RISK MANAGEMENT PLAN
FOR
MINJUVI (TAFASITAMAB)

RMP version to be assessed as part of this application: 4.0

Data lock point for this RMP	10 NOV 2025	Version number	4.0
Date of final sign off	11 NOV 2025		

Rationale for submitting an updated RMP:

Extension of tafasitamab therapeutic indication to follicular lymphoma

Summary of significant changes in this RMP:

Part	Major changes in v 4.0 compared to RMP v 3.0
Part IV	Update of the post-authorization efficacy study (PAES) front-MIND as per the SOB deferral

Other RMP versions under evaluation:

No RMP versions are currently under evaluation.

QPPV name: Achint Kumar

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's (MAH) QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
aaIPI	age adjusted International Prognostic Index
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BR	bendamustine and rituximab
CAR T	chimeric antigen receptor T-cell
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisone/prednisolone
CNS	central nervous system
CR	complete response
CrCL	creatinine clearance
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
ePPND	enhanced pre and postnatal development
ESMO	European Society for Medical Oncology
EU	European Union
Fc	fragment crystallizable
FITC	fluorescein isothiocyanate
FL	follicular lymphoma
FLIPI	follicular lymphoma international prognostic index
GELF	Groupe d'Etude des Lymphomes Folliculaires
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCP	healthcare professional
HDC	high dose chemotherapy

Abbreviation	Definition
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IMiDs	immunomodulatory drugs
IPI	International Prognostic Index
IV	intravenous
JC	John Cunningham
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAH	marketing authorisation holder
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCCN	national comprehensive cancer network
NCI	national cancer institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NKCC	natural killer cell count
OS	overall survival
PK	pharmacokinetics
PL	patient leaflet
PML	Progressive multifocal leukoencephalopathy
POD24	progression of disease within 24 months
Pola-BR	polatuzumab vedotin, bendamustine and rituximab
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone/prednisolone
R-GemOx	rituximab, gemcitabine and oxaliplatin
RMP	Risk Management Plan
R/R	relapsed or refractory
RTX	rituximab
SAE	serious adverse event
SEER	surveillance, epidemiology, and end results
SPMs	secondary primary malignancies
SmPC	summary of product characteristics

Abbreviation	Definition
UK	United Kingdom
ULN	upper limit of normal
US	United States

PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	tafasitamab
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FX12
Marketing Authorisation Applicant	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 BP Amsterdam Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	MINJUVI
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Fc-enhanced monoclonal antibody (mAb) that targets the CD19 antigen
	Summary of mode of action: Tafasitamab is an Fc-enhanced monoclonal antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes. CD19 is broadly and homogeneously expressed across different B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL), and amplifies B-cell receptor signalling and tumour cell proliferation and survival. Upon binding to CD19, tafasitamab mediates B-cell lysis through: • engagement of immune effector cells like natural killer (NK) cells, γδ T cells and phagocytes • direct induction of cell death (apoptosis) The Fc modification results in more potent immune effector cell mechanisms, including enhanced antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).
	Important information about its composition: Tafasitamab is a humanised CD19-specific mAb of the immunoglobulin G (IgG) subclass produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.
Hyperlink to the Product Information	Link to PI in the eCTD sequence

Indication(s) in the EEA	Current: MINJUVI is indicated in combination with lenalidomide followed by MINJUVI monotherapy for the treatment of adult patients with relapsed or refractory (R/R) DLBCL, who are not eligible for autologous stem cell transplant (ASCT).
	Proposed: MINJUVI is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least one line of systemic therapy.
Dosage in the EEA	Current: The recommended dose is 12 mg tafasitamab per kg body weight administered as an intravenous (iv) infusion according to the following schedule: • Cycle 1: Administer the infusion on day 1, 4, 8, 15 and 22 of the cycle. • Cycles 2 and 3: Administer the infusion on day 1, 8, 15 and 22 of each cycle. • Cycle 4 until disease progression: Administer the infusion on day 1 and 15 of each cycle. Each cycle has 28 days. In addition, patients should self-administer lenalidomide capsules at the recommended starting dose of 25 mg daily on days 1 to 21 of each cycle. The starting dose and subsequent dosing may be adjusted according to the lenalidomide product information. MINJUVI plus lenalidomide in combination are given for up to twelve cycles. After a maximum of twelve cycles of combination therapy, stop treatment with lenalidomide and continue MINJUVI infusions as single agent on day 1 and 15 of each 28-day cycle, until disease progression.
	Proposed: The recommended dose of MINJUVI is 12 mg per kg body weight administered as an intravenous infusion according to the following schedule: • Cycle 1 to 3: infusion on day 1, 8, 15 and 22 of each cycle. • Cycles 4 to 12: infusion on day 1 and 15 of each cycle. Each cycle has 28 days.

