SAF; n = number of patients in each category; NHL=non-Hodgkin's lymphoma; PD = progressive disease; PR = partial response; RTX = rituximab; SD = stable disease StD = standard deviation; Q1 = lower quartile; Q3 = upper quartile.

Percentages were based on the number of patients in the SAF, N.

Race, cell of origin (based on immune-histochemistry and gene expression profiling) was collected including before entry into the study, as applicable. In exceptional cases Fcγ samples might have been from a timepoint after start of treatment.

Parameters collected at study entry included: age, weight, BMI, Ann Arbor Staging, IPI, LDH, number of prior regimens, refractoriness to rituximab and to last prior therapy.

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

**As per central pathology assessment based on Hans' algorithm (Hans et al. 2004).

Source: m5.3.5.1/MOR208C203 Amended Sep20/Tab14.1.5.2, Tab14.1.8.2, Data cut-off 30 Nov 2018

Table 18: DLBCL - specific medical history and diagnosis (SAF)

Table 11-3 DLBCL-Specific Medical History and Diagnosis (SAF)

Characteristic	MOR00208 + LEN (N = 81)
Stage at initial diagnosis n (%)	
Stage I	6 (7.4)
Stage II	8 (9.9)
Stage III	21 (25.9)
Stage IV	41 (50.6)
Not Available	5 (6.2)
Stage at screening (current stage) n (%)	
Stage I	4 (4.9)
Stage II	16 (19.8)
Stage III	16 (19.8)
Stage IV	45 (55.6)
Stage I or II	20 (24.7)
Stage III or IV	61 (75.3)
Disease risk (IPI) at screening	
n	81
Median	3.0
Disease risk (IPI) at screening n (%) [a]	
0	5 (6.2)
1	11 (13.6)
2	24 (29.6)
3	24 (29.6)
4	14 (17.3)
5	3 (3.7)
Bulky disease at screening n (%) [b]	
Present	15 (18.5)
Absent	65 (80.2)
Missing	1 (1.2)

Continued

Table 11-3 DLBCL-Specific Medical History and Diagnosis (SAF) (Continued)

Characteristic	MOR00208 + LEN (N = 81)
Time since first DLBCL diagnosis (months)	
n	81
Mean (StD)	39.584 (34.8392)
Median	26.870
Q1, Q3	16.890, 50.500
Min, Max	7.75, 189.27
Time since first DLBCL progression/relapse (months)	
n	81
Mean (StD)	9.797 (14.7679)
Median	4.140
Q1, Q3	1.310, 10.940
Min, Max	0.26, 74.94
Time since last progression/relapse (months)	
n	81
Mean (StD)	1.871 (1.5179)
Median	1.450
Q1, Q3	0.850, 2.300
Min, Max	0.07, 8.18
NHL subtype as assigned by central pathology n (%)	
Composite Lymphoma with DLBCL Component	9 (11.1)
DLBCL	54 (66.7)
DLBCL (Double-Hit Lymphoma)	1 (1.2)
DLBCL (Triple-Hit Lymphoma)	1 (1.2)
EBV-positive DLBCL	2 (2.5)
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	5 (6.2)
T-Cell/Histiocyte Rich Large-B-Cell Lymphoma	2 (2.5)
Unknown	2 (2.5)
Missing	1 (1.2)*
LDH levels at baseline n (%) [c]	
Elevated	45 (55.6)
Not elevated	36 (44.4)

Continued

Table 11-3 DLBCL-Specific Medical History and Diagnosis (SAF) (Continued)

Characteristic	MOR00208 + LEN (N = 81)
Time since discontinuation of last prior anti-DLBCL medication or ASCT (months)	
n	81
Mean (StD)	16.994 (21.8378)
Median	9.200
Q1, Q3	4.860, 20.240
Min, Max	0.62, 121.92
Relapse after initial diagnosis of DLBCL n (%)	
Early relapse (interval between diagnosis of DLBCL and relapse ≤ 12 months)	19 (23.5)
Late relapse (interval between diagnosis of DLBCL and relapse > 12 months)	61 (75.3)
Unknown	1 (1.2)

Abbreviations: ASCT = Autologous stem cell transplantation; DLBCL = Diffuse large B-cell lymphoma; EBV =Epstein-Barr virus; FAS = Full analysis set; IPI =International Prognostic Index; LDH = Lactate dehydrogenase; LEN = Lenalidomide; N =Number of patients in SAF; n =Number of patients in each category; NHL = Non-Hodgkin lymphoma; Q1 =Lower quartile; Q3 =Upper quartile; StD =Standard deviation.

Percentages were based on the number of patients in SAF, N.

* No biopsy material was available for the central pathology assessment for patient 43003-04, (Listing 16.2.4.7)

[a] The IPI score ranging from 0-5, was categorised into low risk and low-intermediate risk (0-2 points) and high risk and intermediate-high risk (3–5 points).

[b] Bulky disease was defined as having a longest lesion diameter of ≥ 7.5 cm as assessed by central radiological assessment.

[c] Baseline refers to pre-treatment test on Cycle 1 Day 1

Data source: Table 14.1.8.2

Updates of the baseline characteristics resulted from availability of additional data from central pathology review (evaluation of additional biopsy material) after the Primary Analysis for two patients. The updates refer to the data categories cell of origin by immuno-histochemistry (IHC), gene expression profiling (GEP) and diffuse large B-cell lymphoma (DLBCL) subtype based on central pathology review.

Table 19: Updates of the baseline characteristics and DLBCL - specific medical history and diagnosis (SAF) as of data cut-off 30 Nov 2019

Characteristic	MOR00208 + LEN (N = 81)
Cell of origin based on immuno-histochemistry/central pathology n (%)**	
GCB	39 (48.1)
Non-GCB	22 (27.2)
Missing	20 (24.7)
Cell of origin based on gene expression profiling n (%)	
GCB	8 (9.9)
ABC	20 (24.7)
Unclassified	6 (7.4)
Not evaluable	5 (6.2)
Missing	42 (51.9)
NHL subtype as assigned by central pathology n (%)	
Composite Lymphoma with DLBCL Component	10 (12.3)
DLBCL	54 (66.7)
DLBCL (Double-Hit Lymphoma)	1 (1.2)
DLBCL (Triple-Hit Lymphoma)	1 (1.2)
EBV-positive DLBCL	2 (2.5)
Histological transformation to DLBCL from indolent NHL	1 (1.2)
T-Cell/Histiocyte-Rich Large B-Cell Lymphoma	2 (2.5)
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)
Missing	1 (1.2)*

Abbreviations: ABC =Activated B-cell; DLBCL =Diffuse large B-cell lymphoma; GCB =Germinal center B-cell; EBV =Epstein-Barr virus; LEN = Lenalidomide; NHL = Non-Hodgkin lymphoma; N =Number of patients in SAF; n =Number of patients in each category; StD =Standard deviation; Q1 =Lower quartile; Q3 =Upper quartile.

Numbers analysed

Table 20: Analysis populations (all patients enrolled)

	MOR00208 + LEN n (%)
Enrolled Patients [a]	81 (100)
Full Analysis Set [b]	80 (98.8)
Excluded from Full Analysis Set	1 (1.2)
Reason for exclusion	
Not dosed at least one dose of MOR00208 and one dose of LEN	1 (1.2)
Per Protocol Set [c]	70 (86.4)
Excluded from Per Protocol Set	11 (13.6)
Reason for exclusion	
Not dosed at least one dose of MOR00208 and one dose of LEN	1 (1.2)
No post-baseline response assessment	8 (9.9)
Major protocol violations*	3 (3.7)
Safety Analysis Set [d]	81 (100)
Excluded from Safety Analysis Set	0
Pharmacokinetic Analysis Set [e]	81 (100)
Excluded from Pharmacokinetic Analysis Set	0
Immunogenicity Analysis Set [f]	81 (100)
Excluded from Immunogenicity Analysis Set	0

Abbreviations: IAS = Immunogenicity Analysis Set; LEN = Lenalidomide; n = Number of patients; PKAS = Pharmacokinetic Analysis Set; PPS = Per Protocol Set; SAF = Safety Analysis Set.

Percentages were based on the number of enrolled patients. A patient may have been counted under more than one reason for being excluded from an analysis population.

* As described in Section 10.2

[a] The Enrolled patient's population consisted of all patients who received at least one dose of any study drug (MOR00208 or LEN).

[b] The FAS included all patients who received at least one dose of MOR00208 and one dose of LEN.

[c] The PPS consisted of all patients in the FAS who had no major protocol deviations.

[d] The SAF included all patients who received at least one dose of MOR00208 or LEN and had at least one post-baseline safety assessment.

[e] The PKAS included all patients who received at least one dose of MOR00208 and have at least one quantifiable serum MOR00208

[f] The IAS included all patients who had at least one anti-MOR00208 antibody assessment.

Data source: Table 14.1.4

One patient was initially excluded since this patient only received tafasitamab. After the submission of the MAA, the applicant detected an error in the adjudication of the central response assessment by the Independent Review Committee (IRC) for one patient (Study MOR208C203), for which the comment of the adjudicating radiologist did not match the selection of the best response by the Adjudicator. Upon detection of these discrepancies, the applicant reviewed and reconciled the data in the efficacy analysis.

Outcomes and estimation

The dossier contains two data cut-offs, 30 Nov 2018 and 30 Nov 2019, unless otherwise specified the data cut-off as of 30 Nov 2019 is presented. Correction of the data was submitted in July 2020. Supplementary data with a cut-off of October 2020 were also provided by the applicant.

Primary endpoint

Table 21: Summary of best response rate as of data cut-off 30 Nov 2019 and corrected as of July 2020

Summary of Best Objective Response Rate (IRC Evaluation) SAF

	MOR00208 + LEN (N = 81) n (%)
Best Objective Response	
Complete Response (CR) [95% Exact CI] [b]	32 (39.5) [28.8, 51.0]
Partial Response (PR) [95% Exact CI] [b]	14 (17.3) [9.8, 27.3]
Stable Disease (SD)	13 (16.0)
Progressive Disease (PD)	13 (16.0)
Not Evaluable (NE)	9 (11.1)
Best Objective Response Rate (ORR) [a]	
Responders [95% Exact CI] [b]	46 (56.8) [45.3, 67.8]
Reason for having not evaluable status	
No valid post-baseline response assessment	9 (11.1)

CI = Confidence interval; SAF = Safety analysis set; IRC =Independent Radiology/Clinical Review Committee; LEN = Lenalidomide; N = Number of patients in SAF; n = Number of patients in each category.
Percentages are based on the number of patients in SAF, N.
[a] The best ORR is defined as the proportion of patients with CR or PR as best response achieved at a ny time during the study.
[b] Using two-sided 95% Clopper-Pearson exact method based on binomial distribution.
Source: D120 ICO Tables/Table 14.2.30.1

Table 22: Updates in ORR and CR rate

	Data cut-off of 30-NOV-2018		Data cut-off of 30-NOV-2019	
	Submitted in MAA	Corrected (JUL-2020)	Submitted in MAA	Corrected (JUL-2020)
ORR, % (n/N) [95% CI]	60.0 (48/80) [48.4 – 70.8]	58.8 (47/80) [47.2 – 69.6]	58.8 (47/80) [47.2 – 69.6]	57.5 (46/80) [45.9 – 68.5]
CR rate, % (n/N) [95% CI]	42.5 (34/80) [31.5 – 54.1]	41.3 (33/80) [30.4 – 52.8]	41.3 (33/80) [30.4 – 52.8]	40.0 (32/80) [29.2 – 51.6]
SD rate, % (n/N) [95% CI]	13.8 (11/80) [7.1 – 23.3]	15.0 (12/80) [8.0 – 24.7]	15.0 (12/80) [8.0 – 24.7]	16.3 (13/80) [8.9 – 26.2]

CI: Confidence Interval; ORR: Overall Response Rate; CR: Complete Response; SD: Stable Disease

Sensitivity Analysis for Primary Endpoint (IRC Evaluation)

For the PPS (N=70), the best objective response per IRC was CR for 33 (47.1%) patients and PR for 13 (18.6%) patients. Based on these data, the best ORR was 65.7% (95% CI: 53.4, 76.7). Eleven (15.7%) patients had SD as their best ORR and 13 (18.6%) patients had a PD.

Table 23 Table 24: Concordance between IRC and Investigator Evaluations for the Primary Endpoint Best Objective Response Rate

Table 1: Correlation matrix for best objective response between IRC and INV assessment, FAS (cut-off date 30Nov2019, IRC correction considered)

	IRC Assessment (N = 80)						
INV Assessment	CR	PR	SD	PD	Not Evaluable	Not Available	Total
CR	27 (84.4)	2 (14.3)	0	0	0	0	29 (36.3)
PR	4 (12.5)	10 (71.4)	7 (53.8)	0	1 (100)	0	22 (27.5)
SD	1 (3.1)	2 (14.3)	5 (38.5)	1 (7.7)	0	0	9 (11.3)
PD	0	0	1 (7.7)	12 (92.3)	0	0	13 (16.3)
Not Evaluable (Indeterminate)	0	0	0	0	0	0	0
Not Available	0	0	0	0	0	7 (100)	7 (8.8)
Total	32 (100)	14 (100)	13 (100)	13 (100)	1 (100)	7 (100)	80 (100)

Note: Percentages in each column are based on the total number of patients with IRC assessment as specified in the header of the respective column.
Agreement for best ORR = 84.3 %.
Source: D120_NOV19_Tables/Table 14.2.1.4

Table 2: Correlation matrix for best objective response between IRC and INV assessment, FAS (cut-off date 30Nov2018, IRC correction considered)

	IRC Assessment (N = 80)						
INV Assessment	CR	PR	SD	PD	Not Evaluable	Not Available	Total
CR	28 (84.8)	1 (7.1)	0	0	0	0	29 (36.3)
PR	4 (12.1)	11 (78.6)	6 (50.0)	0	1 (100)	0	22 (27.5)
SD	1 (3.0)	2 (14.3)	5 (41.7)	1 (7.7)	0	0	9 (11.3)
PD	0	0	1 (8.3)	12 (92.3)	0	0	13 (16.3)
Not Evaluable (Indeterminate)	0	0	0	0	0	0	0
Not Available	0	0	0	0	0	7 (100)	7 (8.8)
Total	33 (100)	14 (100)	12 (100)	13 (100)	1 (100)	7 (100)	80 (100)

Note: Percentages in each column are based on the total number of patients with IRC assessment as specified in th e header of the respective column.
Agreement for best ORR = 86.3 %
Source: D120_NOV18_Tables/Table 14.2.1.4

The efficacy results as of data cut off of 30.11.2019 based on patients who had their DLBCL diagnosis confirmed by central pathology were updated. The comparison of efficacy results between DLBCL as per investigator assessment vs. centrally confirmed DLBCL showed, that estimates for all endpoints were somewhat lower in respect of the centrally confirmed DLBCL. Best ORR were 57.5% (95% IC: 45.9, 68.5) and 54.3% (95% IC: 41.9, 66.3), CR were 40% (95% IC: 29.2, 51.6) and 35.7% (95% IC: 24.6, 48.1), median PFS were 12.1 months (95% IC: 6.3, NR) and 9.1 months (95% IC: 4.7, NR), median OS were 31.6 months (95% IC: 18.3, NR) and 26.4 months (95% IC: 14.9, NR), respectively in the DLBCL as per investigator assessment compared with the centrally confirmed DLBCL. The median DOR were 34.6 months in both set of patients.

Secondary endpoints- DoR

The below table represents data as of Data cut-off of 30 Nov 2019 for all 81 patients in the ITT.

Table 25: Kaplan-Meier Analysis of Duration of Response (IRC Evaluation) SAF

	MOR00208 + LEN (N = 81)
Duration of Response (DoR) [a]	
Patients with Response	46
Progression/death n (%)	13 (28.3)
Progression	12 (26.1)
Death	1 (2.2)
Censored n (%)	33 (71.7)
Kaplan-Meier Estimates	
25th Percentile (months), [95% CI]	21.7 [3.7, NR]
Median (months), [95% CI]	34.6 [26.1, NR]
75th Percentile (months), [95% CI]	34.6 [NR, NR]
1 Month DoR %, [95% CI]	100.0 [100.0, 100.0]
3 Months DoR %, [95% CI]	90.9 [77.6, 96.5]
6 Months DoR %, [95% CI]	79.1 [63.6, 88.5]
12 Months DoR %, [95% CI]	76.4 [60.5, 86.6]
18 Months DoR %, [95% CI]	76.4 [60.5, 86.6]
24 Months DoR %, [95% CI]	71.3 [52.8, 83.7]
30 Months DoR %, [95% CI]	64.8 [43.3, 79.9]

N = Number of patients in SAF.
IRC = Independent Radiology/Clinical Review Committee, CI = Confidence interval, NR = Not reached.
95% CIs for the Median and the 25th and 75th Percentiles are calculated using the method of Brookmeyer and Crowley (1982).
Percentages are based on the number of patients with response.
[a] DoR [months] = (date of assessment of tumour progression or death – date of assessment of first documented response of (CR or PR) + 1)/30.4375.
Source: D120_ICO_Tables/Table 14.2.30.2

As of data cut-off 30-NOV-2019, 8 patients were censored due to other reasons than being ongoing on DoR follow-up. Of these, 6 patients were censored since they had initiated a new anti-tumour therapy, 3 of which due to progressive disease. Two patients were censored due to an event after two or more missing tumour response assessments, one patient suffered from general deterioration and one had grade 4 thrombocytopenia.

Table 26: Updates in the DoR analysis

	Cut-off of 30-NOV-2018		Cut-off of 30-NOV-2019	
	Submitted in MAA	Corrected (JUL-2020)	Submitted in MAA	Corrected (JUL-2020)
Patients with response	48	47	47	46
Progression/death, n [%]	13 [27.1]	13 [27.7]	13 [27.7]	13 [28.3]
Progression, n [%]	12 [25.0]	12 [25.5]	12 [25.5]	12 [26.1]
Death, n [%]	1 [2.1]	1 [2.1]	1 [2.1]	1 [2.2]
Censored, n [%]	35 [72.9]	34 [72.3]	34 [72.3]	33 [71.7]
Kaplan-Meier estimates				
25th percentile, months [95% CI]	8.1 [3.7 - NR]	8.1 [3.7 - NR]	21.7 [3.9 – 34.6]	21.7 [3.7 - NR]
Median DoR, months [95% CI]	21.7 [21.7 - NR]	21.7 [21.7 - NR]	34.6 [26.1 – 34.6]	34.6 [26.1 - NR]
75th percentile, months [95% CI]	NR [21.7 - NR]	NR [21.7 - NR]	34.6 [NR, NR]	34.6 [NR, NR]
1 month DoR, % [95% CI]	100.0 [100.0 – 100.0]	100.0 [100.0 – 100.0]	100.0 [100.0 – 100.0]	100.0 [100.0 – 100.0]
3 month DoR, % [95% CI]	89.1 [75.8 – 95.3]	88.9 [75.3 – 95.2]	91.1 [78.0 – 96.6]	90.9 [77.6 – 96.5]
6 month DoR, % [95% CI]	77.4 [62.1 – 87.2]	76.9 [61.3 – 86.9]	79.5 [64.3 – 88.8]	79.1 [63.6 – 88.5]
12 month DoR, % [95% CI]	71.6 [55.1 – 82.9]	71.1 [54.4 – 82.6]	76.9 [61.2 – 86.9]	76.4 [60.5 – 86.6]
18 month DoR, % [95% CI]	71.6 [55.1 – 82.9]	71.1 [54.4 – 82.6]	76.9 [61.2 – 86.9]	76.4 [60.5 – 86.6]
24 month DoR, % [95% CI]	47.7 [10.5 – 78.4]	47.4 [10.5 – 78.1]	71.8 [53.3 - 84]	71.3 [52.8 – 83.7]
30 month DoR, % [95% CI]	NR [NR, NR]	NR [NR, NR]	65.0 [43.7 – 80.2]	64.8 [43.3 – 79.9]

CI: Confidence Interval; DoR: Duration of Response; NR: Not Reached

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

Percentages were based on the number of patients with response.

[a] DoR [months] = (date of assessment of tumor progression or death – date of assessment of first documented response of (CR or PR) +1)/30.4375.