	The recommended starting dose of rituximab is 375 mg/m^2 administered as an intravenous infusion according to the following schedule: • Cycle 1: on days 1, 8, 15, and 22. • Cycles 2 to 5: on day 1 of each cycle. Each cycle has 28 days. Please refer to the SmPC of rituximab intravenous formulations for information on its method of administration and premedication and prophylactic medications. In addition, patients should self-administer lenalidomide capsules at the recommended starting dose of 20 mg daily on days 1 to 21 of each 28-day cycle. The starting dose and subsequent dosing may be adjusted according to the lenalidomide SmPC. MINJUVI in combination with lenalidomide plus rituximab is given for up to twelve cycles for MINJUVI and lenalidomide, and five cycles for rituximab. Treatment with rituximab should be stopped after five cycles of combination therapy. Patients should continue to receive MINJUVI infusions in combination with oral lenalidomide up to cycle twelve. Treatment with tafasitamab plus lenalidomide should be stopped after a maximum of twelve cycles.
Pharmaceutical form(s) and strengths	Current: 200 mg powder for concentrate for solution for infusion. Each vial contains 200 mg of tafasitamab. After reconstitution each mL contains 40 mg of tafasitamab.
	Proposed: None
Is/will the product be subject to additional monitoring?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Non-Hodgkin lymphoma (NHL) is a heterogenous group of hematological malignancies with lymphoid characteristics that arise from hematopoietic progenitor cells. It is the tenth most common malignancy globally. In Europe, 129,338 cases were diagnosed in 2022 with a mortality of 51,808 cases in total within the same year (Globocan 2022).

II.1 Diffuse large B-cell lymphoma (DLCBL)

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

Incidence and prevalence:

DLBCL is the most common subtype of NHL, constituting 30%-58% of NHL (Tilly et al 2015). 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). Based on data from the European HAEMACARE project, 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). UK data from 2373 patients with DLBCL indicate a median age at diagnosis of 70 years (Smith et al 2015).

Demographics of the population in the proposed indication – age, gender, racial and ethnic origin and risk factors for the disease:

DLBCL can occur at any age, but diagnosis is more common in the elderly, with a median age at diagnosis of >70 years (Smith et al 2011, Smith et al 2015). This was reflected in the population included in the pivotal study MOR208C203 (L-MIND), with a median patient age of 72 years (range 41-86 years), and high age was given as a reason for ineligibility for ASCT for 46.3% of patients.

DLBCL is slightly more common in males than in females (Smith et al 2011). This was again reflected in the enrolment to the MOR208C203 (L-MIND) study, which included slightly more males (54.3%) than females (45.7%).

The incidence of DLBCL has been found to be higher in Caucasians than in African Americans or Asians (Shenoy et al 2011, Morton et al 2006), and this was consistent in study MOR208C203 (L-MIND) in which 88.9% of study participants were White.

As described above, age, gender, and race affect a person's likelihood of developing DLBCL. Exposure to certain chemicals or drugs or radiation, a weakened immune system, autoimmune disease, certain infections, body weight and diet are additional risk factors for NHL in general (American Cancer Society 2020).

Additional baseline characteristics of the study population in the pivotal study MOR208C203 (L-MIND) included Eastern Cooperative Oncology Group [ECOG] performance status of 0, 1, or 2 in 35.8%, 55.6%, and 8.6%, respectively. A similar proportion of patients had IPI category of low and low-intermediate risk (49.4%) or high and intermediate-high risk (50.6%). The majority of study participants were Ann Arbor Stage III and IV (75.3%) with fewer (24.7%) Stage I and II. Slightly more than half the patients (56.8%) did not have rituximab refractoriness, and most (81.5%) did not have primary refractoriness. The majority (88.9%) of study participants did not have a history of prior ASCT.

The main existing treatment options:

The DLBCL treatment landscape is described below, including current therapeutic options for patients with R/R DLBCL who are not eligible for high dose chemotherapy (HDC) and ASCT.

First-Line Treatments

Standard treatment for patients with newly diagnosed DLBCL consists of immuno-chemotherapy with the anti-CD20 monoclonal antibody rituximab (RTX), and the combination chemotherapy regimen CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone/prednisolone) administered for 6-8 cycles (R-CHOP) (Tilly et al 2015). The addition of RTX substantially improves the results of CHOP-chemotherapy, but still a significant proportion of patients are not cured by first-line therapy with R-CHOP (Coiffier et al 2002). The polatuzumab-R-CHP (polatuzumab-vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone) has now been approved for use in untreated patients in the EU and for untreated patients with IPI 2-5 in the USA, based on the results of the Polarix trial (Tilly et al 2022).

Many other therapies and regimens have been investigated in an attempt to improve on the efficacy of R-CHOP but without success. These include the addition of bevacizumab (Seymour et al 2014), bortezomib (Leonard et al 2017), ibrutinib (Younes et al 2019) and lenalidomide (Thieblemont et al 2017, Vitolo et al 2019), dose intensification of RTX (Lugtenburg et al 2016), and use of alternative CD20-directed antibodies such as obinutuzumab (Vitolo et al 2017).

Second Line Treatments

Approximately 20% of patients are refractory to R-CHOP as first-line therapy (primary refractory), and approximately 30% of DLBCL patients relapse despite having achieved complete remission (CR) with R-CHOP (Coiffier and Sarkozy 2016, Sehn and Gascoyne 2015). The treatment of patients with R/R DLBCL mainly depends on their eligibility to intensive treatments such as ASCT and chimeric antigen receptor T-cell (CAR T) therapies.

Traditionally, the standard second-line treatment for patients with R/R DLBCL has been platinum-based salvage chemotherapy (with or without RTX) followed by HDC and ASCT (Tilly et al 2015). This approach can cure 30%-40% of ASCT-eligible patients with R/R DLBCL (Gisselbrecht et al 2010, Crump et al 2017).

Eligibility for intensive regimens depends on performance status, age, and comorbidities (Skrabek et al 2019). In addition, eligibility for ASCT depends on response to induction chemotherapy. Around half of the patients with DLBCL treated actively in the second-line setting will not be eligible for transplantation due to ineffective salvage treatment (Gisselbrecht and Van Den Neste 2018).

In recent years, two CAR T therapies, axicabtagene ciloleucel (Yescarta) and lisocabtagene maraleucel (Breyanzi) have shown improved outcomes when compared to HDC and ASCT in the second-line setting in the ZUMA-7 and TRANSFORM studies, respectively (Locke et al 2022, Abramson et al 2023). These two therapies have received approval for treatment of DLBCL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy [Yescarta 2024, Breyanzi 2024].

Albeit somewhat less stringent than eligibility for ASCT, eligibility for CAR T-cell therapies also depends on performance status and comorbidities. These treatment options have been associated with severe AEs, including Grade ≥3 cytokine release syndrome and neurotoxicity, and can therefore be difficult to administer safely and successfully.

Second-line treatment of patients not eligible for ASCT

Many patients are not fit enough to receive intensive treatments. For patients with R/R DLBCL who are not eligible for ASCT (e.g. because of older age or comorbidities), there are limited treatment options. Consistent with this finding, population-based studies in Canada and Denmark indicate that more than half of the patients with R/R DLBCL are treated palliatively (Skrabek et al 2019).

The European Society of Medical Oncology (ESMO) treatment guidelines recommend participation in clinical studies with novel drugs for patients with R/R DLBCL who are not eligible for ASCT (Tilly et al 2015). Outside of a clinical trial, the guidelines recommend treatment with platinum- and/or gemcitabine-based salvage regimens (with or without RTX). Of note, none of the agents recommended by the ESMO guidelines is specifically approved as a second-line treatment for DLBCL. Of the various non-approved therapies, which may be used in transplant-ineligible patients, efficacy appears to be most established (albeit modest) with the combination of rituximab, gemcitabine and oxaliplatin (R-GemOx) or with the combination of bendamustine and rituximab (BR) (Ohmachi et al 2013, Mounier et al 2013).

Additional options for R/R DLBCL patients who are ineligible for transplant have received approval in recent years, including polatuzumab vedotin (Polivy 2020) in combination with bendamustine and rituximab (POLA-BR), and tafasitamab in combination with lenalidomide (MINJUVI 2024).

Third Line Treatment

There are a few recently approved treatment options for patients who have relapsed or progressed after second-line treatment of their DLBCL. Three CAR T-cell therapies, axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), and lisocabtagene maraleucel (Breyanzi) have been approved in the EU in the last 5 years for patients with R/R DLBCL who have received two or more lines of systemic therapy (Neelapu et al 2017, Schuster et al 2017).

In addition to CAR T-cell therapy, an antibody-drug conjugate (ADC) also targeting CD19, loncastuximab-tesirine (Zynlonta), and two bispecific T-cell engagers targeting CD20xCD3, glofitamab (Columvi) and epcoritamab (Tepkinly) were recently approved for use after two or more systemic lines of therapy.

Because the ESMO guidelines date back to 2015, they do not yet include any recommendations on the use of CAR T-cells, POLA-BR, tafasitamab+lenalidomide, loncastuximab, glofitamab or

epcoritamab in R/R DLBCL. Recommendations relating to pixantrone also reflect the limited data that was available at the time the guidelines were drafted (Tilly et al 2015).