Secondary endpoints – PFS

As of the data cut-off date of 30 Nov 2019 the corrected (as of July 2020) Kaplan-Meier analysis of progression-free survival (PFS) by Independent Radiology/Clinical Review Committee (IRC) evaluation for patients in the Safety Analysis Set (SAF) including Patient 94004-06 (N=81) is summarised.

Table 27: Kaplan Meier analysis of PFS (IRC evaluation) SAF

	MOR00208 + LEN (N = 81)
Progression-free Survival [a]	
Progression/death n (%)	41 (50.6)
Progression	33 (40.7)
Death	8 (9.9)
Censored n (%)	40 (49.4)
Kaplan-Meier Estimates	
25th Percentile (months), [95% CI]	2.7 [1.9, 5.3]
Median (months), [95% CI]	12.1 [5.7, NR]
75th Percentile (months), [95% CI]	NR [36.4, NR]
1 Month progression-free %, [95% CI] [b]	92.3 [83.7, 96.5]
3 Months progression-free %, [95% CI]	74.1 [62.7, 82.4]
6 Months progression-free %, [95% CI]	61.6 [49.6, 71.5]
12 Months progression-free %, [95% CI]	51.0 [38.9, 61.8]
18 Months progression-free %, [95% CI]	47.6 [35.5, 58.7]
24 Months progression-free %, [95% CI]	45.0 [32.6, 56.6]
30 Months progression-free %, [95% CI]	41.5 [28.5, 54.0]
Median follow-up time (PFS) (months), [95% CI] [c]	22.6 [22.2, 30.4]

Percentages are based on the number of patients in SAF, N.
IRC = Independent Radiology/Clinical Review Committee, CI = Confidence interval, NR = Not reached.
95% CIs for the Median and the 25th and 75th Percentiles are calculated using the method of Brookmeyer and Crowley (1982).
[a] PFS time is defined as the time (in months) from the date of the first administration of any study drug to the date of tumor progression or death from any cause.
[b] Progression-free survival % estimate is the estimated probability that a patient will remain progression-free up to the specified point in time.
[c] The median follow-up time for PFS will be calculated using the reverse Kaplan-Meier method, considering the censored patients as events and patients with events as censored.

The majority of patients were censored due to an ongoing PFS follow-up at the data cut-off date.

Table 28: The censoring reasons for PFS-INV and PFS-IRC (SAF; n=81 patients).

	IRC Evaluation (N=81) n (%)	INV Evaluation (N=81) n (%)
Number of censored patients	40 (49.4)	35 (43.2)
Censoring reasons		
Discontinued without event	2 (2.5)	2 (2.5)
Event documented after two or more missing tumour assessments	3 (3.7)	3 (3.7)
New anti-cancer therapy started	10 (12.3)	5 (6.2)
Ongoing	25 (30.9)	25 (30.9)

SAF: safety analysis set. INV : Investigator assessment. IRC : Independent Radiology/Clinical Review Committee.
Percentages are based on the number of patients in the SAF, N.
Source: D180_Nov19 Tables/Tab14.2.3.1.4 and Tab 14.2.3.2.4

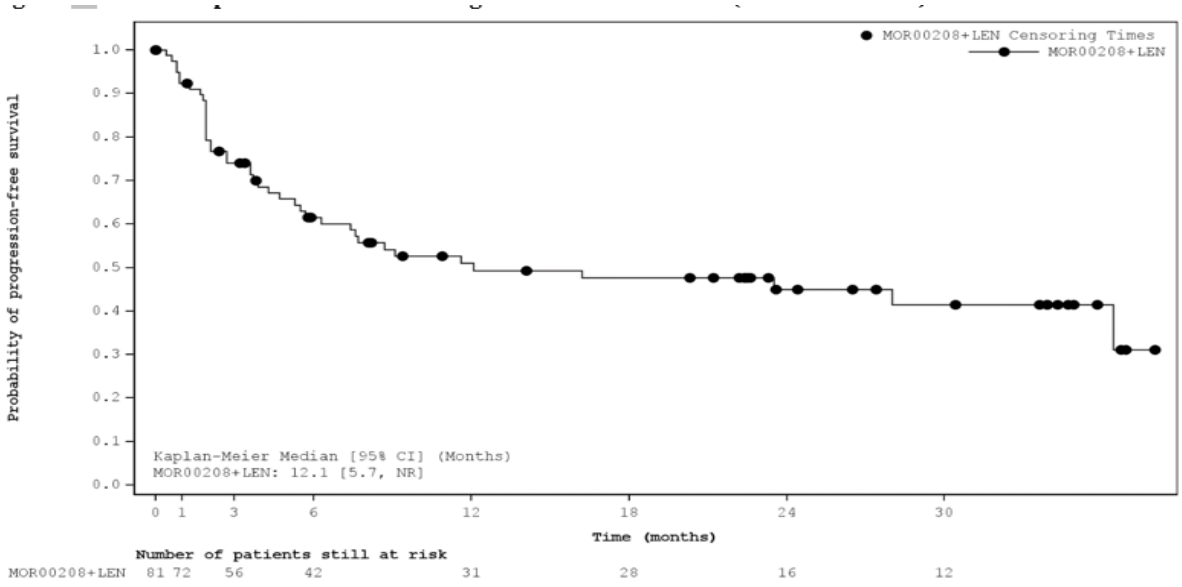
Table 29: Concordance of PFS events and censorings between the investigator (INV) and IRC assessment (SAF; n=81 patients). 30.11.2019 cut-off

		IRC Assessment		
		PFS Event	No PFS Event (Censored)	Total
INV Assessment	PFS Event	40 (49.4)	6 (7.4)	46 (56.8)
	No PFS Event (Censored)	1 (1.2)	34 (42.0)	35 (43.2)
	Total	41 (50.6)	40 (49.4)	81 (100)

Note: percentages are based on numbers of patients in the SAF.
INV: Investigator assessment. IRC : Independent Radiology/Clinical Review Committee.
Concordance rate: 91.4%. The concordance rate is defined as the number of patients who are concordant over the total number of patients in the SAF : [(agreement in PFS events for 40 cases) + (agreement in censoring events for 34 cases)] / 81.
Source: D180_Nov19 Tables/Tab14.2.3.30

The concordance rate was 91.4% (49.4% + 42%).

Figure 23: Kaplan Meier analysis of PFS (IRC evaluation) SAF



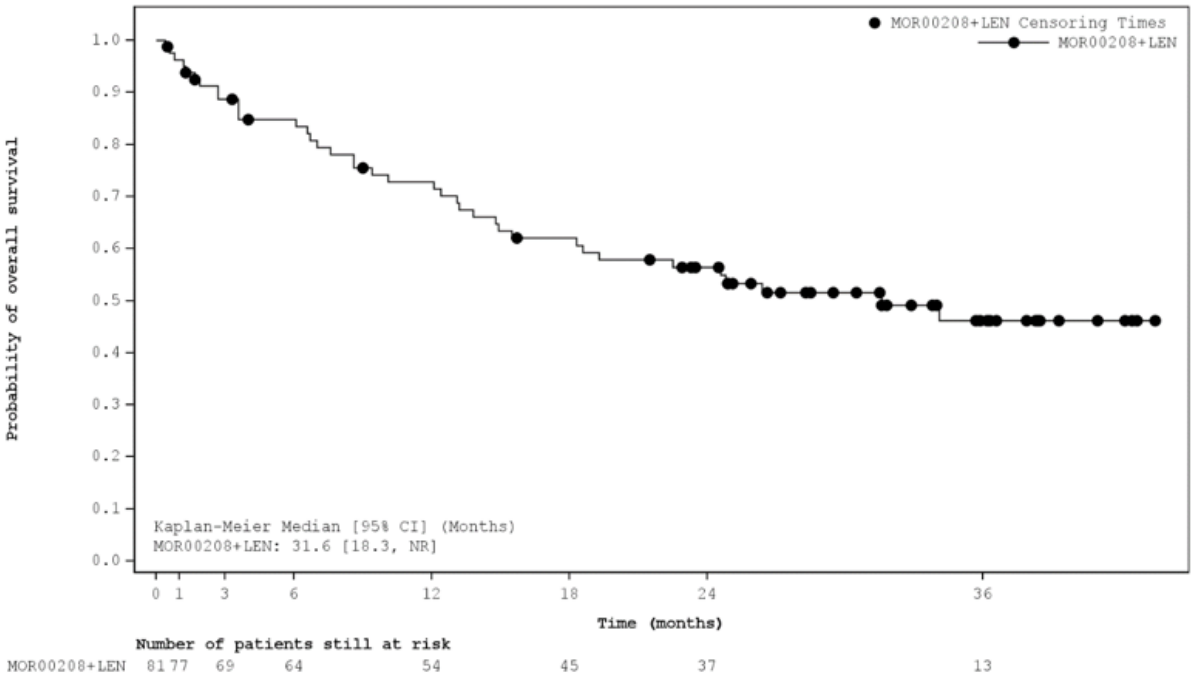
A supplementary analysis, imputing the censored patients, based on data as of the 30-NOV 2019 cut-off, was performed. The sensitivity analyses showed a 12-months PFS rate of 43.1% (for FAS 43.6%) when based on IRC, and 44.3% (for FAS 44.9%), when based on INV, this is considered clinical meaningful.

Secondary endpoints – OS

Median follow-up time for OS was 31.8 months (95% CI: 27.2, 35.9). Overall 38 (46.9) deaths occurred and 43 (53.1) patients were censored in the OS analysis. The Kaplan-Meier estimate for the median OS was 31.6 months (95% CI: 18.3, NR). The figure below shows that the probability of survival decreased gradually until 18 months and remained stable after 18 months. The Kaplan-Meier probability estimate of OS at 12 months was 72.8 (95% CI: 61.3, 81.3), 62.0 (95% CI: 50.1, 71.8) at 18 months, 56.4 (95% CI: 44.5, 66.8) at 24 months, and 46.1 (95% CI: 33.2, 58.0) at 36 months.

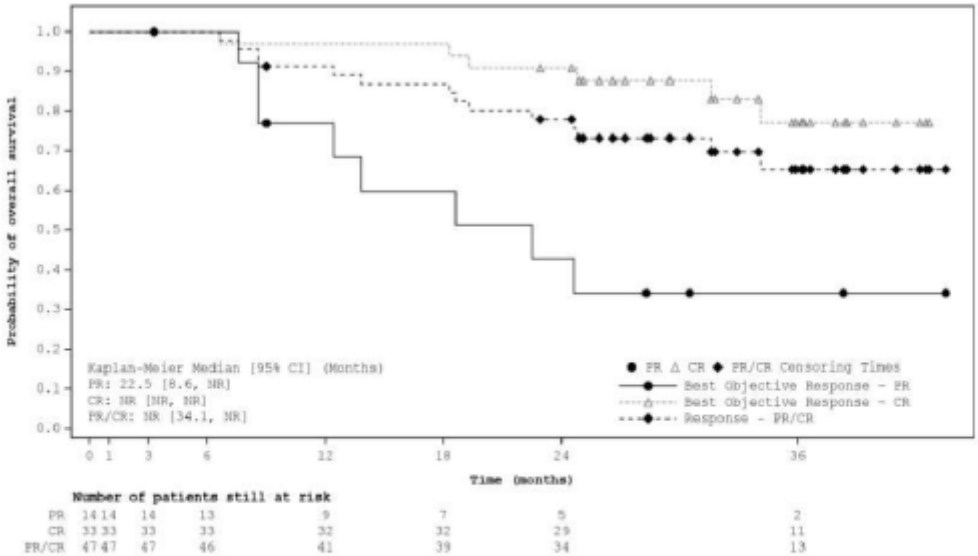
Updated efficacy data (cut-off 30 Nov 2019): The Kaplan-Meier analysis of OS is presented in the figure as follows for patients in the Safety Analysis Set (SAF) (N=81).

Figure 24: Kaplan- Meier Plot of Overall Survival SAF



Source: D120_ICO_Figures/Figure 14.2.30.5

Figure 25: Kaplan- Meier Plot of Overall Survival by ORR, (by IRC, FAS)



Abbreviations: CI = Confidence interval; CR = Complete response; FAS = Full analysis set; N/n = Number of patients; NR = Not reached; PR = Partial response.

In case the median or the respective confidence limits were not calculable by the Kaplan-Meier method, NR was displayed instead.

Thirty-two patients with best objective response not PR or CR were not included in this subgroup analysis.

Other secondary endpoints – TTP, TTNT, EFS

The results of the IRC assessed secondary endpoint analysis based on the 30.11.2019 data cut-off showed median time to progression of 23.5 months (95% CI: 7.6;NR), median time to next treatment of 12.5 months (95% CI: 7.6; 24.7) and median event free survival of 8.7 months (95%CI: 5.3; 23.5).

Ancillary analyses

Table 30: Efficacy outcomes (IRC) by reasons for SCT ineligibility (FAS)

Efficacy Outcomes (IRC) by Reasons for ASCT Ineligibility (FAS)

Outcome	Chemorefractory Disease Patients (N=18)	Comorbidities (N=11)	High Age (N=37)	Refusal of HDT/ASCT (N=13)
ORR, Responders (%)	10 (55.6)	6 (54.5)	24 (64.9)	7 (53.8)
CR rate, Responders (%)	6 (33.3)	4 (36.4)	18 (48.6)	6 (46.2)
Median DoR [95% CI]	NR [4.4, NR]	NR [1.8, NR]	34.6 [26.1, 34.6]	NR [21.7, NR]
24-month DoR rate [95% CI]	NR [NR, NR]	80.0 [20.4, 96.9]	73.8 [50.6, 87.4]	75.0 [12.8, 96.1]
Median PFS [95% CI]	7.6 [1.9, NR]	5.3 [0.6, NR]	28.0 [4.7, NR]	NR [1.9, NR]
24-month PFS rate [95% CI]	38.8 [16.3, 61.1]	46.7 [15.0, 73.7]	51.9 [33.7, 67.4]	51.3 [17.6, 77.4]
Median OS [95% CI]	22.5 [7.6, 31.6]	NR [0.6, NR]	24.8 [13.8, NR]	NR [26.4, NR]
24-month OS rate [95% CI]	45.1 [20.8, 66.8]	54.9 [18.7, 80.6]	52.8 [35.5, 67.4]	84.6 [51.2, 95.9]

Abbreviations: ASCT = Autologous Stem Cell Transplantation; CI = Confidence interval; DoR = Duration of response; HDT = High-Dose Therapy; IRC = Independent Radiology/Clinical Review Committee; N = Number of patients in the respective riskcategory; NR = Not reached; ORR = Objective response rate; OS = Overall survival; PFS = Progression-free survival;

Data source: Tables 14.2.1.22.1, 14.2.4.21.1, 14.2.3.24.1 and 14.2.5.21

Table 31: ORR (IRC) for histological subtypes by central pathology (FAS)

	DLBCL NOS (N* = 53) n (%)	Composite Lymphoma (N* = 10) n (%)	High Grade Lymphoma (DHL/THL) (N* = 2) n (%)	EBV+ & TCHRLBCL DLBCL (N* = 4) n (%)	FL (N* = 3) n (%)	MCL (N* = 1) n (%)	MZL (N*=4) n (%)	t-iNHL (N* = 1) n (%)
CR	19 (35.8)	4 (40.0)	1 (50.0)	1 (25.0)	2 (66.7)	1 (100)	3 (75.0)	1 (100)
PR	10 (18.9)	1 (10.0)	1 (50.0)	1 (25.0)	0	0	0	0
SD	8 (15.1)	2 (20.0)	0	1 (25.0)	1 (33.3)	0	0	0
PD	12 (22.6)	1 (10.0)	0	0	0	0	0	0
NE	4 (7.5)	2 (20.0)	0	1 (25.0)	0	0	1 (25.0)	0
BORR n (%)	29 (54.7)	5 (50.0)	2 (100)	2 (50.0)	2 (66.7)	1 (100)	3 (75.0)	1 (100)
[95% Exact CI]	[40.4, 68.4]	[18.7, 81.3]	[15.8, 100.0]	[6.8, 93.2]	[9.4, 99.2]	[2.5, 100.0]	[19.4, 99.4]	[2.5, 100.0]

Note: N = number of patients in FAS, N* = Number of patients in FAS within the respective risk category. Percentages are based on N*.

Abbreviations: IRC = Independent Radiology/Clinical Review Committee, CI = Confidence interval, NOS= not otherwise specified, DHL= double-hit lymphoma, THL = triple-hit lymphoma, TCHRLBCL = T-cell histiocyte-rich large B-cell lymphoma, FL = Follicular lymphoma, MCL= Mantle Cell Lymphoma, MZL= Marginal Zone Lymphoma, t-iNHL = Histological transformation to DLBCL from indolent NHL, CR= Complete Response, PR= Partial Response, SD = Stable Disease, PD= Progressive Disease, NE= Not Evaluable, BORR= Best Objective Response Rate

[a] The best ORR is defined as the proportion of patients with CR or PR as best response achieved at any time during the study.

[b] Using two-sided 95% Clopper-Pearson exact method based on binomial distribution.

Subgroup Analyses (IRC Evaluation)

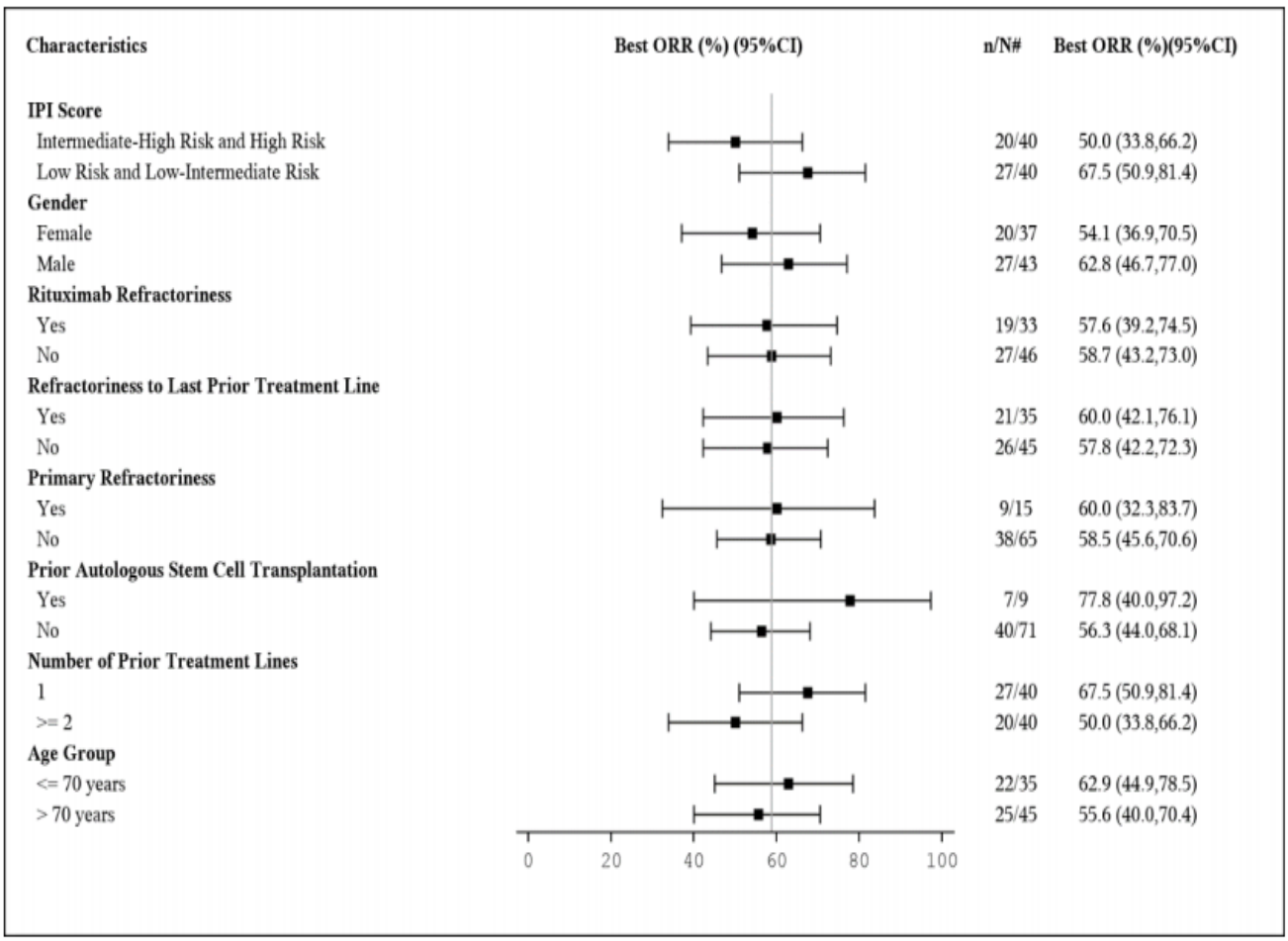
For the primary endpoint ORR, analysis by subgroup is summarised as follows:

Table 32: Objective Response Rate Results for Subgroup Analyses (MOR208C203, data cut-off 30-NOV-2018)

Subgroup (FAS, n[%])	ORR (%, 95% CI)
Age: ≤70 (35 [43.8]) vs >70 (45 [56.3])	**62.9%, (44.9, 78.5) vs 55.6%, (40.0, 70.4)**
Gender: Female (37 [46.3]) vs Male (43 [53.8])	**54.1%, (36.9, 70.5) vs 62.8%, (46.7, 77.0)**
Primary Refractory: Yes (15 [18.8]) vs No (65 [81.3])	**60.0%, (32.3, 83.7) vs 58.5%, (45.6, 70.6)**
Refractory to last therapy: Yes (35 [43.8]) vs No (45 [56.3])	**60.0%, (42.1, 76.1) vs 57.8%, (42.2, 72.3)**
Rituximab-refractory: Yes (33 [41.3]) vs No (46 [57.5])	**57.6%, (39.2, 74.5) vs 58.7%, (43.2, 73.0)**
Prior ASCT: Yes (9 [11.3]) vs No (71 [88.8])	**77.8%, (40.0, 97.2) vs 56.3%, (44.0, 68.1)**
IPI 0-2 (40 [50.0]) vs IPI 3-5 (40 [50.0])	**67.5%, (50.9, 81.4) vs 50.0%, (33.8, 66.2)**
Number of Prior Therapies: 1 (40 [50.0]) vs ≥2 (40 [50.0])	**67.5%, (50.9, 81.4) vs 50.0%, (33.8, 66.2)**
Cell of Origin (IHC): GCB (37 [46.3]) vs Non-GCB (21 [26.3])	**48.6%, (31.9, 65.6) vs 66.7%, (43.0, 85.4)**

Abbreviations: ASCT = Autologous Stem Cell Transplantation; CI = Confidence interval; FAS = Full analysis set; GCB = Germinal centre B-cell; IHC = Immuno-histochemistry; IPI = International Prognostic Index; n = number of patients; ORR = Objective Response Rate; vs = versus.