Overall, patient outcomes with available treatments for R/R DLBCL remain largely unsatisfactory and a substantial proportion of patients do not achieve sustained remission and ultimately die of DLBCL. Patients who are not eligible for HDC with ASCT in particular, have limited therapeutic options for a serious and life-threatening condition and are in urgent need of more tolerable and effective therapies.

Natural history of the indicated condition in the population, including mortality and morbidity: DLBCL is an aggressive lymphoma and patients have a short life expectancy if left untreated. A large US study has been published of patients who relapsed and received second-line therapy, following first-line treatment with anthracycline-based immunochemotherapy between 2002 and 2012 (Farooq et al 2017). The response rate to therapy at first relapse was 54% and 42% of patients ultimately went on to HDC and ASCT. For the whole group (all 244 patients who relapsed and received treatment), OS at 4 years from relapse was 28%. However, for the subgroup of patients who underwent HDC and ASCT, overall survival (OS) after transplant was 51% at 4 years. For the small subgroup of patients (n=23) treated with a non-aggressive salvage regimen (such as BR, R-GemOx or single-agent RTX), median OS was 10.4 months and OS at 4 years was 22%. Overall, patients who relapsed more than a year from initial diagnosis had a 4-year OS of 47% but those with a transient or no response to initial therapy (primary refractory disease) had a 4-year OS of only 13%.

For patients with refractory disease, very poor results of salvage therapy have been shown in the SCHOLAR-1 study, a retrospective analysis of 636 patients with progressive disease or stable disease as best response to chemotherapy or relapse ≤12 months from ASCT (Crump et al 2017). For these patients with refractory DLBCL, the overall response rate was 26% (CR rate 7%) and median OS was 6.3 months. Outcomes were consistently poor across patient subgroups and study cohorts.

Although new second-line salvage treatments have become available since these data were published, CAR-T cell therapies are not a therapeutic option for many patients, and a substantial proportion of patients do not respond to POLA-BR (Sehn et al 2020). The CAR-T cell therapies were studied predominantly in transplant-eligible, younger patients with good performance status (ECOG 0-1). Although they achieve promising response rates, their widespread use has been limited by the time-consuming nature of CAR-T cell production and by the potential for life-threatening toxicities (notably cytokine release syndrome and neurologic toxicities).

The majority of R/R DLBCL patients are older (median age >70 years), have significant comorbidities, and are unsuitable for ASCT or CAR-T cell therapies. There is a major unmet medical need for more effective and well-tolerated therapeutic options for these patients.

Important comorbidities: As per the proposed indication, patients were not eligible for, or refused ASCT. The most common reason for ASCT ineligibility in MOR208C203 (L-MIND) (48 [60.0%] of patients) was high age or comorbidities. In addition, patients may be in an immunocompromised state due to prior lymphoma treatments.

Indeed, all 81 (100%) patients in MOR208C203 (L-MIND) had reported medical history and/or concurrent conditions. The most frequently (≥5%) reported of these were hypertension, dyslipidaemia, hypercholesterolaemia, diabetes mellitus, hypomagnesaemia, obesity, back pain,

spinal osteoarthritis, osteoporosis, appendectomy, hysterectomy, hiatus hernia, chronic gastritis, gastrooesophageal reflux disease, atrial fibrillation, anaemia, thrombocytopenia, benign prostatic hyperplasia, oedema peripheral, fatigue, depression, insomnia, sleep apnoea syndrome, hypothyroidism, and drug hypersensitivity.

II.2 Follicular lymphoma (FL):

MINJUVI is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with previously treated follicular lymphoma (FL).

Incidence:

Indolent NHLs comprise approximately a third of malignant lymphomas (Kanters et al 2023). Follicular lymphoma is the most common indolent NHL subtype and accounts for up to 20% of all lymphomas (Swerdlow et al 2016). In 2016, an estimated 13,960 cases were diagnosed in the US, representing 12.4% of mature NHLs (Teras et al 2016). The rate of new cases of follicular lymphoma was 2.5 per 100,000 men and women per year based on 2017-2021 cases, age-adjusted (NCI SEER 2024).

Prevalence:

The epidemiology of FL is not well characterized and there is sparse information on direct prevalence data. Data reported in publications and European population registries provided complete prevalence estimates ranging from 1.65 per 10,000 individuals in Germany (DARWIN study, Burn and Català 2023) to 5.98 per 10,000 individuals in Slovenia (Slovenian cancer registry). While there is limited data to make international comparisons, FL incidence shows geographic variation. The differences between Western and Eastern European populations may be associated with varying exposure to known risk factors such as pesticides and herbicides (Cerhan 2020, Szumera-Ciećkiewicz et al 2020).