Figure 26: Forest plots of best Overall response for subgroups (IRC evaluation) – FAS (data cut off 30 NOV 2018)



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.

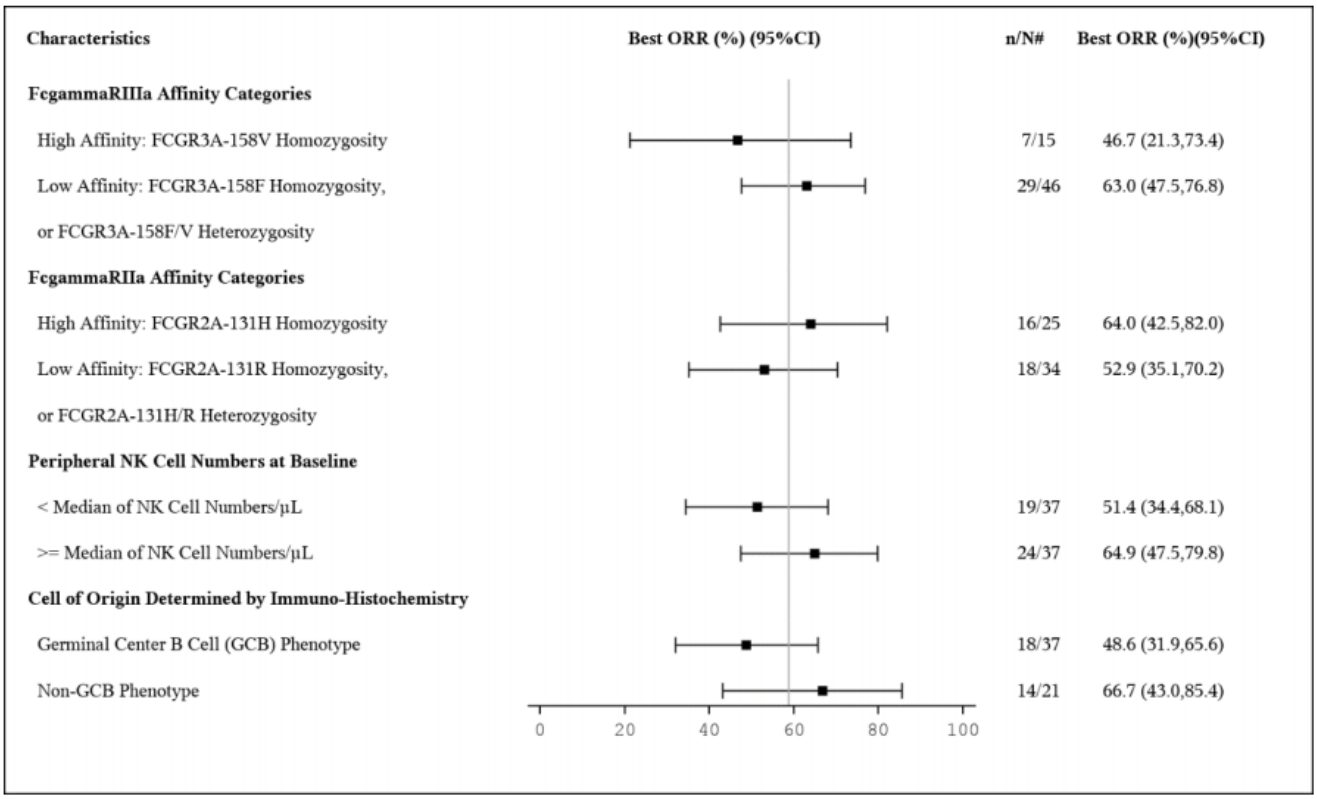
The best ORR was defined as the proportion of patients with CR or PR as best response achieved at any time during the study.

Best ORR in the FAS was 58.8% (indicated by a vertical line in the plot).

CIs were determined via two-sided 95% Clopper-Pearson exact method based on binomial distribution.

Patients with unknown status regarding refractoriness to rituximab were not included in this figure.

Figure 27: Forest plots of best Overall response for subgroups (IRC evaluation) – FAS (data cut off 30 NOV 2018)



Abbreviations: CI = Confidence interval, CR = complete response, FAS = full analysis set; IRC = Independent Radiology/Clinical Review Committee; N# = number of patients within subgroup category, n = number of patients with objective response; ORR = Objective response rate; NK = Natural killer, PR = partial response.

The best ORR was defined as the proportion of patients with CR or PR as best response achieved at any time during the study. Best ORR in the FAS was 58.8% (indicated by a vertical line in the plot).

CIs were determined via two-sided 95% Clopper-Pearson exact method based on binomial distribution.

The median of peripheral NK cells at baseline in the FAS was 119 cells/µL.

Data source: Figure 14.2.1.1.1

Summary of main efficacy results

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

Title: Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of 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).	
Study identifier	MOR00208 (L-MIND)
Design	Open-label multicentre phase 2 study to evaluate the effects of tafasitamab in combination with lenalidomide in patients with relapsed or refractory DLBCL, including DLBCL transformed from low grade lymphoma, who are ineligible for ASCT.

	Initiation of study phase Data cut-off		29 March 2016 30 Nov 2019
Hypothesis	Exploratory		
Treatments groups	Tafasitamab + LEN		
Endpoints and definitions	Primary endpoint	ORR	The proportion of patients with CR and PR (CR+PR) as assessed by the Investigators and central read by independent reviewers, using the revised IWG Response Criteria (Cheson et al. 2007).
	Secondary endpoint	DoR	The time from first meeting of criteria for response (i.e., CR or PR) to first documentation of relapse or progression.
	Secondary endpoint	PFS	The time from study entry (first dosing) until lymphoma progression or death as a result of any cause.
Database cut-off	30 Nov 2019		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Intent to treat	
Descriptive statistics and estimate variability	Treatment group	Tafasitamab + LEN
	Number of subjects	81
	ORR (range) (CR +PR)	56.8% (45.3; 67.8)
	DoR median (months) (95% CI)	34.6 (26.1; NR)
	PFS, median (months) (95% CI)	12.1 (5.7; NR)
	OS, median (months) (95% CI)	31.6 (18.3; NR)

The applicant provided supplementary data with the cut-off of 30 Oct2020 in the response to the day120 questions.

Table 33: Efficacy results in patients with relapsed or refractory diffuse large B-cell lymphoma in the MOR208C203 (L-MIND) study (Data cut off 30 OCT 2020)

Efficacy parameter	Tafasitamab + lenalidomide (N = 81 [ITT]*) Median exposure time: 9.2 months (range: 0.23, 54.67 months).
Primary endpoint	
Best objective response rate (per IRC)	
Overall response rate, n (%) (95% CI)	46 (56.8) [45.3, 67.8]
Complete response rate, n (%) (95% CI)	32 (39.5) [28.8, 51.0]
Partial response rate, n (%) (95% CI)	14 (17.3) [9.8, 27.3]
Key secondary endpoints	
Overall duration of response (complete + partial response) [a]	
Median, months (95% CI)	43.9 [26.1, NR]

ITT=intention to treat; NR = not reached

*One patient received only tafasitamab

CI: Binomial exact confidence interval using Clopper Pearson method

[a] Kaplan Meier estimates

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

Not applicable

Clinical studies in special populations

	Age <65 (Older subjects number/ %)	**Age 65-74 (Older subjects number /%)**	**Age 75-84 (Older subjects number /%)**	**Age 85+ (Older subjects number /%)**
Controlled Trials		NA	NA	NA

Non Controlled trials MOR208C203 (L-MIND), N=81 (100) R/R DLBCL	23 (28.4)	27 (33.3)	30 (37.0)	1 (1.2)

Percentages are calculated row-wise.

Supportive studies

Study MOR208C201 and **Study MOR208C206 (RE-MIND)**.

Study MOR208C201, an open-label, multicenter, phase IIa study of single-agent tafasitamab evaluating efficacy, safety, PK, and PD of tafasitamab in adult patients with different subtypes of relapsed or refractory Non-Hodgkin lymphoma, who have received at least one prior therapy containing rituximab (RTX) as one of the treatments.

The study employed a 2-stage design, where the decision to further enrol any NHL subtype in Stage 2 depended on best responses after 2 or 3 cycles in Stage 1. In both stages, tafasitamab was administered via IV infusion at a dose of 12.0 mg/kg weekly for 8 weeks (2 treatment Cycles). Patients with at least SD after 8 weeks continued with weekly tafasitamab administration for 4 additional weeks (i.e., up to 12 weeks, 3 treatment cycles). Patients with an ongoing response of at least PR at the end of Cycle 3 (regardless of Stage 1 or 2) were eligible to receive further study drug until progression, either once every two or four weeks, based on investigator's decision. In Stage 1, 51 patients in total from 4 NHL subtypes were enrolled: 14 FL, 14 DLBCL, 12 MCL and 11 other indolent NHLs (MZL, mucosa associated lymphoid tissue [MALT] lymphoma, etc.). In Stage 2, an additional 21 DLBCL and 20 FL patients (41 patients total) were enrolled. The DLBCL cohort (N=35) was similar to patients treated in the pivotal L-MIND study.

Only results of R/R DLBCL population are described here.

Assessment of the antitumour activity was the primary objective, secondary objectives were DoR, safety, tolerability, PK/PD and potential immunogenicity. Endpoints were ORR (CR + PR), DoR, PFS, TTP and SD rate.

Of the 35/41 patients who received tafasitamab, 10 patients discontinued from the study prior to completion of the 2 cycles, mainly due to PD (5 [50.0%]), and death (3 [30.0%]). The ORR was 6/35 (17.1%) for patients with R/R DLBCL, 8.6% achieved CR and 8.6% achieved PR. The results indicate a benefit in terms of ORR, but since this is a very small and uncontrolled study, it is regarded as exploratory.

Study MOR208C206 (RE-MIND), a multicenter, observational, retrospective study of the efficacy of lenalidomide monotherapy in adult patients with relapsed or refractory DLBCL.

The objective of the study was to characterize the effectiveness of LEN monotherapy in the treatment of R/R DLBCL patients and to compare the effectiveness of LEN monotherapy with the efficacy outcomes with tafasitamab-LEN combination therapy. Efficacy endpoints were similar to the tafasitamab-LEN combination study, MOR208C203 (L-MIND): ORR (CR+PR) – primary endpoint, secondary endpoints being: OS, CR, DCR, DoR, PFS, TTNT and EFS. The same eligibility criteria as in L-MIND study were applied to the observational cohort with respect to the histological subtypes, number of prior therapy lines, prior therapy types allowed, and ineligibility to receive ASCT. There were however certain differences between the 2 protocols:

- In view of the comparable response noted in several primary refractory patients in the MOR208C203 (L-MIND) cohort (as against the non-primary refractory patients), this exclusion criterion was not applied in the MOR208C206 (RE-MIND) study. A comparable distribution of primary refractory patients between the tafasitamab + LEN and the LEN monotherapy cohorts was ensured by having primary refractoriness (yes vs. no) as a baseline covariate for ePS-based matching.
- ECOG score of 0-2 at baseline, was not a prerequisite for the LEN monotherapy study.
- Pre-specified laboratory values on bone marrow -, kidney - or liver function, hepatitis serology testing was not pre-specified in the LEN monotherapy study.

Patients were matched using a propensity score approach with following variables: Age (as categorical variable with subgroups < 70 vs. ≥70 years of age); Ann Arbor Stage I/II vs. III/IV; Refractoriness to last therapy line (Yes vs. No); Number of prior lines of therapy (1 vs. 2/3); History of primary refractoriness (Yes vs. No); Prior ASCT (Yes vs No); Elevated lactate dehydrogenase (LDH; LDH > upper limit of normal [ULN] vs. LDH ≤ upper limit of normal [ULN]); Neutropenia (absolute neutrophil count [ANC] < 1.5 x 109/L vs. ANC ≥ 1.5 x 109/L); Anaemia (haemoglobin [Hb] <10 g/dL vs. Hb ≥10 g/dL).

For estimates of efficacy, patients from the two treatment cohorts were considered as independent sets. As such, analyses for unpaired data were conducted. However, matched data are not independent and analysis methods for paired (correlated) data were also included as sensitivity analyses.

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 Matched Analysis Set (MAS25).

Table 34: Patient Disposition (MAS25) - MOR208C206

	Tafasitamab+LEN n (%) (N=76)	LEN-mono n (%) (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 at any time in the analysis window	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 at any time in the analysis window	48 (63.2)	-
Primary reason for permanent discontinuation of tafasitamab		
Adverse event	8 (10.5)	-
Death	2 (2.6)	-
Disease relapse	35 (46.1)	-
Other	1 (1.3)	-
Withdrawal by patient	2 (2.6)	-

LEN = lenalidomide; MAS25 = Matched analysis set 25 - percentage calculated on Full Analysis Set (FAS)25, a subset of the population containing patients with a LEN starting dose of 25 mg/day; SD = standard deviation

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

Percentage/statistics are calculated based on the number of patients in each cohort.

Source: m5.3.5.1/MOR208C206/Tab 5

In total, 76 patients were matched (1:1) to L-MIND patients. While some baseline characteristics are similar between groups (age, refractoriness to last prior therapy), others are very different. For the IPI Score: 52.6 % of patients in tafasitamab+LEN (L-MIND) have an IPI Score 0-2 and 21.1 % in LEN-mono (RE-MIND). For ECOG, 38.2 % of patients in tafasitamab+LEN (L-MIND) have ECOG 0 compared with 6.6 % in LEN-mono (RE-MIND). Further 10 % of the patients in RE-MIND study have missing ECOG value. Both ECOG and IPI score are of vital importance for the response and prognosis in DLBCL.

The comparison of ORR in RE-MIND indicated that best ORR was 51 patients (95 % CI 55.4; 77.5) and 26 patients (95 % CI 23.7;46.0) for tafasitamab+LEN (L-MIND) and LEN-mono (RE-MIND) respectively, odds ratio being 1.96 (95 % CI 1.37;3.04). The proportions were compared using Fisher exact test (p-value = <0.0001). The McNemar test was used as sensitivity analysis and provided concordant results. The median DoR was 20.5 months (95 % CI 3.3; 13.9) and 4.1 months (95 % CI 1.5;5.2) for tafasitamab+LEN (L-MIND) and LEN-mono (RE-MIND) respectively. The median PFS was 12.1 months (95 % CI 5.9; NR) and 4.0 months (95 % CI 3.1;7.4) for tafasitamab+LEN (L-MIND) and LEN-mono (RE-MIND) respectively. The median OS (Kaplan-Meier estimate) was NR (95% CI: 15.5, NR) months in the tafasitamab + LEN (L-MIND) and 9.4 (95% CI: 5.1, 20.0) months in the LEN monotherapy (RE-MIND).

The response assessment in the L-MIND and the RE-MIND study was not similar. A validation study was performed to compare the physician's response assessment to those made by an IRC. The overall concordance for individual categories is around 56 and 65 %. Most differences were observed in the CR category.

The heterogeneity in the study populations in the tafasitamab+LEN (L-MIND) and LEN-mono (RE-MIND), the uncertainties in the matching, and differences in standard of care received during treatment hampers

the interpretation of the results. Therefore, the results of the RE-MIND study can only be regarded as exploratory.

2.5.3. Discussion on clinical efficacy

Three clinical studies were submitted within the dossier to demonstrate efficacy of tafasitamab + LEN in the R/R DLBCL setting in patients being ineligible for autologous stem cell transplant (ASCT).

Study MOR208C203 (L MIND) is considered the pivotal study. The primary clinical study report with data cut-off 30 Nov 2018 was updated as of 30 Nov 2019 and a correction was added 28 July 2020.

The other submitted studies; MOR208C201 is considered supportive, while the retrospective registry study MOR208C206 (RE-MIND) is considered exploratory.

Design and conduct of clinical studies

The pivotal study MOR208C203 (L-MIND) is a phase 2, single-arm, open-label, multicentre study of tafasitamab + LEN, followed by tafasitamab monotherapy until progression in patients with R/R DLBCL who were not eligible for HDC/ASCT. Treatment options for HDC/ASCT ineligible patients who have relapsed or progressed after first-line treatment DLBCL are limited, the prognosis is dismal, and there is no consensus or guidelines regarding the optimal treatment. Several regimens have been introduced including monotherapy lenalidomide, but usually treatment is administered in combination with a monoclonal antibody. The combination of a CD19 targeted monoclonal antibody in combination with antineoplastic therapy is therefore in principle endorsed.

Study L-MIND had a double objective, (i) induction phase with the MOR208C203 + LEN combination plus (ii) maintenance phase with tafasitamab monotherapy on the basis of a very small amount of immature data. Although the study design comprises a combination treatment phase (tafasitamab + lenalidomide) and a monotherapy phase (tafasitamab only), the applicant confirmed that there was no plan for separate assessment of the two phases. The primary endpoint is assessed at any time across both treatment phases. Consequently, the sample size and corresponding study power were determined for the entire treatment period, i.e. not separately for combination and monotherapy phases. This is acceptable.

The initial claimed indication for tafasitamab is "in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with R/R DLBCL, including DLBCL arising from low grade lymphoma, who are not eligible for, or refuse, autologous stem cell transplant (ASCT)." The primary reason that patients were not candidates to ASCT included high age (46.3%), refractoriness to salvage chemotherapy (22.5%), comorbidities (13.8%), and refusal of high dose chemotherapy (16.3%). Of those who refused ASCT, only 4 had no comorbidities and refused due to personal reasons. Moreover, there is a lack of objectivity to consider the subgroup of patients who are eligible to transplant but who refuse and thus a selection bias cannot be excluded, especially in the context of a single arm trial. Finally, this would mean that tafasitamab would be indicated for patients with R/R DLBCL regardless of eligibility to transplant. The term "or refuse" has therefore been deleted from the indication, and number of subjects who refused ASCT has been added in the SmPC.