Survival:

The 5-year relative survival rate for FL for cases diagnosed between 2000-2016 ranged from 80-90%, and were similar by gender. The 5-year relative survival rate for FL in the EUROCARE-5 study of 20 countries increased from 2000-2002 (64.1%) to 2003-2005 (69.0%) to 2006-2008 (74.3%), while in the UK it was 86.5% for cases diagnosed 2004-2012 (Cerhan 2020).

Demographics of the population in the proposed indication – age, gender, racial and ethnic origin and risk factors for the disease:

The etiology of the disease in most patients is poorly understood, although it has been suggested that age, gender, and ethnicity may affect a person's likelihood of developing FL (Friedberg 2023). FL can occur at any age, but incidence of FL increases sharply with age and diagnosis is more common in the elderly, with a median age at diagnosis of 64 years (NCI SEER 2024). FL is slightly more common in males than in females (NCI SEER 2024). The population enrolled in Study INCMOR 0208-301 was generally consistent with the characteristics of subjects with FL: median age of study participants was 64 years (range 65-74 years, and the study enrolled slighty more males (54.6%) than females (45.4%)).

Variations in racial incidence are found throughout the world. The incidence of follicular lymphomas is low in China and Japan, but people of Ashkenazi Jewish ancestry have a higher

incidence of lymphoma. In the US, 2-3 times higher incidence of FL has been reported in Caucasians compared to African Americans or Asians (NCI SEER 2024). This is consistent with study MOR208C203 (L-MIND) in which 80.4% of study participants were White.

Main existing treatment options

Follicular lymphoma demonstrates a variable clinical course, with options for management ranging from active surveillance for asymptomatic patients to chemoimmunotherapy, immunotherapy, or treatment with targeted agents for those with symptomatic disease. Treatment of FL depends on the stage of the disease at presentation.

First-line treatment

Patients with low tumor burden:

For the small proportion of patients who present with localized disease (stage I-II) and low tumor burden, the ESMO guidelines recommend radiotherapy-based treatment, as the sole curative option available in FL. When radiotherapy is not feasible, watch and wait or systemic treatment with rituximab monotherapy may be applied. For patients with advanced disease (stage III-IV), watch and wait is the preferred option if tumor burden is low. Systemic treatment with rituximab monotherapy may be considered in selected cases for advanced FL with low tumor burden (Dreyling et al 2021).

Patients with high tumor burden:

Most patients are diagnosed at advanced stages of the disease. For those patients, no curative therapy is yet established. Treatment should be initiated only upon the development of symptoms or signs due to lymphoma, including B symptoms, and the therapeutic approach should be based on clinical risk factors, symptoms and patient perspective. An anti-CD20 antibody, rituximab or obinutuzumab, in combination with chemotherapy such as CHOP, bendamustine, or cyclophosphamide, vincristine and prednisone (CVP) is the recommended treatment choice by ESMO guidelines for newly diagnosed advanced FL patients in need of treatment, followed by optional anti-CD20 maintenance therapy (Dreyling et al 2021). In patients with low-risk profile or for which conventional chemotherapy is contraindicated, rituximab monotherapy (or R-chlorambucil) can be used as alternatives. The combination of rituximab with lenalidomide can also be used in selected cases (off-label at the time of publication of ESMO guidelines).

Relapsed or Refractory Disease Treatment

Most patients treated with systemic therapies for FL will have an initial response to therapy, up to 80% demonstrating a complete response, depending on the initial regimen used. However, conventional therapy for advanced FL is not curative and most of these patients will ultimately develop progressive or relapsed disease. Of these, approximately 20% progress within 24 months of initial treatment (POD24; Casulo et al 2015, Rodgers et al 2021). This group of patients is enriched with patients who develop histologic transformation and with chemo-refractory disease (Rodgers et al 2021). Patients with POD24 have poor prognosis with a markedly diminished OS compared with those who do not progress within 24 months after initial therapy (5-year OS: 50% vs 90%, respectively; Casulo et al 2015).

There is no standard treatment for patients with relapsed FL (Dreyling et al 2021, NCCN 2024, Zucca et al 2020) but a similar approach to first line therapy is suggested (i.e. decision based on

disease stage and tumor burden). For patients with limited stage at relapse, radiotherapy is a valid option while for advanced stage cases with low tumor burden ESMO guidelines recommend watch-and-wait or rituximab monotherapy as applicable (Dreyling et al 2021). Several immune-chemotherapy regimens are recommended by the ESMO guidelines for symptomatic patients with high tumor burden at relapse combining an anti-CD20 monoclonal antibody with a non-cross-resistant regimen, such as: bendamustine after CHOP, or vice-versa; platinum-based or alkylating agents-based regimens; lenalidomide. Treatment choice is usually based on the duration of response to prior therapies, types of prior therapies, and patient age and or/comorbidities.