Tafasitamab was administered together with lenalidomide for up to 12 cycles via IV infusion five times per 28 days in cycle 1, fourth times per 28 days from cycles 2 to 3 and bi-weekly thereafter. Lenalidomide (25mg) was orally and daily taken from D1-21 of each cycle of 28 days. After cycle 12, tafasitamab was administered in monotherapy until disease progression.

The primary objective was to assess the activity of the combination of lenalidomide and tafasitamab in terms of ORR. Secondary endpoints for efficacy were DCR, DoR, PFS, TTP, OS and TNT. The selected objective/endpoints are considered acceptable.

The aim of the study is mainly exploratory as no formal statistical hypothesis testing was performed. The combination therapy was assumed to improve the ORR of lenalidomide from a value of 20% (under monotherapy) to 35% (under combination therapy). Analysis aimed at excluding a 32% ORR was assumed to lead to the conclusion that the outcome was statistically superior to outcomes observed previously for the monotherapy.

Inconsistencies of the data in relation to response evaluation, evaluation of the biopsy material and whether the patients fulfil the inclusion criteria were adequately addressed. An adjudication of central response assessment and inclusion of patients with unknown or missing histology has been reviewed and comments were reconciled; the error on adjudication, has adequately been corrected and resulted in a minor change of the efficacy endpoints of the L-MIND study, which did not impact the overall interpretation of the study results.

Several protocol amendments (inclusion/exclusion criteria, objectives/endpoints…) were performed during the study, a detailed description of which was provided. The protocol amendments do not indicate a significant impact to the main analysis methods. A GCP issue at a UK site has adequately been addressed.

The histology of the enrolled patients, whether some patients having missing or unknown histology, and trial eligibility was questioned. As per protocol, all patients were included in the study based on local pathology diagnosis of DLBCL. A central pathology review was implemented as a mandatory but retrospective assessment. As per central pathology review, 10 patients could not be classified as DLBCL. In total, 70 out of 80 patients (87.5%) in the primary efficacy analysis set (Full Analysis Set, FAS) and 71 out of 81 patients (87.7%) in the safety analysis set (SAF) were centrally confirmed as DLBCL. Nevertheless the ITT principle in analysing the results and the criteria for enrolment in Study MOR208C203 (L-MIND) are considered to be appropriate for the proposed indication.

The sample size determination has been conducted using various possible monotherapy and combination effect ORR rates and various power assumptions. The applicant confirmed that the number of patients enrolled was determined for the entire treatment period. Enrolment numbers were not planned separately for the combination treatment phase (tafasitamab + lenalidomide) and monotherapy phase (tafasitamab only). This approach is consistent with the primary endpoint being measured at any time over the whole study period. The applicant provided 4 references (Wiernik 2008, Witzig 2011, Wang 2013, MOR208C201 study), which are said to be the basis for sample size determination. The protocol states that "for the determination of a suitable sample size, it is assumed that the combination treatment could improve the ORR from a value of 20% (under monotherapy) to 35% (under combination therapy)."

This reference ORR value of 20% under monotherapy is lower than the ORR observed in the largest study with lenalidomide monotherapy (Witzig 2011, n=108) provided by the applicant as the data source for sample size assumptions. The Witzig 2011 study reported an ORR of 28%. The applicant provided Wiernik 2008 as another reference for lenalidomide monotherapy, with a reported ORR of 19%. Therefore, this initial protocol assumption of a 20% ORR under monotherapy treatment is not deemed to be an accurate monotherapy estimate. Of note, this observation tends to be confirmed by the higher response rate reported with lenalidomide monotherapy in the RE-MIND study.

The sample size determination has been conducted using various possible monotherapy and combination effect ORR rates and various power assumptions. The number of patients enrolled was determined for

the entire treatment period. Enrolment numbers were not planned separately for the combination treatment phase (tafasitamab + lenalidomide) and monotherapy phase (tafasitamab only). This approach is consistent with the primary endpoint being measured at any time over the whole study period.

Efficacy data and additional analyses

A total number of 81 patients were enrolled in the trial, 1 patient received only tafasitamab monotherapy. The definition of the main analysis set (FAS) includes all patients who received at least one dose of tafasitamab *and* lenalidomide. This definition was not endorsed by the CHMP, the ITT population including all randomised 81 patients was used as denominator for the efficacy results and has adequately been reflected.

Overall, the median age of the enrolled population was 72.0 years old, and the majority (71.3%, 57/80) were ≥65 years of age. The patients were pre-treated with a median of 2 prior therapies (range 1-4). This is considered in line with the claimed indication. Population were balanced in terms of risks as 50% presented an IPI score 0-2 and the other 50% presented an IPI score 3 -5. Overall, 15 (18.8%) patients were primary refractory.

In the single arm study of tafasitamab + LEN, it was considered difficult to isolate the treatment effect of tafasitamab. The retrospective, observational study of lenalidomide monotherapy, the MOR208C206 (RE-MIND) study, is considered exploratory, as a result of heterogeneity in the study populations, the uncertainties in the matching, and differences in standard of care received during treatment. Some of these drawbacks were also pointed out in the scientific advice received by the applicant in June 2019, (EMA/CHMP/SAWP/341711/2019). The applicant further addressed these concerns on the basis of the mechanism of action of tafasitamab and lenalidomide. The scientific hypothesis of combining tafasitamab and lenalidomide is based on pre-clinical models. Lenalidomide activates NK cells and promotes NK cell proliferation, ADCC which is a major mode of action of tafasitamab is predominantly mediated by NK cells. LEN is therefore hypothesised to provide tafasitamab with a larger and more potent NK cell pool for ADCC-mediated tumour cell killing (Horton et al, 2008; Awan et al, 2010, Haslett et al., 2003; Galustian et al., 2009; Gribben et al, 2015; Pan et al, 2012; Saloura and Grivas, 2010; Wiernik, 2013) (see also Non-Clinical Pharmacology).

The applicant also reviewed the literature on the clinical effect of monotherapy tafasitamab and lenalidomide respectively. Single-agent tafasitamab in a small cohort of 35 patients, median age 71 years (range 35-90) with R/R DLBCL in study MOR208C201, showed an ORR of 26% (95% CI 12.5, 43.3), 2 patients (6%) achieving CR. The median DoR was 20.1 months (95% CI: 1.1, NR). Single-agent lenalidomide has been used in several studies, prospective as well as retrospective, in patients with R/R DLBCL, showing ORR in the range of 19-29.4%, and a CR rate in the range of 7-23.5%(Witzig et al, 2011; Wiernik et al, 2008; Czuczman et al, 2017; Hernandez-Ilizaliturri et al, 2011; Broccoli et al, 2019). The median DoR ranged between 5-17 months, the median PFS ranged between 2.6-6 months and the median OS ranged between approximately 7-14 months. Thus, the activity of both tafasitamab – and lenalidomide monotherapy in R/R DLBCL is rather modest.

Although not directly comparable, the effect in the L-MIND trial, of the combination of tafasitamab +LEN, show a better outcome in respect of an ORR of 56.8%, a CR rate of 39.5% and a median DoR of 34.6 months for the ITT population, which has been accepted by the CHMP. The L-MIND study indicate a synergistic effect of the combination tafasitamab + LEN, which is considered encouraging and clinical meaningful considering the dismal prognosis of this specific setting of R/R DLBCL. The design of the L-MIND study, and the objective of continuing tafasitamab monotherapy until progression to maintain the treatment response in patients with CR or PR as long as possible, is also considered clinically meaningful.

From the primary analysis, it was not quite clear, how many patients that were censored, who were not on-going with treatment at data cut-off in the analysis for DoR, this has been adequately clarified by the applicant. As of data cut-off 30-NOV-2019, 8 patients were censored due to other reasons than being ongoing on DoR follow-up. Of these, 6 patients were censored since they had initiated a new anti-tumour therapy, 3 of which due to progressive disease. Two patients were censored due to an event after two or more missing tumour response assessments, one patient suffered from general deterioration and one had grade 4 thrombocytopenia. The applicant performed sensitivity analyses for IRC-DoR as requested: events were imputed for patients discontinuing DoR follow-up without documented progressive disease, administration of new anti-lymphoma therapy before disease progression, and death or progression after two or more missing tumour response assessments. The sensitivity analyses for IRC-DOR showed a median DoR of 26.5 months (17,8;NR) which although shorter is considered clinical meaningful.

Median duration of response was not reached in complete responders (95% CI: 43.9; not reached) and was 5.6 months in patients with partial response as best response. However, as these results are based on a small number of patients, further confirmation is needed through a post authorisation study.

Further clarification was provided about the median PFS results obtained in the primary analysis compared to the updated analysis. The reason for the change in median PFS is a prolonged PFS follow-up time due to an extended study duration of additional 12 months for the updated analysis (cut-off of 30-NOV-2019) as compared to the Primary Analysis (cut-off of 30-NOV-2018) resulting in more mature data for the time-dependent endpoints including PFS. Moreover, the concordance between the investigators and IRC assessment was high for ORR and PFS, and comparable for the primary and the updated analysis (78.8% vs. 76.3% for ORR; 90.0% vs. 91.3% for PFS/censoring events).

The updated median OS reached is almost the double of the magnitude of the updated median PFS. The applicant has provided further information related to the type of subsequent treatment that discontinued patients received. Data on response to new anti-lymphoma therapies or progression dates following new anti-lymphoma therapies were not collected in Study L-MIND. Therefore, PFS2 analyses are not possible. However, Kaplan-Meier analyses of OS2 (from End of Treatment in L-MIND until death) were performed as surrogate for PFS2. As of the data cut off of 30 NOV 2019, 58 patients (out of 80 in the FAS) discontinued study treatment in L-MIND. Following discontinuation of therapy in L-MIND, the majority of patients (31/58) went on to receive subsequent new anti-lymphoma therapies (systemic therapy and radiotherapy). For this subset of patients, a median OS of 12.7 months was reported. Of 58 patients who discontinued treatment in L-MIND at the data cut off 30 Nov2019, 30 patients (52%) received at least one subsequent systemic therapy, with the majority of next-line treatments being "standard" salvage therapy regimens. Two patients proceeded to receive CAR-T therapy and two additional patients received a stem cell transplantation after L-MIND. The applicant specified that 2 patients could then receive CAR-T therapy after tafasitamab and lenalidomide failure. Despite limited to descriptive data, these results are reassuring on the fact that the use of tafasitamab would not be a loss of therapeutic chance to access CAR-T cells treatment in a later treatment line.

In clinical practice, the treatment of DLBCL is the same, whether de novo DLBCL or arising from low grade lymphoma, and the wording of indication has accordingly been amended by deleting the sentence "…, *including DLBCL arising from low grade lymphoma*,.." from the wording of the indication.

The primary reason that patients were not candidates to ASCT included high age (46.3%), refractoriness to salvage chemotherapy (22.5%), comorbidities (13.8%), and refusal of high dose chemotherapy (16.3%). Of those who refused ASCT, only 4 had no comorbidities and refused due to personal reasons. For patients eligible to transplant but who refuse there is a concern that by including this subgroup of patients as part of the indication, may represent a loss of chance, as these patients that could receive a potentially curative option. For these reasons, the wording *"or refuse"* was deleted from the indication.

However, the section 5.1 of the product information should inform that in the study L-MIND 16% of enrolled patients had earlier refused HDC/ASCT.

The clinical efficacy results have been sufficiently reflected in section 5.1. of the SmPC.

Additional efficacy data needed in the context of a conditional MA

As discussed above the clinically relevant effect of tafasitamab is consistently seen throughout sensitivity analyses, different histologies or reasons for ASCT ineligibility. However due to the small sample size the data cannot be considered comprehensive; a further single arm trial with an optimised design and sample size in line with an agreed protocol has been requested by the CHMP.

2.5.4. Conclusions on the clinical efficacy

Main evidence supporting this application comes from a single-arm pivotal phase II study to evaluate tafasitamab in combination with lenalidomide in 81 patients with R/R DLBCL who were not eligible for ASCT. Tafasitamab in combination with lenalidomide showed encouraging results with a high ORR with long DoR and improvements in PFS and OS in a setting with a dismal prognosis.

The CHMP considers the following measures necessary to address the additional efficacy data needed in the context of a conditional MA:

In order to confirm the efficacy of tafasitamab in combination with lenalidomide in diffuse Large B cell lymphoma in patients not eligible for ASCT, the MAH should conduct and submit the results of a single-arm study of tafasitamab in combination with lenalidomide in the approved indication according to an agreed protocol.

2.6. Clinical safety

Only the pivotal study MOR208C203 (L-MIND) employed the combination of lenalidomide (LEN) and tafasitamab followed by tafasitamab monotherapy, for which approval in R/R DLBCL is sought. Three other studies using tafasitamab monotherapy in haematological malignancies (n=141 patients) are also included in the safety analysis set (SAS) and presented individually and pooled: MOR208C201 (N= 92; 35 with R/R DLBCL), MOR208C202 (N=22 ALL patients), and XmAb5574-01 (N=27 R/R CLL patients of which 16 received the highest dose of 12 mg/kg corresponding to the dose in the pivotal study).

Patient exposure

A total of 222 patients received tafasitamab as SA or in combination with lenalidomide, all histologies included. AEs were collected up to 30 days after the last treatment dose and later if considered related to study treatment.

Treatment schedule in the pivotal study was 12 cycles in combination with lenalidomide, followed by tafasitamab monotherapy until PD. The frequency of injection progressively decreased to twice per cycle. The registration dose of 12.0mg/kg was used in all studies included in the safety analysis, except for phase I study XmbAB5574-01 in R/R CLL, which tested increasing doses up to 12 mg/kg.

Treatment schedule was similar across studies, until PD (2 doses per cycle) in most of them except for study XmbAB5574-01, with a maximum of 7 cycles.

The median treatment duration was 232.0 days (1;1170) in L-Mind study, longer than in pooled monotherapy studies (51.0 days (1; 1198)). Consequently, cumulative dose is higher in L-MIND study, more than twice higher than in pooled monotherapy studies.

Most of patients received more than 5 cycles in L-MIND study (61.7%), while most of patients in pooled monotherapy studies received up to 5 cycles (84.4%). In L-MIND study, 28.4% of subjects received tafasitamab monotherapy for more than 12 months after lenalidomide withdrawal.

Few patients received long-term treatment: In the pivotal combination study (MOR208C203) 13 patients received 12-24 cycles and 21 patients > 24 cycles of tafasitamab therapy (combined + monotherapy) (data cut-off 30JUN2019). The corresponding numbers for the pooled monotherapy studies were 2 and 9 patients. DLBCL is an aggressive disease and only a limited number of patients would be expected to live long enough to receive long-term treatment (>12 months) as opposed to patients with indolent lymphomas.

Patients in study MOR208C203 were mainly ECOG 0-1 and white, and the number of prior treatments were for most patients 1 (49.4%) or 2 (43.2%). Patients with hepatic, renal, or cardiovascular impairment were excluded. MOR208C203 (L-MIND) excluded patients with known 'double/triple hit' DLBCL at study entry.

For baseline- and disease-characteristics in the pivotal study MOR208C203 see Efficacy section.

Table 12-1 Study Drug Administration (SAF)

Characteristic Study Drug	MOR00208 + LEN (N = 81)
All Study Treatment	
Duration of exposure to Study Treatment (months)	
n	81
Mean (StD)	11.303 (9.7356)
Median	9.200
Q1, Q3	2.170, 18.790
Min, Max	0.23, 32.10
Duration of exposure to Combination Therapy or LEN only (months) [a]	
n	80
Mean (StD)	6.605 (4.2752)
Median	6.210
Q1,Q3	2.100, 10.855
Min, Max	0.10, 12.48
Duration of exposure to monotherapy with MOR00208 after LEN discontinuation (months) [b]	
n	52
Mean (StD)	6.948 (7.1556)
Median	4.025
Q1,Q3	0.445, 12.615
Min, Max	0.07, 20.83
Exposure to MOR00208	
Total number of infusions	
n	81
Mean (StD)	28.5 (21.22)
Median	23.0
Q1, Q3	10.0, 45.0
Min, Max	1, 75
Patients with temporary interruptions of MOR00208 therapy (at least one temporary interruption of MOR00208) n	61
Reason for infusion interruption n (%)	
Infusion Related Reaction	3 (4.9)
Cytokine release syndrome	0

Continued

Table 12-1 Study Drug Administration (SAF) (Continued)

Characteristic Study Drug	MOR00208 + LEN (N = 81)
Adverse Event	47 (77.0)
Unacceptable toxicity	1 (1.6)
Other	33 (54.1)
Patients who discontinued MOR00208 permanently n (%) [c]	53 (65.4)
Withdrawal by subject	3 (3.7)
Adverse event	10 (12.3)
Disease relapse	36 (44.4)
Death	2 (2.5)
Other	2 (2.5)
Exposure to LEN	
Duration of exposure to LEN (weeks)	
n	80
Mean (StD)	28.72 (18.593)
Median	27.00
Q1, Q3	9.10, 47.20
Min, Max	0.4, 54.3
Patients with temporary interruptions of LEN n	28
Reason for temporary interruption of LEN n (%)	
Adverse Event	25 (89.3)
Unacceptable Toxicity	1 (3.6)
Other	4 (14.3)
Dose reductions	
Patients with any dose reductions n (%)	37 (45.7)
Patients with one-step reduction to a minimum of 20 mg	19 (23.5)
Patients with two-step reductions to a minimum of 15 mg	12 (14.8)
Patients with three-step reductions to a minimum of 10 mg	3 (3.7)
Patients with four-step reductions to a minimum of 5 mg	3 (3.7)
Patients who had no reduction at all	43 (53.1)

Continued

Table 12-1 Study Drug Administration (SAF) (Continued)

Characteristic Study Drug	MOR00208 + LEN (N = 81)

Abbreviations: LEN = Lenalidomide; Q1 = Lower quartile; Q3 = Upper quartile; StD = Standard deviation, N = Number of patients in SAF; n = Number of patients in the specified category with non-missing values; SAF = Safety analysis set.

Percentages were based on the number of patients in SAF, N.

If a group had less than five observations, only n, Mean, Median, Min and Max were displayed.

Duration of exposure to study drug (MOR00208 or LEN) included the combination of both drugs and the monotherapy with the individual drug as allowed per protocol.

One patient (94004-06) in the SAF never received any dose of LEN and was therefore not included in all pertaining summaries. One patient did not receive LEN

[a] Duration of exposure to Combination Therapy or LEN only was the time from first administration of study drug to the last date of administration of LEN or the last date of exposure to MOR00208 during combination treatment.

[b] Duration of exposure to monotherapy with MOR00208 was the time from first administration of MOR00208 after discontinuation of LEN to the last date of exposure to MOR00208.

[c] Permanent discontinuation of study drug included discontinuation for any reason including discontinuation as per protocol for LEN.