For relapse/progression occurring after less than 6 months, obinutuzumab-containing regimens, such as obinutuzumab-bendamustine, could be considered followed by obinutuzumab maintenance. In cases who relapsed/progressed 6-12 months after a first line rituximab-containing treatment, anti-CD20 may be reused. Fit patients with short duration remission after rituximab-containing regimens can also be candidates for high-dose chemotherapy followed by ASCT. Non-chemotherapy regimens are also recommended by ESMO in selected cases for patients in first relapse: R2 may be considered for patients with short remissions after chemotherapy; rituximab monotherapy as palliative option for frail patients (Dreyling et al 2021). Ibritumomab tiuxetan is also recommended for elderly patients not eligible for chemotherapy, yet the product was not available on the EU market in the last years and the EU marketing authorisation consequently elapsed in July 2024. In subsequent relapses (≥ 3L), immunochemotherapy approaches are recommended for patients with long duration of prior remissions, otherwise non-chemotherapy regimens mainly rituximab monotherapy or R2 may be considered. In selected cases, and subject to eligibility, ASCT, radioimmunotherapy, idelalisib or allo-ASCT can also be used (Dreyling et al 2021).

Recently approved novel treatment options that are not yet reflected in current ESMO guidelines include CD20xCD3 bispecific Abs in monotherapy (mosunetuzumab, epcoritamab or odronextamab; Bartlett 2022, Budde et al 2022, Linton et al 2024, Ayyappan et al 2023), CAR T-cell therapy (axicabtagene ciloleucel, or tisagenlecleucel; Fowler et al 2022, Jacobson et al 2022), and the BTK inhibitor zanubrutinib in combination with obinutuzumab (NCCN 2024, Zinzani et al 2023).

Natural history of the indicated condition in the population, including mortality and morbidity:

Patients with FL usually present with asymptomatic lymphadenopathy; however, the majority of patients are diagnosed with advanced disease (Ann Arbor Stage III/IV). Patients with advanced FL are not cured with available conventional therapies.

Clinical behaviour of FL is variable, ranging from an indolent course over decades to a clinically more aggressive course with increasing refractoriness and decreasing duration of response to therapy. The Follicular Lymphoma International Prognostic Index (FLIPI) is the most widely used prognostic scoring system to predict survival in newly diagnosed patients, dependent on identified clinical risk factors (age > 60 years, stage III-IV, hemoglobin < 120 g/L, number of nodal areas > 4, and serum LDH level above normal).

Most patients treated with systemic therapies for FL will have an initial response to therapy, with up to 80% demonstrating a complete response, depending on the initial regimen used. However,

conventional therapy for advanced FL is not curative and most patients will ultimately develop progressive or relapse disease.

Multiple relapses in FL are common, and remissions become shorter in depth and duration over time, with increased refractoriness with each subsequent progression/relapse (Link et al 2019; Rivas-Delgado et al 2019). Beyond the front-line setting, prognosis is influenced by several factors, including number of prior regimens, refractory status, and progressive decline of bone marrow reserve (Smith 2013). A relatively high risk of death is observed in patients with early progression of disease, specifically within 24 months of commencing first-line immunochemotherapy (Casulo et al 2017, Seymour et al 2019).

With each successive line of therapy treatment becomes more challenging, and patients eventually succumb to progressive lymphoma and its complications. Follicular lymphoma can also undergo histologic transformation to high-grade NHL that is clinically more aggressive at a rate of approximately 2-3% of patients with FL per year (NCCN 2024). Transformation is associated with poor survival outcome.

Overall, FL is a serious life-threatening disease with poor prognosis that remain incurable. The survival rates vary depending on factors such as age, stage at diagnosis, and response to initial therapy. The 10-year survival rate is around 75% (Sarkozy et al 2019).

Important comorbidities:

As the mean age of patients with FL is more than 60 years old, comorbidities in these patients include those expected in the general population of the same age. In France, a multicentre study involving patients with R/R FL treated from 2013 to 2015 reported comorbidities of cardiovascular disease (29.5%), diabetes (28.6%), and respiratory failure (9.8%) (Solal-Céligny et al 2018). Other comorbidities included renal failure, history of thrombosis, and history of neuropathy in 3% to 8% of the patients. In Serbia, newly diagnosed patients with no history of lymphoma were identified from 3 medical institutions from 2000 to 2014. Overall, the most common comorbidities were arterial hypertension (16.5%), heart disease (14.7%), diabetes mellitus (8%), and autoimmune disorders (2.7%) (Mihaljevic et al 2016). In a single medical center in Japan, the most common comorbidities reported in recently diagnosed FL patients between 2001-2014 included tumours without metastasis (19.5%), diabetes (14.2%), and connective tissue disease (7.1%). Other comorbidities included chronic pulmonary disease (5.3%), liver disease (4.4%), cardiac disease (4.4%), cerebrovascular disease (2.7%), ulcers (2.7%), metastatic solid tumours (1.8%), and peripheral vascular disease (0.9%) (Watanabe et al 2015).