Data source: Table 14.3.8.2, Table 14.3.8.5 and Table 14.1.1.3

Adverse events

Table 7 Overall Summary of Adverse Events

Number (%) of Patients	Monotherapy Studies				MOR208C203 (L-MIND)[a]		
	X01 N = 27	C201 N = 92	C202 N = 22	Pooled N = 141	Overall N = 81	Combination Therapy N = 80[b]	Extended Tafasitamab Monotherapy N = 40[b]
TEAEs (All Grades)	**27 (100.0)**	**78 (84.8)**	**22 (100.0)**	**127 (90.1)**	**81 (100.0)**	**79 (98.8)**	**33 (82.5)**
TEAEs (Grade 3-5)	**10 (37.0)**	**36 (39.1)**	**19 (86.4)**	**65 (46.1)**	**63 (77.8)**	**61 (76.3)**	**15 (37.5)**
TEAE Related to Tafasitamab or LEN	24 (88.9)	41 (44.6)	15 (68.2)	80 (56.7)	68 (84.0)	67 (83.8)	18 (45.0)
TEAE Related to Tafasitamab Only	24 (88.9)	41 (44.6)	15 (68.2)	80 (56.7)	31 (38.3)	23 (28.8)	15 (37.5)
TEAE Related to LEN Only	NA	NA	NA	NA	51 (63.0)	50 (62.5)	5 (12.5)[c]
TEAE Related to both Tafasitamab and LEN	NA	NA	NA	NA	51 (63.0)	51 (63.8)	2 (5.0)
TEAE (Grade 3-5) Related to Tafasitamab or LEN	5 (18.5)	10 (10.9)	9 (40.9)	24 (17.0)	46 (56.8)	46 (57.5)	8 (20.0)
TEAE (Grade 3-5) Related to Tafasitamab Only	5 (18.5)	10 (10.9)	9 (40.9)	24 (17.0)	11 (13.6)	4 (5.0)	7 (17.5)
TEAE (Grade 3-5) Related to LEN Only	NA	NA	NA	NA	31 (38.3)	30 (37.5)	1 (2.5)
TEAE (Grade 3-5) Related to both Tafasitamab and LEN	NA	NA	NA	NA	32 (39.5)	32 (40.0)	1 (2.5)
Serious Fatal TEAE	**0**	**1 (1.1)**	**3 (13.6)**	**4 (2.8)**	**4 (4.9)**	**4 (5.0)**	**0**
Serious TEAE	**4 (14.8)**	**18 (19.6)**	**15 (68.2)**	**37 (26.2)**	**42 (51.9)**	**35 (43.8)**	**9 (22.5)[d]**
Serious TEAE Related to Tafasitamab or LEN	2 (7.4)	4 (4.3)	4 (18.2)	10 (7.1)	17 (21.0)	14 (17.5)	3 (7.5)
Serious TEAE Related to Tafasitamab Only	2 (7.4)	4 (4.3)	4 (18.2)	10 (7.1)	4 (4.9)	2 (2.5)	2 (5.0)
Serious TEAE Related to LEN Only	NA	NA	NA	NA	5 (6.2)	4 (5.0)	1 (2.5)
Serious TEAE Related to both Tafasitamab and LEN	NA	NA	NA	NA	12 (14.8)	11 (13.8)	1 (2.5)
TEAE Leading to Discontinuation of Tafasitamab	1 (3.7)	9 (9.8)	0	10 (7.1)	12 (14.8)	11 (13.8)	1 (2.5)
TEAE Leading to Discontinuation of LEN	NA	NA	NA	NA	18 (22.2)	18 (22.5)	0
TEAE Leading to Discontinuation of both Tafasitamab and LEN	NA	NA	NA	NA	10 (12.3)	10 (12.5)	0

C201=MOR208C201; C202=MOR208C202; LEN=lenalidomide; NA=not applicable; TEAE=treatment-emergent adverse event; X01=XmAb5574-01.

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 LEN + 30 days, and the Extended Tafasitamab Monotherapy phase includes AEs starting after the last date of treatment with LEN + 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 study discontinuation for any reason.

b. One patient (94004-06) received infusions of tafasitamab on Days 1 and 4 of Cycle 1, but LEN 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.

c. Investigator could relate AEs to LEN as the pharmacodynamic effect of LEN may last beyond its administration period.

d. Data in this table correspond to the data cut-off 30 Jun 2019. As of 30 Nov 2019, two additional SAEs were reported in the extended monotherapy phase, leading to 10 (25.0%) patients with serious TEAEs. Please see Section 2.7.4.2.1.8.2 for details.

Source: m5.3.5.3/ISS/Tab2.1

Source: SCS

The most frequently reported adverse events (overall) in the L-MIND study were AEs in the SOCs Infections and Infestations (72.8%), Blood and Lymphatic System Disorders (65.4%), Gastrointestinal Disorders (64.2%), and General Disorders and Administration Site Conditions (58.0%) (Table 8/SCS).

Well-known lenalidomide ADRs (see lenalidomide SmPC) included in the SOCs Infections and Infestations, Blood and Lymphatic System Disorders, Gastrointestinal Disorders, and General Disorders and Administration Site Conditions occurred more frequently (> 10% difference) in the combination therapy part of study MOR208C203 than in both the monotherapy studies and the monotherapy extension part of study MOR208C203 (Table 8/SCS), suggesting that these were mainly due to lenalidomide. On the other hand, the difference between the pooled monotherapy studies and the extension part of study MOR208C203 was most pronounced for the SOC Infections and Infestations; 38.3% vs 55.0% potentially reflecting the detrimental effect of the previously administered more toxic combination with lenalidomide in study MOR208C203 or the effect of long-term treatment with tafasitamab (34 patients in MOR208C203 and 11 patients in monotherapy study C201 received ≥12 months of tafasitamab treatment). A phase 3, randomised, controlled study could possibly clarify the underlying mechanism.

Table 335: Treatment-Emergent Adverse Events in ≥5% (Preferred Term) of Patients Either in L-MIND (Overall) or in the Pooled Monotherapy Studies- Safety Analysis Set

MedDRA System Organ Class Preferred Term	Tafasitamab Monotherapy Studies				MOR208C203 (L-MIND)[a]		
	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 N = 22 n (%)	Pooled N = 141 n (%)	Overall N = 81 n (%)	Combination Therapy N = 80[b] n (%)	Extended Tafasitamab Monotherapy N = 40[b] n (%)
Infections and infestations	**13 (48.1)**	**30 (32.6)**	**11 (50.0)**	**54 (38.3)**	**59 (72.8)**	**54 (67.5)**	**22 (55.0)**
Bronchitis	1 (3.7)	6 (6.5)	0	7 (5.0)	13 (16.0)	9 (11.3)	5 (12.5)
Nasopharyngitis	0	1 (1.1)	0	1 (0.7)	8 (9.9)	4 (5.0)	6 (15.0)
Pneumonia	0	3 (3.3)	2 (9.1)	5 (3.5)	8 (9.9)	6 (7.5)	2 (5.0)
Respiratory tract infection	1 (3.7)	1 (1.1)	0	2 (1.4)	8 (9.9)	6 (7.5)	3 (7.5)
Upper respiratory tract infection	5 (18.5)	11 (12.0)	0	16 (11.3)	8 (9.9)	7 (8.8)	2 (5.0)
Urinary tract infection	1 (3.7)	1 (1.1)	1 (4.5)	3 (2.1)	8 (9.9)	7 (8.8)	1 (2.5)
Gastroenteritis	1 (3.7)	0	0	1 (0.7)	5 (6.2)	5 (6.3)	1 (2.5)
Blood and lymphatic system disorders	**14 (51.9)**	**19 (20.7)**	**12 (54.5)**	**45 (31.9)**	**53 (65.4)**	**53 (66.3)**	**15 (37.5)**
Neutropenia	8 (29.6)	9 (9.8)	1 (4.5)	18 (12.8)	41 (50.6)	39 (48.8)	11 (27.5)

MedDRA System Organ Class Preferred Term	Tafasitamab Monotherapy Studies				MOR208C203 (L-MIND)[a]		
	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 N = 22 n (%)	Pooled N = 141 n (%)	Overall N = 81 n (%)	Combination Therapy N = 80[b] n (%)	Extended Tafasitamab Monotherapy N = 40[b] n (%)
Anaemia	6 (22.2)	5 (5.4)	4 (18.2)	15 (10.6)	29 (35.8)	27 (33.8)	5 (12.5)
Thrombocytopenia	8 (29.6)	5 (5.4)	2 (9.1)	15 (10.6)	25 (30.9)	25 (31.3)	1 (2.5)
Leukopenia	0	1 (1.1)	0	1 (0.7)	12 (14.8)	12 (15.0)	5 (12.5)
Febrile neutropenia	1 (3.7)	1 (1.1)	5 (22.7)	7 (5.0)	10 (12.3)	9 (11.3)	0
Lymphopenia	0	0	1 (4.5)	1 (0.7)	5 (6.2)	4 (5.0)	1 (2.5)
Gastrointestinal disorders	**11 (40.7)**	**35 (38.0)**	**15 (68.2)**	**61 (43.3)**	**52 (64.2)**	**47 (58.8)**	**13 (32.5)**
Diarrhoea	8 (29.6)	8 (8.7)	4 (18.2)	20 (14.2)	29 (35.8)	23 (28.8)	9 (22.5)
Constipation	4 (14.8)	6 (6.5)	6 (27.3)	16 (11.3)	14 (17.3)	12 (15.0)	2 (5.0)
Nausea	1 (3.7)	9 (9.8)	6 (27.3)	16 (11.3)	12 (14.8)	12 (15.0)	2 (5.0)
Vomiting	1 (3.7)	3 (3.3)	2 (9.1)	6 (4.3)	12 (14.8)	10 (12.5)	2 (5.0)
Abdominal pain	2 (7.4)	4 (4.3)	4 (18.2)	10 (7.1)	8 (9.9)	7 (8.8)	1 (2.5)
General disorders and administration site conditions	**7 (25.9)**	**31 (33.7)**	**16 (72.7)**	**54 (38.3)**	**47 (58.0)**	**47 (58.8)**	**15 (37.5)**
Asthenia	0	7 (7.6)	1 (4.5)	8 (5.7)	19 (23.5)	19 (23.8)	2 (5.0)
Oedema peripheral	1 (3.7)	7 (7.6)	3 (13.6)	11 (7.8)	19 (23.5)	17 (21.3)	5 (12.5)
Pyrexia	5 (18.5)	5 (5.4)	6 (27.3)	16 (11.3)	19 (23.5)	17 (21.3)	6 (15.0)
Fatigue	3 (11.1)	8 (8.7)	9 (40.9)	20 (14.2)	14 (17.3)	12 (15.0)	4 (10.0)
Mucosal inflammation	0	0	2 (9.1)	2 (1.4)	6 (7.4)	5 (6.3)	2 (5.0)
Chills	4 (14.8)	3 (3.3)	3 (13.6)	10 (7.1)	1 (1.2)	1 (1.3)	0
Metabolism and nutrition disorders	**17 (63.0)**	**14 (15.2)**	**14 (63.6)**	**45 (31.9)**	**42 (51.9)**	**34 (42.5)**	**11 (27.5)**
Decreased appetite	3 (11.1)	3 (3.3)	1 (4.5)	7 (5.0)	18 (22.2)	16 (20.0)	2 (5.0)
Hypokalaemia	3 (11.1)	4 (4.3)	6 (27.3)	13 (9.2)	15 (18.5)	15 (18.8)	0
Hypomagnesaemia	0	3 (3.3)	4 (18.2)	7 (5.0)	8 (9.9)	7 (8.8)	2 (5.0)
Hypocalcaemia	5 (18.5)	1 (1.1)	3 (13.6)	9 (6.4)	5 (6.2)	5 (6.3)	0
Hyperglycaemia	5 (18.5)	2 (2.2)	6 (27.3)	13 (9.2)	4 (4.9)	4 (5.0)	1 (2.5)
Hypoalbuminaemia	6 (22.2)	0	1 (4.5)	7 (5.0)	0	0	0
Musculoskeletal and connective tissue disorders	**12 (44.4)**	**21 (22.8)**	**5 (22.7)**	**38 (27.0)**	**40 (49.4)**	**34 (42.5)**	**12 (30.0)**
Back pain	4 (14.8)	8 (8.7)	0	12 (8.5)	15 (18.5)	12 (15.0)	4 (10.0)
Muscle spasms	6 (22.2)	1 (1.1)	0	7 (5.0)	12 (14.8)	11 (13.8)	1 (2.5)
Arthralgia	1 (3.7)	1 (1.1)	0	2 (1.4)	7 (8.6)	5 (6.3)	2 (5.0)

MedDRA System Organ Class Preferred Term	Tafasitamab Monotherapy Studies				MOR208C203 (L-MIND)[a]		
	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 N = 22 n (%)	Pooled N = 141 n (%)	Overall N = 81 n (%)	Combination Therapy N = 80[b] n (%)	Extended Tafasitamab Monotherapy N = 40[b] n (%)
Pain in extremity	1 (3.7)	4 (4.3)	1 (4.5)	6 (4.3)	7 (8.6)	6 (7.5)	2 (5.0)
Respiratory, thoracic and mediastinal disorders	**6 (22.2)**	**28 (30.4)**	**9 (40.9)**	**43 (30.5)**	**40 (49.4)**	**36 (45.0)**	**12 (30.0)**
Cough	4 (14.8)	8 (8.7)	4 (18.2)	16 (11.3)	21 (25.9)	15 (18.8)	9 (22.5)
Dyspnoea	2 (7.4)	7 (7.6)	5 (22.7)	14 (9.9)	10 (12.3)	10 (12.5)	1 (2.5)
Oropharyngeal pain	2 (7.4)	3 (3.3)	1 (4.5)	6 (4.3)	5 (6.2)	5 (6.3)	0
Investigations	**12 (44.4)**	**15 (16.3)**	**10 (45.5)**	**37 (26.2)**	**39 (48.1)**	**35 (43.8)**	**12 (30.0)**
C-reactive protein increased	0	0	0	0	8 (9.9)	8 (10.0)	0
Blood creatinine increased	1 (3.7)	2 (2.2)	2 (9.1)	5 (3.5)	7 (8.6)	7 (8.8)	0
Gamma-glutamyl transferase increased	2 (7.4)	1 (1.1)	3 (13.6)	6 (4.3)	5 (6.2)	5 (6.3)	2 (5.0)
Alanine aminotransferase increased	6 (22.2)	0	2 (9.1)	8 (5.7)	4 (4.9)	4 (5.0)	0
Aspartate aminotransferase increased	5 (18.5)	1 (1.1)	3 (13.6)	9 (6.4)	4 (4.9)	4 (5.0)	0
Nervous system disorders	**8 (29.6)**	**25 (27.2)**	**12 (54.5)**	**45 (31.9)**	**39 (48.1)**	**33 (41.3)**	**9 (22.5)**
Headache	5 (18.5)	10 (10.9)	3 (13.6)	18 (12.8)	7 (8.6)	7 (8.8)	2 (5.0)
Paraesthesia	1 (3.7)	2 (2.2)	3 (13.6)	6 (4.3)	6 (7.4)	5 (6.3)	0
Dysgeusia	0	1 (1.1)	1 (4.5)	2 (1.4)	5 (6.2)	4 (5.0)	1 (2.5)
Sciatica	0	0	0	0	5 (6.2)	4 (5.0)	1 (2.5)
Dizziness	2 (7.4)	9 (9.8)	2 (9.1)	13 (9.2)	3 (3.7)	3 (3.8)	0
Skin and subcutaneous tissue disorders	**9 (33.3)**	**10 (10.9)**	**4 (18.2)**	**23 (16.3)**	**39 (48.1)**	**36 (45.0)**	**5 (12.5)**
Pruritus	2 (7.4)	1 (1.1)	0	3 (2.1)	8 (9.9)	8 (10.0)	0
Rash	5 (18.5)	4 (4.3)	0	9 (6.4)	7 (8.6)	6 (7.5)	2 (5.0)
Vascular disorders	**2 (7.4)**	**6 (6.5)**	**7 (31.8)**	**15 (10.6)**	**23 (28.4)**	**18 (22.5)**	**5 (12.5)**
Hypertension	0	3 (3.3)	4 (18.2)	7 (5.0)	7 (8.6)	5 (6.3)	2 (5.0)
Hypotension	0	1 (1.1)	2 (9.1)	3 (2.1)	6 (7.4)	5 (6.3)	1 (2.5)
Injury, poisoning and procedural complications	**19 (70.4)**	**22 (23.9)**	**14 (63.6)**	**55 (39.0)**	**15 (18.5)**	**11 (13.8)**	**6 (15.0)**
Infusion related reaction	18 (66.7)	12 (13.0)	13 (59.1)	43 (30.5)	5 (6.2)	4 (5.0)	1 (2.5)
Renal and urinary disorders	**4 (14.8)**	**5 (5.4)**	**7 (31.8)**	**16 (11.3)**	**15 (18.5)**	**12 (15.0)**	**3 (7.5)**
Dysuria	2 (7.4)	1 (1.1)	0	3 (2.1)	5 (6.2)	2 (2.5)	3 (7.5)

MedDRA System Organ Class Preferred Term	Tafasitamab Monotherapy Studies				MOR208C203 (L-MIND)[a]		
	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 N = 22 n (%)	Pooled N = 141 n (%)	Overall N = 81 n (%)	Combination Therapy N = 80[b] n (%)	Extended Tafasitamab Monotherapy N = 40[b] n (%)
Psychiatric disorders	**8 (29.6)**	**11 (12.0)**	**6 (27.3)**	**25 (17.7)**	**13 (16.0)**	**10 (12.5)**	**4 (10.0)**
Anxiety	0	1 (1.1)	2 (9.1)	3 (2.1)	6 (7.4)	3 (3.8)	3 (7.5)
Insomnia	6 (22.2)	7 (7.6)	2 (9.1)	15 (10.6)	4 (4.9)	3 (3.8)	2 (5.0)
Immune system disorders	**1 (3.7)**	**3 (3.3)**	**1 (4.5)**	**5 (3.5)**	**7 (8.6)**	**5 (6.3)**	**3 (7.5)**
Hypogammaglobulinemia	1 (3.7)	1 (1.1)	0	2 (1.4)	5 (6.2)	2 (2.5)	3 (7.5)

C201=MOR208C201; C202=MOR208C202; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event; X01=XmAb5574-01.

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

MedDRA Version 21.0.

Sorted in descending order of frequency in L-MIND (overall), by SOC, preferred term within SOC, then alphabetically.

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 LEN + 30 days; and the Extended Tafasitamab Monotherapy phase includes AEs starting after the last date of treatment with LEN + 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 study discontinuation for any reason.

b. One patient (94004-06) received infusions of tafasitamab on Days 1 and 4 of Cycle 1, but LEN 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.

Source: m5.3.5.3/ISS/Tab2.2.1

Source: SCS, Table 8

In study MOR208C203 and the pooled monotherapy studies, the most frequently reported Grade 3-5 TEAEs were in the SOC Blood and Lymphatic System Disorders [56.8% (overall) / 17.5% (extension part) and 18.4%, respectively] and Infections and Infestations [29.6% (overall) / 12.5% (extension part) and 13.5%, respectively] (Table 10/SCS). Given the underlying haematological diseases in a relapse/refractory setting, this is not surprising, but to what extent tafasitamab contributes can only be answered satisfactorily in an RCT.