Approximately 93% of participants enrolled in study INCMOR 0208-301 reported prior and/or concurrent medical condition at screening. The most-frequently (≥5%) reported medical history conditions reported were reflective of expectations for the population under study and included hypertension (37.2%), hypothyroidism (8.9%), gastroesophageal reflux disease (8.6%), dyslipidemia (8.4%), fatigue (8.4%), insomnia (8.0%), hypercholesterolemia (7.8%), benign prostatic hyperplasia (7.7%), hyperlipidemia (7.5%), depression (6.6%), constipation (6.2%), diabetes mellitus (6.0%), osteoporosis (5.3%), osteoarthritis (4.9%), anemia (4.9%), hypogammaglobulinemia (4.9%), anxiety (4.9%), back pain (4.7%), and atrial fibrillation (4.7%). Recruitment to this study occurred during the global coronavirus-19 pandemic, with the first study participant entering the study on 16-Apr-2021. Medical history data reports 8.0% of

FL participants had previous COVID-19 infections, and 1.1% had a prior history of COVID-19 pneumonia.

Secondary primary malignancies (SPMs) are also a known survivorship issue for patients with follicular lymphoma. An analysis of SEER-13 data that evaluated 15,517 patients with FL reported 9.9% incidence of SPMs, and a cumulative incidence of 11.06% at 10 years. A multivariate regression analysis showed that patients aged > 65, male, or received prior radiation were at higher risk for SPMs (Giri et al 2017).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A review of tafasitamab cross-reactivity concluded that the antibody recognises CD19 from humans and macaques, but not from common laboratory animals such as the mouse, rat, rabbit, or dog. Therefore, the cynomolgus monkey was considered the most relevant test species for the safety assessment of tafasitamab. Toxicology studies in other species were not conducted.

Key safety findings from non-clinical studies and relevance to human usage are summarised in Table Part II: Module SII.1

Table Part II: Module SII.1: Key Safety Findings for Tafasitimab Non-clinical Development Programme

Single or repeat-dose toxicity studies	**Key findings:** The toxicological assessment of tafasitamab in cynomolgus monkeys included three non-pivotal single dose range-finding studies (XC9-07907, XC9-08007, and XC9-05707) and the pivotal 8-week (XC9-14408) and 13-week (MOR208P008) repeat-dose iv infusion toxicity studies. Additionally, tissue cross-reactivity studies were performed using panels of human and cynomolgus monkey tissues (XC9-17208a and XC9-17208b). The results of the pivotal toxicology studies revealed that tafasitamab was well tolerated following repeated-dose iv administration to cynomolgus monkeys at doses up to 100 mg/kg for 13 weeks and thus supported the safe use of tafasitamab in humans. The expected B-cell clearance response observed in these studies represents the anticipated pharmacologic mechanism of action for the proposed therapeutic intervention in B-cell malignancies. **Relevance to human usage:** no concerns raised
Reproductive and developmental toxicity	**Key findings:** No studies were performed to evaluate the reproductive and developmental toxicity of tafasitamab. This is considered acceptable as tafasitamab administration in the proposed indication and intended patient population is in combination with a drug known to be teratogenic or causing embryofetal lethality (lenalidomide). The conduct of an additional embryofetal development or (enhanced) pre- and postnatal development (ePPND) study in cynomolgus monkeys would not further support a marketing application and also would not be considered ethical for animal welfare reasons. Based on these considerations, EMA concurred that an ePPND study with tafasitamab would not be required (EMA/CHMP communication received January 26, 2017). Potential

	effects of tafasitamab on male and female fertility were determined by standard histopathology evaluation of the reproductive tract and by menstrual cycle assessment in females during the pivotal 13-week, repeat-dose toxicity study in sexually mature cynomolgus monkeys, with no changes observed (MOR208P008). **Relevance to human usage:** Use in pregnancy and lactation is included as missing information in this RMP.
Genotoxicity and carcinogenicity	**Key findings:** Genotoxicity and carcinogenicity studies were not performed with tafasitamab in accordance with guidance provided in ICH S6(R1) and ICH S9. The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals per ICH S6(R1), and carcinogenicity studies are not warranted to support marketing applications for therapeutics intended to treat patients with advanced cancer as per the ICH S9 guidance. Moreover, there were no drug-related pre-neoplastic, neoplastic, or non-neoplastic proliferative lesions in the organs and tissues examined in completed GLP-compliant, pivotal, repeat-dose toxicity studies using weekly or bi-weekly iv administration of tafasitamab in cynomolgus monkeys for a total of 8 or 13 weeks (XC9-14408 and MOR208P008). Tafasitamab was well tolerated in these repeat-dose toxicity studies. No adverse effects beyond the anticipated and reversible exaggerated pharmacodynamic effect of B-cell depletion were observed. **Relevance to human usage:** no concerns raised
Safety pharmacology	**Key findings:** 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. Based on these assessments, tafasitamab treatment at doses up to 100 mg/kg/week for 13 weeks was found to have no effect on neurobehavioural function, body temperature, blood pressure, respiratory rate or electrocardiography. **Relevance to human usage:** no concerns raised
Local tolerance	**Key findings:** No stand-alone studies were performed to evaluate the local tolerance of tafasitamab. Local tolerability was assessed after iv administration as part of the repeat-dose toxicology studies and did not reveal any adverse effects at the infusion sites. **Relevance to human usage:** no concerns raised.