Table 34: Grade 3-5 Treatment-Emergent Adverse Events Reported in ≥2% of Patients in L-MIND (Overall) - Safety Analysis Set

MedDRA Preferred Term	Monotherapy Studies				MOR208C203 (L-MIND)[a]		
	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 N = 22 n (%)	Pooled N = 141 n (%)	Overall N = 81 n (%)	Combination Therapy N = 80[b] n (%)	Extended Tafasitamab Monotherapy N = 40[b] n (%)
Any	**10 (37.0)**	**36 (39.1)**	**19 (86.4)**	**65 (46.1)**	**63 (77.8)**	**61 (76.3)**	**15 (37.5)**
Blood and lymphatic system disorders	**8 (29.6)**	**10 (10.9)**	**8 (36.4)**	**26 (18.4)**	**46 (56.8)**	**44 (55.0)**	**7 (17.5)**
Neutropenia	6 (22.2)	7 (7.6)	1 (4.5)	14 (9.9)	40 (49.4)	38 (47.5)	7 (17.5)
Thrombocytopenia	3 (11.1)	2 (2.2)	2 (9.1)	7 (5.0)	14 (17.3)	14 (17.5)	0
Febrile neutropenia	1 (3.7)	1 (1.1)	5 (22.7)	7 (5.0)	10 (12.3)	9 (11.3)	0
Leukopenia	0	1 (1.1)	0	1 (0.7)	9 (11.1)	6 (7.5)	3 (7.5)
Anaemia	1 (3.7)	3 (3.3)	2 (9.1)	6 (4.3)	6 (7.4)	6 (7.5)	0
Lymphopenia	0	0	0	0	3 (3.7)	3 (3.8)	0
Infections and infestations	**4 (14.8)**	**6 (6.5)**	**9 (40.9)**	**19 (13.5)**	**24 (29.6)**	**20 (25.0)**	**5 (12.5)**

MedDRA Preferred Term	Monotherapy Studies				MOR208C203 (L-MIND)[a]		
	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 N = 22 n (%)	Pooled N = 141 n (%)	Overall N = 81 n (%)	Combination Therapy N = 80[b] n (%)	Extended Tafasitamab Monotherapy N = 40[b] n (%)
Pneumonia	0	3 (3.3)	1 (4.5)	4 (2.8)	6 (7.4)	5 (6.3)	1 (2.5)
Lower respiratory tract infection	0	0	0	0	2 (2.5)	1 (1.3)	2 (5.0)
Upper respiratory tract infection	0	0	0	0	2 (2.5)	2 (2.5)	0
Urinary tract infection	0	0	0	0	2 (2.5)	2 (2.5)	0
Cardiac disorders	**0**	**2 (2.2)**	**1 (4.5)**	**3 (2.1)**	**8 (9.9)**	**8 (10.0)**	**0**
Atrial fibrillation	0	0	0	0	3 (3.7)	3 (3.8)	0
Cardiac failure congestive	0	0	0	0	2 (2.5)	2 (2.5)	0
General disorders and administration site conditions	**0**	**4 (4.3)**	**6 (27.3)**	**10 (7.1)**	**7 (8.6)**	**5 (6.3)**	**2 (5.0)**
Asthenia	0	1 (1.1)	0	1 (0.7)	2 (2.5)	1 (1.3)	1 (2.5)
Fatigue	0	2 (2.2)	2 (9.1)	4 (2.8)	2 (2.5)	1 (1.3)	1 (2.5)
Respiratory, thoracic and mediastinal disorders	**1 (3.7)**	**3 (3.3)**	**3 (13.6)**	**7 (5.0)**	**7 (8.6)**	**7 (8.8)**	**0**
Pulmonary embolism	0	0	0	0	4 (4.9)	4 (5.0)	0
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (4.5)**	**1 (0.7)**	**7 (8.6)**	**7 (8.8)**	**0**
Dermatitis allergic	0	0	0	0	3 (3.7)	3 (3.8)	0
Metabolism and nutrition disorders	**1 (3.7)**	**3 (3.3)**	**10 (45.5)**	**14 (9.9)**	**6 (7.4)**	**6 (7.5)**	**0**
Hypokalaemia	0	2 (2.2)	2 (9.1)	4 (2.8)	5 (6.2)	5 (6.3)	0
Investigations	**1 (3.7)**	**7 (7.6)**	**10 (45.5)**	**18 (12.8)**	**5 (6.2)**	**5 (6.3)**	**1 (2.5)**
Transaminases increased	0	0	0	0	2 (2.5)	2 (2.5)	1 (2.5)
Musculoskeletal and connective tissue disorders	**0**	**3 (3.3)**	**0**	**3 (2.1)**	**5 (6.2)**	**4 (5.0)**	**2 (5.0)**
Back pain	0	2 (2.2)	0	2 (1.4)	2 (2.5)	2 (2.5)	0
Renal and urinary disorders	**0**	**0**	**0**	**0**	**4 (4.9)**	**3 (3.8)**	**0**
Renal failure	0	0	0	0	2 (2.5)	2 (2.5)	0
Vascular disorders	**0**	**1 (1.1)**	**3 (13.6)**	**4 (2.8)**	**4 (4.9)**	**3 (3.8)**	**1 (2.5)**
Hypertension	0	1 (1.1)	3 (13.6)	4 (2.8)	3 (3.7)	2 (2.5)	1 (2.5)

C201=MOR208C201; C202=MOR208C202; MedDRA=Medical Dictionary for Regulatory Activities; NS=not stated; PT=preferred term; SOC=System Organ Class, TEAE=treatment-emergent adverse event; X01=XmAb5574-01.

MedDRA Version 21.0.

Sorted in descending order of frequency in L-MIND (overall), by SOC, preferred term within SOC, then alphabetically.

A TEAE is an AE that either starts or worsens in severity on or after the first treatment date/time and on or before the end of the on-treatment phase (i.e., the earliest of the treatment end date + 30 days/data cut date/death date).

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. 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 LEN + 30 days, and the Extended Tafasitamab Monotherapy phase includes AEs starting after the last date of treatment with LEN + 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 study discontinuation for any reason.

b. One patient (94004-06) received infusions of tafasitamab on Days 1 and 4 of Cycle 1, but LEN 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.

Source: m5.3.5.3/ISS/Tab2.3.1

Source: SCS, Table 10

The applicant has also compared TEAEs and grade 3/4 TEAEs (Table 12/SCS) in the combination part of the pivotal study MOR208C203 to the USPI for lenalidomide. The studies are conducted in MDS, multiple myeloma, and Mantle cell lymphoma. The latter could be considered the disease most relevant to compare to R/R DLBCL, and the TEAEs are generally of the same magnitude. As trial design, population, disease etc are not the same, no further emphasis will be placed on this comparison.

Table 12 Grades 3/4 Treatment-Emergent Adverse Events Reported in ≥2% of Patients in L-MIND Overall or in the Pooled Monotherapy Versus LEN Published Studies - Safety Analysis Set

	Monotherapy Studies				L-MIND[a]			LEN Monotherapy Studies[b]		
MedDRA Preferred Term	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 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 (%)	CALGB[d]/ Alliance 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)
Anaemia	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)
Hypokalaemia	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)

C201=MOR208C201; C202=MOR208C202; MedDRA=Medical Dictionary for Regulatory Activities; NS=not stated; PT=preferred term; TEAE=treatment-emergent adverse event; X01=XmAb5574-01.
MedDRA Version 21.0.

A TEAE is an AE that either starts or worsens in severity on or after the first treatment date/time and on or before the end of the on-treatment phase (i.e., the earliest of the treatment end date + 30 days/data cut date/death date).

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. 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 LEN + 30 days, and the Extended Tafasitamab Monotherapy phase includes AEs starting after the last date of treatment with LEN + 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 study discontinuation for any reason.

b. REVLIMID USPI, Revised: 10/2019

c. One patient (94004-06) received infusions of tafasitamab on Days 1 and 4 of Cycle 1, but LEN 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 LEN versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma.

Source: m5.3.5.3/ISS/Tab2.2.5

Source: SCS, Table 12

Patients Treated >12 Cycles (L-MIND study and study MOR208C201)

In L-MIND overall, a total of 34 patients were treated with tafasitamab alone for >12 cycles and 21 patients were treated with tafasitamab alone for >24 cycles. Patients treated for more than 12 cycles received tafasitamab alone following the end of LEN therapy after 12 cycles per protocol. After 12 cycles, 26/34 (76.5%) patients experienced 193 TEAEs. As patients continued treatment >24 cycles, 16/21 (76.2%) patients experienced 82 TEAEs. For comparison, the frequency of TEAEs experienced in Cycles 1-12 was 33/34 (97.1%). The most commonly reported TEAEs in patients treated >12 cycles were in the SOC of Infections and Infestations: 16/34 (47.1%) patients during cycle 13-24, with main PTs of bronchitis (4/34 [11.8%] patients) and nasopharyngitis (4/34 [11.8%] patients). Twenty events of neutropenia were reported for 8/34 (23.5%) patients after 12 cycles and 5 events of neutropenia were reported for 3/21 (14.3%) patients after 24 cycles.

Adverse events of special interest

TEAEs of special interest was determined for tafasitamab based on preclinical and/or clinical safety data for tafasitamab and/or comparable class label statements and/or regulatory authority requirements. The following AESIs were specified: anaphylaxis, DILI, QT prolongation, tumour flare, tumour lysis syndrome, second primary malignancy, infusion-related reactions, allergic reaction to study drug (Grade 3 or higher), rash/skin reactions other than allergic reactions, cytokine release syndrome, overdose, diarrhoea, acute renal failure, infections, neutropenia, embolic and thrombotic events.

In Study MOR208C203 *a*dverse events of special interest as defined per protocol were tumour flare, tumour lysis syndrome, second primary malignancies, infusion related reactions (≥ Grade 3), allergic reactions to study drug (≥ Grade 3), cytokine release syndrome and overdoses.

Allergic reactions

No events of anaphylaxis or anaphylactoid reaction were reported as an AE for any patient. There were four events of ≥ grade 3 allergic reaction in MOR208C203. In two cases LEN was suspected and interrupted, and in the other two cases both drugs were suspected and discontinued.

Table 37: Analysis of Allergic Reaction to Study Drug, Grade 3 or Higher

Study Patient ID	Age/Sex/Race	MedDRA Preferred Term	Toxicity [Serious]	Onset Day/Cycle [Duration]	Causality Tafasitamab LEN	Outcome
MOR208C203 38001-03	73/F/White	Dermatitis allergic VT=EXANTHEMA (ALLERGIC REACTION)	Grade 3 [No]	D16/C1 [13]	Not Suspected Suspected	Resolved
MOR208C203 38005-02	82/M/White	Hypersensitivity VT=ALLERGY	Grade 3 [No]	D112/C4 [4]	Not Suspected Not Suspected	Resolved
MOR208C203 51007-02	75/M/White	Dermatitis allergic VT=ALLERGIC REACTION WITH SYMPTOM OF CUTANEOUS RASH	Grade 3 [No]	D13/C1 [41]	Not Suspected Suspected	Resolved
MOR208C203 72001-07	63/M/White	Dermatitis allergic VT=MACULOPAPULAR RASH (ALLERGIC REACTION)	Grade 3 [No]	D55/C2 [46]	Suspected Suspected	Resolved with sequelae

C=cycle; D=day; F=female; ID=identification; M=male; MedDRA=Medical Dictionary for Regulatory Activities; VT=verbatim term.

Hepatic Disorders and Drug Induced Liver Injury (DILI):

No events of hepatic injury or DILI were reported by Investigators.

Five cases of elevated liver enzyme values in the monotherapy studies were not considered related to treatment, as there were other explanations for the laboratory abnormalities.

Torsades de pointes and QT Prolongation:

The AE of ""Electrocardiogram QTc prolonged" was reported for 1 patient in MOR208C203 (L-MIND) and 2 patients in MOR208C201. A medical review of these cases showed that the patients had confounding factors for QTc prolongation." and "Four patients with syncope (3 in L-MIND and 1 in MOR208C202) and 1 with loss of consciousness in L-MIND were identified and upon review of these cases none were associated with QTc prolongation or Torsades de pointes." Going through the narratives no definite link to tafasitamab could be assessed as there were other likely explanations.

Tumour Flare Reaction

In MOR208C203 the three events of tumour flare all occurred in Cycle 1 with severity ranging from Grade 1 to Grade 3. One case was considered to be serious.

Table 358: Analysis of Tumour Flare Reaction

Study Patient ID	Age/Sex/Race	MedDRA Preferred Term	Toxicity [Serious]	Onset Day/Cycle [Duration]	Causality Tafasitamab LEN	Outcome
MOR208C203 26001-01	71/M/White	Tumour flare	Grade 2 [No]	D8/C1 [17]	Not Suspected Suspected	Resolved
MOR208C203 51001-05	74/M/White	Tumour flare	Grade 1 [No]	D2/C1 [7]	Not Suspected Suspected	Resolved
MOR208C203 51007-03	69/F/White	Tumour flare	Grade 3 [Yes]	D4/C1 [16]	Suspected Suspected	Resolved w/sequelae

C=cycle; D=day; F=female; ID=identification; M=male; MedDRA=Medical Dictionary for Regulatory Activities

Tumour Lysis Syndrome

No events of tumour lysis syndrome were reported for MOR208C203. Overall, 6 actual or potential cases of tumour lysis syndrome were reported or identified in the monotherapy studies.

Infusion-Related Reactions

In MOR208C202 (ALL patients) a total of 15 infusion-related reactions in 13/22 (59.1%) patients were reported.

In XmAb5574-01 (CLL/SLL patients):18/27 (66.7%) patients experienced an infusion-related reaction. All were Grade 1 or 2 and resolved after symptomatic treatment.

In MOR208C201 (various lymphoma patients): infusion-related reactions were experienced by 12/92 (13.0%) patients, mostly during the first infusion, and all but one were non-serious in nature and of toxicity Grade 1 or 2. The most probable explanation for the high frequency seen in study MOR208C202 and XmAb5574-01 is that in leukaemia patients a high number of tumour cells are present in the peripheral blood and thus are prone to immediate lysis.

In MOR208C203 (DLBCL patients) a total of 5/81 (6.2%) patients experienced an infusion-related reaction; all except for one occurring during the first infusion of tafasitamab; all were Grade 1 in severity.

Cytokine-Release Syndrome

Cytokine release syndrome was not reported as an AE in in the pooled monotherapy studies or in MOR208C203

Second Primary Malignancies.

At the cutoff date of 30NOV2019 there was another patient with a basal cell carcinoma of the sternum and nose, increasing the number of patients with a SPM to 3/81 and in addition one with MDS. Patient data were reviewed for SPM using the SMQ Non-haematological malignant tumours to identify potential cases. There was also one case of myelodysplastic syndrome (MDS) in study MOR208C203.

Overdose (CMQ)

There were no events that meet the criteria for overdose reported in MOR208C203 or in any of the monotherapy studies.

Diarrhoea

In the pooled monotherapy studies 20/141 (14.2%) patients experienced 25 events of diarrhoea and in study MOR208C203 a total of 29/81 (35.8%) patients experienced 60 events of diarrhoea. Only 2 cases were grade 3 (no grade 4; see Table 20, SCS). Diarrhoea is a common adverse reaction of LEN (>20%), which might explain the higher incidence in study MOR208C203.

Non-allergic skin reactions ≥ Grade 3:

In the pooled monotherapy studies, a total of 14/141 (9.9%) patients experienced skin events (any grades) that were potentially not of allergic origin compared with 30/81 (37.0%) patients in MOR208C203. Non-allergic skin reactions of Grade 3 were reported for 4 patients in the MOR208C203 study; none were associated with skin infections.

Embolic and Thrombotic Events

There were one thrombotic and one embolic event in monotherapy study MOR208C201. In MOR208C203 11 (13.6%) patients had 6 serious events and 11 nonserious events. Thromboembolism is a well-known ADR for lenalidomide. Whether tafasitamab adds to this could potentially be answered in an RCT.

Infections

Table 369: Summary of SEAs: Infections

Table 2.4.1
Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Analysis Set)

	MOR00208 Monotherapy												MOR00208 + LEN Combination (L-MIND) [1]								
	X01 N = 27			C201 N = 92			C202 N = 22			Total Monotherapy N = 141			Overall N = 81			Combination Therapy N = 80			Extended Monotherapy N = 40		
System Organ Class Preferred Term	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Any TEAE	4	(14.8)	6	18	(19.6)	25	15	(68.2)	28	37	(26.2)	59	42	(51.9)	76	35	(43.8)	59	9	(22.5)	14
Infections and infestations	3	(11.1)	4	7	(7.6)	10	6	(27.3)	8	16	(11.3)	22	21	(25.9)	32	18	(22.5)	23	4	(10.0)	8
Pneumonia	0			3	(3.3)	5	1	(4.5)	1	4	(2.8)	6	6	(7.4)	6	5	(6.3)	5	1	(2.5)	1
Bronchitis	0			0			0			0			2	(2.5)	2	2	(2.5)	2	0		
Lower respiratory tract infection	0			0			0			0			2	(2.5)	4	1	(1.3)	1	2	(5.0)	3
Bronchopulmonary aspergillosis	0			0			0			0			1	(1.2)	2	1	(1.3)	2	0		

Source: ISS

Search for infectious risk was focused on serious AEs from SOC infections and infestations, and CMQ including infectious pneumonia, sepsis and UTI. Infectious risk was observed with tafasitamab monotherapy, in a similar trend in SAEs between pooled monotherapy studies (11.3%) and L-MIND extended monotherapy phase (10.0%). The risk was increased when combined to lenalidomide (22.5%).

Neutropenia

Events of neutropenia (and febrile neutropenia) occurred more frequently in patients receiving tafasitamab-LEN combination therapy (39/80 (48.8%) patients; 181 events) compared with the monotherapy extension phase of MOR208C203 [11/40 (27.5%) patients; 24 events]. In the pooled monotherapy studies the frequency of neutropenia was even lower [15/141 (12.8%) patients; 17 events], despite the fact that there were ALL patients in this pool [27/141 of which 6/27 (22%) had neutropenia; 6/14 neutropenic patients in the pooled monotherapy were ALL patients]. The majority of the neutropenia events were Grade 3 or higher.

Table 40: Summary of grade 3 or higher TEAEs : Blood and lymphatic system disorders

Table 2.3.1
Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Analysis Set)

	MOR00208 Monotherapy												MOR00208 + LEN Combination (L-MIND) [1]								
	X01 N = 27			C201 N = 92			C202 N = 22			Total Monotherapy N = 141			Overall N = 81			Combination Therapy N = 80			Extended Monotherapy N = 40		
System Organ Class Preferred Term	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Any TEAE	10	(37.0)	23	36	(39.1)	67	19	(86.4)	88	65	(46.1)	178	63	(77.8)	295	61	(76.3)	258	15	(37.5)	33
Blood and lymphatic system disorders	8	(29.6)	11	10	(10.9)	19	8	(36.4)	14	26	(18.4)	44	46	(56.8)	180	44	(55.0)	165	7	(17.5)	14
Neutropenia	6	(22.2)	6	7	(7.6)	9	1	(4.5)	1	14	(9.9)	16	40	(49.4)	109	38	(47.5)	98	7	(17.5)	11
Thrombocytopenia	3	(11.1)	3	2	(2.2)	4	2	(9.1)	2	7	(5.0)	9	14	(17.3)	25	14	(17.5)	25	0		
Febrile neutropenia	1	(3.7)	1	1	(1.1)	1	5	(22.7)	9	7	(5.0)	11	10	(12.3)	11	9	(11.3)	10	0		
Leukopenia	0			1	(1.1)	1	0			1	(0.7)	1	9	(11.1)	15	6	(7.5)	12	3	(7.5)	3
Anaemia	1	(3.7)	1	3	(3.3)	3	2	(9.1)	2	6	(4.3)	6	6	(7.4)	11	6	(7.5)	11	0		

MedDRA Version 21.0.
[1] Overall includes adverse events starting during the entire on-treatment phase, Combination Therapy includes adverse events starting between the start of the on-treatment phase and the last date of treatment with LEN + 30 days, Extended Monotherapy includes adverse events starting after the last date of treatment with LEN + 30 days through the end of the on-treatment phase.
Planned treatment for L-MIND is 12 28-day cycles of combination therapy followed by MOR00208 Extended Monotherapy until progressive disease or unacceptable toxicity or study discontinuation for any reason.
A TEAE is an adverse event that either starts or worsens in severity on or after the First Treatment Date/Time and on or before the end of the on-treatment phase (i.e. the earliest of the treatment end date + 30 days/data cut date/death date).
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.

Serious adverse event/deaths/other significant events

Serious Adverse Events (SAEs)

In study MOR208C203 and the pooled monotherapy studies, the most frequently reported SAEs were observed in the SOC Infections and Infestations. Counting all infections (also those occurring in only 1 patient) 24/42 patients (57%) had an SAE in this SOC.

Table 41: Serious Treatment-Emergent Adverse Events as of 30 Nov 2019 Reported for ≥2% of Patients in L-MIND or in the Pooled Monotherapy Studies - Safety Analysis Set

MedDRA Preferred term	Pooled Monotherapy[a] N = 141		L-MIND					
			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)**	**78**	**35 (43.8)**	**59**	**10 (25.0)**	**16**
Pneumonia	4 (2.8)	6	7 (8.6)	6	5 (6.3)	5	2 (5.0)	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
Tumour lysis syndrome	3 (2.1)	3	0	0	0	0	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment emergent adverse event
MedDRA version 21.0.

A TEAE is an AE that either starts or worsens in severity on or after the First Treatment Date/Time and on or before the end of the on-treatment phase (i.e., the earliest of the treatment end date + 30 days/data cut date/death date).

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 studies XmAb5574-01, MOR208C201, and MOR208C202.

There were three fractures in study MOR208C203: One pathological fracture, one lower limb fracture in a 65-year old and one in a 78-year old female after a fall. They had received steroids as part of prior treatment making them susceptible to steroid-induced osteoporosis.

There were three SAEs of pulmonary embolism in study MOR208C203 in the combination period and none in the extension period or the monotherapy studies. Venous thromboembolism is a Very common ADR of lenalidomide.

Deaths

A total of 50 (22.5%) deaths were reported in 222 patients overall: 10 (10.9%) deaths in MOR208C201, 6 (27.3%) deaths in MOR208C202, and 34 (42.0%) deaths in MOR208C203. There were no deaths reported in XmAb5574-01.

As of the submission cut-off date of 30 Jun 2019, a total of 12 death events (on-treatment and post-treatment) were assessed as not related to disease progression (see table below though with a later update but with no change in deaths. Four of these deaths occurred off-treatment and were therefore not considered as TEAEs and are not discussed further.

Table 42: Summary of Deaths as of 30 Nov 2019 - Safety Analysis Set

	Monotherapy Studies[a]				L-MIND Overall N = 81 n (%)	All Deaths N = 222 n (%)
	X01 N = 27 n (%)	C201 N = 92 n (%)	C202 N = 22 n (%)	Pooled N = 141 n (%)		
Deaths	0	10 (10.9)	6 (27.3)	16 (11.3)	**38 (46.9)**	**54 (24.3)**
On-Treatment Phase[b] 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	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[c] Cause of Death	0	2 (2.2)	3 (13.6)	5 (3.5)	**30 (37.0)**	**35 (15.8)**
Disease Progression	0	2 (2.2)	1 (4.5)	3 (2.1)	**25 (30.9)**	**28 (12.6)**
Not Related to Disease Progression	0	0	2 (9.1)	2 (1.4)	5 (6.2)	7 (3.2)

C201=MOR208C201; C202=MOR208C202; N=total number of patients in category of interest; n=number of patients with event of interest (death); X01= XmAb5574-01.

a. There were no fatal serious AEs reported during XmAb5574-01.

b. 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.

c. Post-treatment phase includes any events occurring after on-treatment phase.

Going through the eight adverse events death narratives, there was one case of PML (progressive multifocal leukoencephalopathy) in study MOR208C203 diagnosed post-mortem but with neurological symptoms present before treatment start. The patient received four doses of tafasitamab and 15 days of lenalidomide. This patient had received three different courses of chemotherapy over the course of five years all with rituximab added. It is not considered likely that PML developed due to tafasitamab after four doses.

There was one case of sclerosing cholangitis in a patient with ALL (study MOR208C202). Going through the narrative this event seems most likely related to GvHD; the patient had an allogeneic transplantation (HSCT) 3 months before study start and the event occurred on d. 98 of the study corresponding to approximately 6 months after HSCT.

Table 43: Death cases (treatment-emergent and not related to disease progression) by patient, as of 30 Jun 2019 - Safety Analysis Set

Patient Age/sex	Onset/death date	Preferred term	Related?
MOR208C201			
76/M	25 Jul 2013/ 25 Jul 2013 (for all events)	Pneumonia Respiratory failure Cardiac failure	No No No
MOR208C202			
46/F	25 Sep 2013/ 22 Oct 2013	Cholangitis sclerosing	Yes*
53/M	27 Oct 2013/ 19 Nov 2013	Sepsis	No
33/M	07 Oct 2013/ 09 Oct 2013	Sepsis	No
MOR208C203			
81/F	10 Nov 2017/ 12 Nov 2017	Cerebrovascular accident	No
76/M	5 Oct 2016/ 5 Oct 2016	Sudden death	No
55/M	11 Dec 2017/ 19 Dec 2017	Respiratory failure	No
79/M	5 Aug 2017/ 18 Oct 2017	Progressive multifocal leukoencephalopathy	No

*The patient developed sclerosing cholangitis on Study Day 97. The patient 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 acute hepatitis A which was diagnosed 10 days prior to death and had suspected acute graft versus host disease involving the gastrointestinal tract and liver, both of which could potentially lead to liver failure.

Laboratory findings

As expected by the mode of action of tafasitamab, there was a decrease of lymphocytes.

Neutropenia, disorders of the liver, and acute renal failure are discussed in the AESI section.

Table 44: Summary of Hematology and Coagulation Results Shift from Baseline Grade 0/1 to Worst On-Treatment CTCAE Grade 3/4 - Safety Analysis Set

Parameters	Pooled Monotherapy Studies[a] N = 141				MOR208C203 (L-MIND) N = 81			
		Baseline[b]		Worst[c]		Baseline[b]		Worst[c]
	n	Grade 0	Grade 1	Grade 3/4	n	Grade 0	Grade 1	Grade 3/4
Haemoglobin	49	28 (57.1)	4 (8.2)	1 (2.0)	81	39 (48.1)	34 (42.0)	1 (1.2)
Leukocytes	49	32 (65.3)	6 (12.2)	11 (22.4)	81	76 (93.8)	2 (2.5)	8 (9.9)
Lymphocytes	49	31 (63.3)	4 (8.2)	7 (14.3)	81	40 (49.4)	16 (19.8)	4 (4.9)
Neutrophils	49	24 (49.0)	6 (12.2)	12 (24.5)	81	77 (95.1)	2 (2.5)	14 (17.3)
Platelets	49	27 (55.1)	3 (6.1)	2 (4.1)	81	64 (79.0)	14 (17.3)	1 (1.2)
aPTT	49	40 (81.6)	9 (18.4)	0	81	61 (75.3)	17 (21.0)	2 (2.5)
Prothrombin INR	27	26 (96.3)	1 (3.7)	0	81	52 (64.2)	23 (28.4)	1 (1.2)

aPTT=activated partial thromboplastin time; CTCAE=Common Terminology Criteria for Adverse Events: INR=international normalised ratio.

Toxicity graded according to NCI-CTCAE version 4.0

a. Monotherapy Studies MOR208C202 and XmAb5574-01. MOR208C201 was excluded as CTCAE grading was not applied to laboratory results for this study. MOR208C202 does not have laboratory results for Prothrombin INR.

b. Baseline is defined as the last non-missing value recorded prior to first study treatment.

c. Worst on-treatment grade is the worst CTCAE grade observed during the on-treatment phase, in this case Grade 3/4. 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.

Safety in special populations

There were a higher number of SAEs and discontinuations with higher age (see table below). No consistent pattern of specific AEs particularly related to higher age could be seen, which could be due to the relative low number of patients. No major differences related to gender were seen. Due to few non-white patients in the SAS no meaningful racial differences could be discerned.

No geographic differences could be evaluated as most patients (93%) in MOR208C203 came from Europe.

As patients with severe renal or hepatic impairment were excluded from clinical trials, the applicant identified retrospectively patients with mild to moderate renal impairment or non-severe hepatic impairment; no issues were noted.

Table 37: Frequency (% of Patients) of Adverse Events based on Age Cohorts

MedDRA Terms	**Age <65 number of patients (%)**	**Age 65-74 number of patients (%)**	**Age 75-84 number of patients (%)**	**Age 85+ number of patients (%)**
Total N = 81	**N = 23**	**N = 27**	**N = 30**	**N = 1**
Total AEs	23 (100.0)	27 (100.0)	30 (100.0)	1 (100.0)
Serious AEs – Total	9 (39.1)	14 (51.9)	19 (63.3)	0 (0.0)
- Fatal	1 (4.3)	0 (0.0)	3 (10.0)	0 (0.0)
- Hospitalisation/prolong existing hospitalisation	9 (39.1)	14 (51.9)	18 (60.0)	0 (0.0)
- Life-threatening	3 (13.0)	1 (3.7)	4 (13.3)	0 (0.0)
- Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Other (medically significant)	0 (0.0)	4 (14.8)	3 (10.0)	0 (0.0)
AE leading to drop-out (discontinuation of tafasitamab due to AE)	3 (13.0)	2 (7.4)	7 (23.3)	0 (0.0)

MedDRA Terms	Age <65 number of patients (%)	Age 65-74 number of patients (%)	Age 75-84 number of patients (%)	Age 85+ number of patients (%)
AE leading to drop-out (discontinuation of lenalidomide due to AE)	4 (17.4)	4 (14.8)	10 (33.3)	0 (0.0)
AE leading to drop-out (discontinuation of any study treatment due to AE)	4 (17.4)	5 (18.5)	11 (36.7)	0 (0.0)
Psychiatric disorders (SOC)	3 (13.0)	8 (29.6)	2 (6.7)	0 (0.0)
Nervous system disorders (SOC)	13 (56.5)	12 (44.4)	14 (46.7)	0 (0.0)
Accidents and injuries (SMQ)	3 (13.0)	6 (22.2)	1 (3.3)	0 (0.0)
Cardiac disorders (SOC)	1 (4.3)	3 (11.1)	8 (26.7)	0 (0.0)
Vascular disorders (SOC)	5 (21.7)	9 (33.3)	9 (30.0)	0 (0.0)
Cerebrovascular disorders (SMQ: Central nervous system vascular disorders)	0 (0.0)	0 (0.0)	2 (6.7)	0 (0.0)
Infections and infestations (SOC)	17 (73.9)	18 (66.7)	23 (76.7)	1 (100.0)
Anticholinergic syndrome (SMQ)	6 (26.1)	15 (55.6)	11 (36.7)	0 (0.0)
Quality of life decreased (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension (PT), falls (PT fall), black outs (PT loss of consciousness), syncope (PT), dizziness (PT), ataxia (PT), fractures (HLGT)	3 (13.0)	3 (11.1)	3 (10.0)	0 (0.0)
Other AE appearing more frequently in older patients*:				
Neutropenia (PT)	10 (43.5)	15 (55.6)	16 (53.3)	0 (0.0)
Anaemia (PT)	6 (26.1)	9 (33.3)	13 (43.3)	1 (100.0)
Thrombocytopenia (PT)	8 (34.8)	7 (25.9)	10 (33.3)	0 (0.0)
Febrile neutropenia (PT)	4 (17.4)	0 (0.0)	6 (20.0)	0 (0.0)
Oedema peripheral (PT)	3 (13.0)	5 (18.5)	11 (36.7)	0 (0.0)
Asthenia (PT)	3 (13.0)	9 (33.3)	6 (20.0)	1 (100.0)
Decreased appetite (PT)	5 (21.7)	5 (18.5)	7 (23.3)	1 (100.0)
Diarrhoea (PT)	7 (30.4)	11 (40.7)	11 (36.7)	0 (0.0)
Bronchitis (PT)	5 (21.7)	3 (11.1)	4 (13.3)	1 (100.0)
Upper respiratory tract infection (PT)	2 (8.7)	2 (7.4)	4 (13.3)	0 (0.0)
Hypokalemia (PT)	2 (8.7)	7 (25.9)	6 (20.0)	0 (0.0)
Constipation (PT)	4 (17.4)	6 (22.2)	4 (13.3)	0 (0.0)
Blood creatinine increased (PT)	2 (8.7)	1 (3.7)	4 (13.3)	0 (0.0)
Back pain (PT)	3 (13.0)	7 (25.9)	5 (16.7)	0 (0.0)
Paraesthesia (PT)	1 (4.3)	1 (3.7)	4 (13.3)	0 (0.0)
Hypotension (PT)	1 (4.3)	1 (3.7)	4 (13.3)	0 (0.0)

Reference: D120_Safety_A1/Table EMA.5.
*: 'Other AE appearing more frequently in older patients' is defined as follows: Most common TEAEs reported in >10% patients of age group >75 years in MOR208C203
PT = MedDRA Preferred Term, SOC = System Organ Class, SMQ = Standardised MedDRA Query

Immunological events

The clinical assessment of immunogenicity for tafasitamab was evaluated in 245 patients, of which 81 (33.1%) of the 245 patients were part of MOR208C203. The other 164 (66.9%) patients were derived from the 4 other clinical studies (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 2 years.

A low number of patients were tested ADA-positive before start of tafasitamab treatment suggesting the presence of pre-existing antibodies, i.e., 17 (6.9%) of the 245 patients overall (including 2 patients from MOR208C203). Only 6 of these patients with pre-existing ADAs were ADA positive on an intermittent basis also after start of tafasitamab treatment (i.e., ADA positive at 1 to 7 sampling time points; none within MOR208C203). The other 11 of these patients with pre-existing ADAs did not show any positive ADA assessment during treatment. Thus, in all 5 clinical studies, no treatment-emergent or treatment-boosted ADAs could be detected. The ADA titres were low and there was no apparent clinical impact of ADAs on PK, safety, or efficacy.

In conclusion, no cases of treatment-emergent ADA occurred. In MOR208C203 the mean exposure time to tafasitamab was 49.3 weeks. - See also section of Clinical pharmacology.

Safety related to drug-drug interactions and other interactions

See section of Clinical pharmacology.

Discontinuation due to adverse events

Overall, 10 TEAEs (7.1%) in pooled monotherapy studies and 12 (14.8%) in L-MIND study led to tafasitamab discontinuation. The main reported SOCs included Infections and Infestations, and Blood and Lymphatic system disorders. No PT was reported more than once.

There seem to be no pattern of reasons for discontinuation but the total number of patients having received tafasitamab is low and more patients and an RCT may reveal specific ADRs leading to discontinuation. The reasons for discontinuation of lenalidomide are in line with the listed ADRs.

The applicant discussed TEAEs leading to treatment discontinuation. The applicant later provided a discussion on TEAE leading to treatment interruption as no treatment modification was allowed for tafasitamab. Treatment interruption occurred mostly in the first 2 cycles similarly to treatment discontinuation. These TEAE leading to treatment interruption were often manageable and patients were able to restart treatment.

Post marketing experience

Tafasitamab was only approved by the FDA in July 2020. No post marketing data is currently available.

2.6.1. Discussion on clinical safety

This is an application for the use of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy in adult patients with relapsed or refractory DLBCL who are not eligible for or refuse ASCT on the basis of Study MOR208C203 (L-MIND) which is considered the main source of safety information.

The pivotal study MOR208C203 consists of 81 R/R DLBCL patients (one patient received tafasitamab only) of which 40 continued to the monotherapy part. The median duration of exposure to study treatment (MOR00208 + LEN) was 9.2 months (range: 0.23, 32.10 months). The median duration of exposure to MOR00208 was 6.2 months (range: 0.1, 12.4). The median duration of exposure to LEN was 4.2 months (range: 0.07, 20.83) (see CSR, Table 12-1 and Table 2, SCS). 30/81 patients received the intended 12 months of lenalidomide therapy. Few patients received long-term treatment: 13 patients

received 12-24 cycles and 21 patients > 24 cycles of tafasitamab therapy (combined + monotherapy) (data cut-off 30JUN2019).

As supportive safety data the applicant has pooled three tafasitamab monotherapy studies performed in patients with various haematological malignancies and in one study also in various doses. In the phase 2 study MOR208C201 35/92 patients had R/R DLBCL and the rest various other lymphomas. The phase 2 study MOR208C202 consisted of 22 relapsed B-ALL patients and the phase 1 study XmAb5574-01 consisted of 27 R/R CLL patients of which 16 received the same dose as in the pivotal DLBCL study (12 mg/kg). With regards to exposure 2 patients received 12-24 cycles and 9 patients > 24 cycles in the pooled monotherapy studies.

AEs incidence was significantly higher when combined with lenalidomide, with expected AEs according to the known lenalidomide safety profile. The most frequently reported adverse events (overall) in the L-MIND study were AEs in the SOCs Infections and Infestations (72.8%), Blood and Lymphatic System Disorders (65.4%), Gastrointestinal Disorders (64.2%), and General Disorders and Administration Site Conditions (58.0%). The difference between the pooled monotherapy studies and the extension part of study MOR208C203 was most pronounced for the SOC Infections and Infestations; 38.3% vs 55.0%, respectively, potentially reflecting the previously administered more toxic combination with lenalidomide in study MOR208C203 or the effect of long-term treatment with tafasitamab. The difference between the extension arm and the pooled monotherapy studies is even larger when focussing on lymphoma patients only, as the patients in the CLL and ALL studies, not unexpectedly, had a higher incidence of infections compared to the lymphoma study (13/27=48.1% and 11/22=50%, respectively vs 30/92=32.6%). A phase 3, randomised, controlled study could possibly clarify to what extent tafasitamab contributes compared to LEN.

In study MOR208C203 and the pooled monotherapy studies, the most frequently reported Grade 3-5 TEAEs were in the SOC Blood and Lymphatic System Disorders [56.8% (overall) / 17.5% (extension part) and 18.4%, respectively] and Infections and Infestations [29.6% (overall) / 12.5% (extension part) and 13.5%, respectively] (Table 10/SCS). Given the underlying haematological diseases this is not surprising, but to what extent tafasitamab contributes can only be answered satisfactorily in an RCT. The incidence of grade ≥ 3 TEAEs was higher in overall L-MIND study (77.8%) than in pooled monotherapy studies (46.1%), driven by combination therapy. Grade ≥ 3 TEAE frequencies in tafasitamab extended monotherapy were similar to pooled monotherapy studies.

With regards to AESIs it seems that infections and neutropenia are related to tafasitamab. Fatal and serious infections, including opportunistic infections, occurred in patients during treatment with tafasitamab. Tafasitamab should be administered to patients with an active infection only if the infection is treated appropriately and well controlled. Patients with a history of recurring or chronic infections may be at increased risk of infection and should be monitored appropriately. (see SmPC section 4.4). As these PTs are also frequently seen during LEN treatment the part that tafasitamab plays is undetermined.

Not unexpectedly, infusion-related reaction (IRRs) are an AESI, although most of them seem to be low-grade and thus manageable. Warnings on IRRs have been included in the SmPC section 4.4. Infusion-related reactions may occur and have been reported more frequently during the first infusion (see SmPC section 4.8). Patients should be monitored closely throughout the infusion. Patients should be advised to contact their healthcare professionals if they experience signs and symptoms of infusion-related reactions including fever, chills, rash or breathing problems within 24 hours of infusion. A premedication should be administered to patients prior to starting tafasitamab infusion. Based on the severity of the infusion-related reaction, tafasitamab infusion should be interrupted or discontinued and appropriate medical management should be instituted (see SmPC section 4.2).

The following SAEs are reported with TAFA+LEN combination, not described with TAFA only: pulmonary embolism, atrial fibrillation, bronchitis, cardiac failure congestive. These SAEs reflect the known safety profile of lenalidomide, and are included in the proposed SmPC for TAFA+LEN combination.

Related SAEs reported with TAFA only (L-MIND study, extended phase) included pneumonia (1) and streptococcal sepsis (1). Additionally, from pooled monotherapy studies, related SAEs included febrile neutropenia (3) tumour lysis syndrome (3), infections (n=3, including one fungal infection and one genital herpes zoster), and infusion related reaction (1).

AEs leading to tafasitamab discontinuation concerned 7.1% of patients in pooled monotherapy studies and 14.8% in L-MIND study; the main reported SOCs included Infections and Infestations, and Blood and Lymphatic system disorders. TEAEs leading to treatment modification, interruption or dose reduction were not discussed. Moreover, the timing for treatment discontinuation or interruption should also be discussed.

Infections, neutropenia and IRR seem to be related to tafasitamab to a certain degree. No clear pattern of adverse events for SAEs and deaths related to tafasitamab can be seen, but any clear conclusion as to tafasitamab ADRs is hampered by the concomitant use of lenalidomide, the small safety population, and in particular the lack of a comparator. The applicant has presented data updated by 16 months. The median exposure is still 9.2 months but the longest treatment has increased from 32.1 to 54.7 months. Six patients moved from treatment for 1-2 years to ≥ 2 years so that altogether 27 patients were exposed for ≥2 years. Nineteen patients are still ongoing. Looking at safety no new deaths or discontinuations while on treatment occurred. There was a slight increase in adverse events (All and ≥ Grade 3) related to the SOCs Blood and lymphatic disorders and Infections and infestations, which is not unexpected.

Treatment with tafasitamab can cause serious and/or severe myelosuppression including neutropenia, thrombocytopenia and anaemia (see section 4.8). Complete blood counts should be monitored throughout treatment and prior to administration of each treatment cycle. Based on the severity of the adverse reaction, tafasitamab infusion should be withheld. Refer to the lenalidomide SmPC for dosage modifications.

Neutropenia, including febrile neutropenia, has been reported during treatment with tafasitamab. Administration of granulocyte colony-stimulating factors (G-CSF) should be considered, in particular in patients with Grade 3 or 4 neutropenia. Any symptoms or signs of developing infection should be anticipated, evaluated and treated.

Thrombocytopenia has been reported during treatment with tafasitamab. Withholding of concomitant medicinal products that may increase bleeding risk (e.g. platelet inhibitors, anticoagulants) should be considered. Patients should be advised to report signs or symptoms of bruising or bleeding immediately.

Patients with high tumour burden and rapidly proliferative tumour may be at increased risk of tumour lysis syndrome. In patients with DLBCL, tumour lysis syndrome during treatment with tafasitamab has been observed. Appropriate measures/prophylaxis in accordance with local guidelines should be taken prior to treatment with tafasitamab. Patients should be monitored closely for tumour lysis syndrome during treatment with tafasitamab.

Treatment with tafasitamab in combination with lenalidomide should not be initiated in female patients unless pregnancy has been excluded (see SmPC section 6.6). Please also refer to the SmPC of lenalidomide.

The safety of immunisation with live vaccines following tafasitamab therapy has not been investigated and vaccination with live vaccines is not recommended concurrently with tafasitamab therapy.

Few patients received long-term treatment with tafasitamab with or without lenalidomide. The applicant has presented data updated by 16 months. The median exposure is still 9.2 months but the longest treatment has increased from 32.1 to 54.7 months. Six patients moved from treatment for 1-2 years to ≥ 2 years so that altogether 27 patients were exposed for ≥2 years; 19 patients are ongoing at the time of this report. No new deaths or discontinuations while on treatment occurred by the latest cut-off. There was a slight increase in adverse events (All and ≥ Grade 3) related to the SOCs Blood and lymphatic disorders and Infections and infestations, which is not unexpected.

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

Additional safety data needed in the context of a conditional MA

The median exposure to tafasitamab in the pivotal L-MIND study that include 81 patients was 6.2 months. Few patients received long-term treatment; rare adverse events and long-term adverse events are not expected to be fully elucidated at the moment. Since the data cannot be comprehensive enough to support a full MA, a conditional MA was proposed and further data will be submitted so that safety will be reconfirmed through an expanded database in a new single arm trial with the combination of tafasitamab and lenalidomide in the indicated patient population and through the Front-MIND trial. Further, long term safety of tafasitamab with bendamustine will be studied in the B-MIND trial.

2.6.2. Conclusions on the clinical safety

The pivotal study L-MIND study showed a high incidence of AEs (all grades) in the SOCs Infections and Infestations (72.8%), Blood and Lymphatic System Disorders (65.4%), especially neutropenia, and Gastrointestinal Disorders (64.2%). These AEs are as to be expected in haematological diseases in a relapsed/refractory setting and considered manageable. The dossier may not be considered comprehensive to support a full approval in the proposed indication.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA

- In order to confirm the efficacy and safety of Tafasitamab in combination with lenalidomide in diffuse Large B cell lymphoma in patients not eligible for ASCT, the MAH should conduct and submit the results of a single-arm study of Tafasitamab in combination with lenalidomide in the approved indication according to an agreed protocol.
- In order to confirm the safety profile of tafasitamab in combination with lenalidomide the applicant should submit the results of a phase 3, multicentre, randomised, double-blind, placebo-controlled trial comparing tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP in previously untreated, high-intermediate and high-risk patients with newly-diagnosed diffuse large B-cell lymphoma (DLBCL).
- In order to confirm long term safety of tafasitamab the applicant should submit the results of a Phase 2/3, Randomised, Multicentre Study of Tafasitamab 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).

2.7. Risk Management Plan

Safety concerns

Table 38: Summary of the Safety Concerns

Important identified risks	None
Important potential risks	Progressive multifocal leukoencephalopathy
Missing information	Use in pregnancy and lactation Use in patients with recent use of B-cell depleting drugs or chemotherapy Long-term safety

Pharmacovigilance plan

Table 39: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study MOR208C204 (B-MIND) is a Phase II/III Randomised, Multicentre Study of MOR00208/tafasitamab 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) Status: Ongoing	In order to confirm long term safety of tafasitamab the applicant shall submit the results of a Phase 2/3, Randomised, Multicentre Study of Tafasitamab 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). **Rationale and study objectives:** This is a randomised, open-label clinical trial to compare the safety and efficacy of MOR00208 with bendamustine versus rituximab with bendamustine, an accepted standard of care for this patient population. **Primary Objective:** To determine the efficacy of a combination of MOR00208 with bendamustine versus a combination	Long term safety	Final clinical study report	March 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	of rituximab with bendamustine in terms of progression-free survival in: • Adult patients with R-R DLBCL (overall population) • A subgroup of adult patients with R-R DLBCL with low baseline peripheral blood NK-cell count, defined as 100 or less NK cells per µl blood at baseline. **Secondary Objectives:** To determine and compare both study arms, MOR00208 with bendamustine versus rituximab with bendamustine, for the overall population and NKCC-low subgroup in terms of: a) best objective response rate based on the best response achieved at any time during the study b) duration of response c) overall survival d) disease control rate e) time to progression f) time to next treatment g) safety, based on the frequency, incidence and severity of adverse events h) quality of life To assess the potential immunogenicity of MOR00208 (anti-MOR00208 antibody formation) To assess the pharmacokinetic profile of MOR00208			
Category 3 - Required additional pharmacovigilance activities				
None				

Risk minimisation measures

Table 40: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Progressive multifocal leukoencephalopathy	Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in pregnancy and lactation	Routine risk communication: SmPC sections 4.6, 5.3 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with recent use of B-cell depleting drugs or chemotherapy	Routine risk communication: SmPC sections 4.4 PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study MOR208C204 (B-MIND) A Phase II/III Randomised, Multicentre Study of MOR00208/tafasitamab 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).

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.7 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle

with the international birth date (IBD). The IBD is 31.07.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

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

2.10. Product information

2.10.1. User consultation

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

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Minjuvi (tafasitamab) is included in the additional monitoring list as it as it pertains a conditional marketing authorisation for a product containing a new active substance and contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Minjuvi is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).

3.1.2. Available therapies and unmet medical need

Standard treatment for patients with newly diagnosed DLBCL consists of immuno-chemotherapy with the anti-CD20 monoclonal antibody rituximab (RTX), and CHOP administered for 6-8 cycles (R-CHOP) (Tilly et al. 2015). The addition of RTX has substantially improved the results of CHOP-chemotherapy, yielding complete and sustained remission in about 60% of cases (Coiffier et al, 2002). But still approximately 30-40% of patients ultimately will relapse and are not cured by first-line therapy with R-CHOP, and approximately 10% of patients are refractory to R-CHOP as first-line therapy (primary refractory) (Coiffier et al., 2010).

In patients progressing or relapsing after first-line treatment, the main consideration for further treatment is whether the patients is a candidate for HDT and ASCT. Salvage chemotherapy followed by HDT and ASCT is standard treatment for transplant-eligible patients, and may offer a second chance of cure for about 30-40% of the patients (Crump 2017, Gisselbrecht 2010). However, the majority of R/R DLBCL patients are ineligible for ASCT due to comorbidities and older age. The treatment options for patients who have relapsed or progressed after second-line treatment of DLBC, or who are not eligible for ASCT are limited. For these patients, the European Society of Medical Oncology (ESMO) guidelines recommend participation in clinical studies, treatment with platinum- and/or gemcitabine-based salvage regimens (with or without RTX) (Tilly et al. 2015). Of note, none of the agents recommended by the ESMO guidelines (Tilly et al. 2015) is specifically approved as a second-line treatment for DLBCL, and there is no consensus regarding the optimal treatment, which focuses on prolongation of survival and not having a curative intent. The outcome is dismal with generally no prolonged periods of disease control (Thieblemont and Coiffier 2007). Despite new approved therapies, such as CAR-T and Polatuzumab, there remains an unmet medical need for patients with R/R DLBCL who are ineligible for or fail ASCT.

3.1.3. Main clinical studies

The main evidence of efficacy and safety submitted is a phase 2 single-arm, multicentre, open-label study (MOR208C203 (L MIND; n=81) of tafasitamab combined with lenalidomide followed by tafasitamab monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and who are ineligible for or refuse autologous stem cell transplant (ASCT). Two supportive studies were also included in order to demonstrate the contribution of each agent to the combination;

- NHL study (MOR208C201): A Phase IIa, open-label, multicentre study of single-agent MOR00208 in patients with relapsed or refractory B-Cell non-Hodgkin's lymphoma

- RE-MIND (MOR208C206): An observational retrospective cohort study of lenalidomide monotherapy in R/R DLBCL to generate a historical control for clinical trial MOR208C203

3.2. Favourable effects

Tafasitamab in combination with lenalidomide in centrally confirmed DLBCL patients based on the updated data cut-off as of 30-Oct-2020 within ITT (n=81) showed:

- an ORR of 56.8% (95%CI: 45.3; 67.8), a CR rate of 39.5% (95%CI: 28.8;51.0)

- a median DoR by IRC of 43.9 months (95% CI: 26.1; NR). Median duration of response was not reached in complete responders (95% CI: 43.9; not reached) and was 5.6 months in patients with partial response as best response.

- a median PFS by IRC of 11.6 months (95% CI: 5.7; 45.7) and

- a median OS of 31.6 months (95%CI: 18.3; NR) after a median follow-up time of 42.7 months (95% CI: 38.0;47.2)

- results from secondary endpoints such as EFS, TTP and TNT were in line with primary and key secondary endpoint.

3.3. Uncertainties and limitations about favourable effects

Main evidence supporting this application comes from a single-arm pivotal phase II study to evaluate tafasitamab in combination with lenalidomide in 81 patients with R/R DLBCL who were not eligible for ASCT. The patient population in study L-MIND is considered small and the clinical package cannot be considered comprehensive. A further single arm trial with an optimised design and sample size in line with an agreed protocol has been requested by the CHMP as a specific obligation in the context of the CMA (see Annex II).

3.4. Unfavourable effects

In the L-MIND study a high incidence of AEs (all grades) in the SOCs Infections and Infestations (72.8%), Blood and Lymphatic System Disorders (65.4%), Gastrointestinal Disorders (64.2%), and General Disorders and Administration Site Conditions (58.0%) were observed.

In study MOR208C203 and the pooled monotherapy studies, the most frequently reported Grade 3-5 TEAEs were in the SOC Blood and Lymphatic System Disorders [56.8% (overall) / 17.5% (extension part) and 18.4%, respectively] and Infections and Infestations [29.6% (overall) / 12.5% (extension part) and 13.5%, respectively] (Table 10/SCS). Given the underlying haematological diseases in a relapsed/refractory setting AEs in these SOCs are to be expected, but to what extent lenalidomide + tafasitamab contributes is uncertain.

With regards to AESIs it seems that infections and neutropenia are related to tafasitamab. As these PTs are also frequently seen during LEN treatment the part that tafasitamab plays is undetermined. Not unexpectedly, infusion-related reactions (IRRs) are observed, although most of them seem to be low-grade and thus manageable.

3.5. Uncertainties and limitations about unfavourable effects

The median exposure to tafasitamab in the pivotal L-MIND study that included 81 patients was 35 weeks (8.05 months). Rare adverse events and long-term adverse events are not expected to be fully elucidated at the moment therefore further data is needed to confirm the long-term safety of tafasitamab.

Few patients received long-term treatment: 13 patients received 12-24 cycles and 21 patients > 24 cycles of tafasitamab therapy (combined + monotherapy) (data cut-off 30 June 2019; another 6 patients were added with the data cut-off 30 October 2020).

Further safety data will be submitted through the specific obligations:

- Study Front-MIND will provide data on the safety profile of tafasitamab in combination with lenalidomide in addition to R-CHOP versus R-CHOP in previously untreated, high-intermediate and high-risk patients with newly-diagnosed diffuse large B-cell lymphoma (DLBCL) (see RMP and Annex II).
- Study B-MIND, a Phase 2/3, Randomised, Multicentre Study of Tafasitamab 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), will look into long term safety (see RMP and Annex II).

3.6. Effects Table

Table 49: Effects Table for [Lenalidomide/ tafasitamab, L-MIND (Efficacy cut-off: 30 OCT 2020, Safety Cutoff 30JUN2019)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR by IRC	Overall response rate (CR + PR)	%	56.8% (45.3;67.8)	N/A	Small sample size	Trial L-MIND
DoR by IRC	Duration of response	Median months	43.9 (95% CI: 26.1; NR)	N/A		
PFS by IRC	Progression – free survival by IRC	Median months	11.6 (95% CI: 5.7; 45.7)	N/A		
OS (95% CI)	Median By IRC	months	31.6 (18.3, NR)	N/A		
Unfavourable Effects						
Infections (SOC)	Incidence of Infections	%	72.8 Gr. 3-5: 29.6 SAEs: 25.9	-	Both lenalidomide and tafasitamab contributes to AEs in a population predisposed to the most common AEs observed (infections and myelosuppression). The lack of a comparator weakens the real incidence of AEs.	SAS[1] 2.4.1[2]
Blood & lymph. (SOC)	Incidence	%	65.4 Gr. 3-5: 56.8			Safety Analysis set (SAS), Clinical Safety discussion
Neutro-penia	Incidence	%	50.6 Gr. 3-5: 49.4			
Anaemia	Incidence	%	35.8 Gr. 3-5: 7.4			
Thrombo-cytopenia	Incidence	%	30.9 Gr. 3-5: 17.3			
Febrile neutro-penia	Incidence	%	12.3 Gr. 3-5: 12.3			

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
GI disorders (SOC)	Incidence	%	64.2 Gr. 3-5: 2.5			
Diarrhoea	Incidence	%	35.8 Gr. 3-5: 1.2			
Infusion related reactions	Incidence	%	6.2			

Abbreviations: GI: gastrointestinal, SCS; summary of clinical safety, Gr.: grade
Notes:1: SCS, 2: ISS. Safety Cutoff 30JUN2019 (ISS)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For patients with R/R DLBCL ineligible to HDT and ASCT, no standard treatment exists, and the prognosis remains poor. For these patients, the European Society of Medical Oncology (ESMO) treatment guidelines recommend participation in clinical studies, treatment with platinum- and/or gemcitabine-based salvage regimens (with or without RTX) (Tilly et al. 2015). Of note, none of the agents recommended by the ESMO guidelines (Tilly et al. 2015) is specifically approved as a second-line treatment for DLBCL, and no particular therapy appears to be favoured over the others by the guidelines. Recently, Polatuzumab received indications in 2L+ setting and CAR-T therapies received indications in 3L+ setting for R/R DLBCL.

Compared with historical data with monotherapy of tafasitamab and lenalidomide, an ORR of > 50% is considered highly clinically meaningful in the relapse-refractory setting of DLBCL not eligible to high dose chemotherapy and ASCT. Although based on limited numbers in a single-arm study, the ORR data and CR rate of 39.5% are considered a clinically meaningful outcome in patients with R/R – DLBCL. The clinically relevant effect of tafasitamab is consistently seen throughout sensitivity analyses, different histologies or reasons for ASCT ineligibility.

The pivotal study L-MIND study showed a high incidence of infections, neutropenia and gastrointestinal disorders. These AEs are as to be expected in haematological diseases in a relapsed/refractory setting and considered manageable. Being a single arm phase 2 study, makes it difficult to disentangle to what extent tafasitamab contributes to the efficacy and the overall AEs. Further, the safety profile should be seen in context of the clinical meaningful efficacy results.

As data for the product was not considered comprehensive, the applicant requested a conditional MA during the assessment and has justified the requirements for a conditional approval.

3.7.2. Balance of benefits and risks

An ORR of 56.8% and a CR rate of 39.5% is considered clinically meaningful and sufficient to establish efficacy in a R/R DLBCL setting not eligible to ASCT. Overall, the safety profile is considered manageable; more comprehensive and long- term safety data with tafasitamab will be provided post authorisation.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant during the assessment.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as R/R DLBCL not eligible to ASCT is considered a serious and life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

As confirmative studies (SOB) in the context of CMA, the applicant will seek to confirm the efficacy and safety of tafasitamab in combination with lenalidomide in diffuse Large B cell lymphoma in patients not eligible for ASCT, by conducting another single-arm study of tafasitamab in combination with lenalidomide in the approved indication according to an agreed protocol. The protocol will be submitted for the review of the CHMP no later than 3 months after the Commission Decision.

Further, the applicant will provide data from the B-MIND in order to investigate further the long-term safety. B-MIND is an ongoing study in R/R DLBCL, MOR208C204 (B-MIND) of tafasitamab and bendamustine vs rituximab and bendamustine, and it is proposed as a SOB to confirm the safety of tafasitamab.

The applicant is also planning to conduct a phase 3, randomised, double-blind, placebo-controlled trial, Front-MIND (EudraCT number 2020-002990-84) comparing the efficacy and safety of tafasitamab + lenalidomide in addition to R-CHOP versus R-CHOP alone in previously untreated, high-intermediate/high-risk patients with newly-diagnosed diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL). This study was agreed as an SOB to further expand the safety database and evaluate the safety of tafasitamab+ lenalidomide in combination with SOC in 1L DLBCL.

- Unmet medical needs will be addressed.

The incidence of DLBCL increases with age, and DLBCL patients over 60 years of age (median age was 67y, range 60–88) have a poorer prognosis and inferior outcomes than younger DLBCL patients. Standard treatment for newly diagnosed DLBCL is an anthracycline based immune-chemotherapy regimen, R-CHOP or R-CHOEP. Although the outcome has improved over the last decades, 10-15% of the patients are primary refractory and 20-30% relapse. For patients who relapse or are refractory to their first line therapy, a key determinant for their subsequent treatment is the performance status and whether the patient is eligible to high dose chemotherapy and ASCT.

For patients who are ineligible for transplant, the goal of second-line therapy is to induce a remission as long as possible and prolong survival although not with curative intent. Poor outcomes are observed among patients who are ineligible for SCT (mOS: 6 to 11 months) or have refractory disease (mOS: 6.1 to 7.1 months) after any line of treatment (Arcari et al 2016; Crump et al 2017; Czuczman et al 2017). For patients receiving second-line salvage therapy OS range from 11 to 17.2 months while patients receiving third-line salvage therapy had a shorter OS, ranging from 5.9 to 8.0 months (Lenz et al 2018).

Additional treatment options are needed in R/R DLBCL in patients not eligible for ASCT, aiming to achieve control and remission of the disease for as long as possible given that all patients eventually relapse and

become resistant to available treatments, where the remission duration generally decreases with each subsequent treatment regimen, and where the toxicity of different regimens is significant and quite different between products. In this context, medicinal products with a positive benefit-risk balance and new mechanism of action can provide a major therapeutic advantage to patients if they offer possible alternative or additional treatment options based on a different safety profile, or based on therapeutic efficacy when other products are not expected to be effective.

Tafasitamab has a mechanism of action that is different from that of authorised treatments and has shown to be associated with a 53.5% objective response rate, a CR rate of 35.2% (95%CI: 28.8;51.0) and a median duration of response of 34.6 months in this group of R/R patients with a dismal prognosis. Tafasitamab has a distinct toxicity profile compared to approved products. However, AEs of tafasitamab are mostly reversible, and clinically manageable. Treatment is tolerated when adverse effects are closely monitored and actively managed, mainly by dose modifications. Therefore, tafasitamab can be considered a major therapeutic advantage in the proposed target population for whom there are very limited and often no other treatment options available, in particular when available options are unlikely to be efficacious, or when it is the preferred option in view of its efficacy and safety profiles.

In conclusion, patients who are not eligible to HDC and ASCT do have an unmet medical need for effective, tolerable and more accessible medicines.

- The benefits to the public health of the immediate availability of the product outweigh the risks inherent in the fact that additional data are still required.

Patients with R/R DLBCL who are not eligible to ASCT have limited therapeutic options. An ORR of > 50% and a DoR of 34.6 months is considered clinically meaningful and of benefit to public health in a disease characterised of rapid progression. The safety profile of tafasitamab is considered manageable in the clinical setting. The benefits to the public health of the immediate availability of the product outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall B/R of Minjuvi is positive. The MA shall be subject to the conditions specified in Annex II.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Minjuvi is not similar to Polivy, Kymriah and Yescarta within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

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

Minjuvi in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of tafasitamab in combination with lenalidomide in diffuse Large B cell lymphoma in patients not eligible for ASCT, the MAH should conduct and submit the results of a single-arm study of tafasitamab in combination with lenalidomide in the approved indication according to an agreed protocol.	December 2026

Description	Due date
In order to re-confirm the safety profile of tafasitamab in combination with lenalidomide the applicant should submit the results of a phase 3, multicentre, randomised, double-blind, placebo-controlled trial comparing tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP in previously untreated, high-intermediate and high-risk patients with newly-diagnosed diffuse large B-cell lymphoma (DLBCL).	December 2025
In order to confirm long term safety of tafasitamab the applicant should submit the results of a Phase 2/3, Randomised, Multicentre Study of tafasitamab 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)	March 2025

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tafasitamab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.