Other toxicity studies	Immunogenicity **Key findings:** Immunogenicity assessments were primarily performed in the 8- and 13-week repeated dose toxicity studies (XC9-14408 and MOR208P008) in cynomolgus monkeys. As expected for the application of a humanised antibody in non-human primates, immunogenicity was observed and varied between the different studies performed. In case anti-drug antibodies (ADAs) were observed, the finding was mainly associated with drug clearing effects but not with any other laboratory or clinical findings. The detected immunogenicity responses did not limit the conclusiveness of the performed toxicology studies. **Relevance for human usage:** In 245 patients treated with tafasitamab no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed. Pre-existing anti-tafasitamab antibodies were detected in 17/245 patients (6.9%) with no impact on pharmacokinetics (PK), efficacy, or safety of tafasitamab (MINJUVI SmPC Section 4.8). Tissue-cross reactivity **Key findings:** To identify tissues with the potential to be associated with tafasitamab systemic toxicities, the binding of fluorescein isothiocyanate (FITC) labelled tafasitamab to cynomolgus monkey and human tissue panels was evaluated using immuno-histochemical staining in frozen sections of normal tissues (XC9-17208a and XC9-17208b). The binding pattern for tafasitamab to human tissues was consistent with the published literature (Nadler et al 1983; Nadler et al 1984; Zhou et al 1994). Specifically, tafasitamab-FITC bound to lymphocytes in the blood, further to mononuclear leukocytes which based on morphology and/or location were presumed to be B-lymphocytes, in numerous tissues. Some haematopoietic precursor cells in the bone marrow also stained. Under the conditions of the study, it was not possible to determine the stage of B-cell development for these precursor cells. Staining in cynomolgus monkey tissues (toxicity species) closely paralleled that seen in human tissues. **Relevance for human usage:** no concerns raised

Part II: Module SIII CLINICAL TRIAL EXPOSURE

The primary safety database for this RMP comprises analysis of the clinical safety data from the MOR208C203 (L-MIND) study, employing the combination of tafasitamab with lenalidomide followed by tafasitamab monotherapy (in 81 patients with DLBCL, of whom 80 patients received at least one dose of both tafasitamab and lenalidomide). Another 141 patients' safety data come from 3 monotherapy trials of tafasitamab (XmAb5574-01 [= Xencor trial], MOR208C201, and MOR208C202 = pooled monotherapy trials). Also, 327 patients's safety data come from the INCMOR 0208-301 (inMIND) study, employing the combination of tafasitamab with lenalidomide and rituximab.

All reported adverse events (AEs) (regardless of seriousness) received to the time of writing have been reviewed for any potential impact on the identified safety concerns (see Section Part II: Module SVII).

An overview of patient characteristics in MOR208C203 (L-MIND), the pooled monotherapy trials (XmAb5574-01 [= Xencor trial], MOR208C201, and MOR208C202) and INCMOR 0208-301 (inMIND) is presented in Table Part II: Module SIII.2

Table Part II: Module SIII.2: Summary of Demographics (Safety Analysis Set)

Characteristics	Pooled Monotherapy[a] N = 141	L-MIND[b] N = 81	inMIND[c] N=327	Overall N = 549
n	141	81	327	549
Mean (SD)	62.3 (14.39)	69.3 (9.53)	65.2 (10.92)	65.1 (11.90)
Median	63.0	72.0	66	66
Q1, Q3	55.0, 73.0	62.0, 76.0	59, 73	58, 74
Min, Max	16, 90	41, 86	30, 88	16, 90
<18	1 (0.7)	0	0	1 (0.2)
≥18 - ≤65	76 (53.9)	25 (30.9)	161 (49.2)	262 (47.7)
>65 - ≤75	44 (31.2)	33 (40.7)	108 (33.0)	185 (33.7)
>75 - ≤85	17 (12.1)	22 (27.2)	54 (16.5)	93 (16.9)
>85	3 (2.1)	1 (1.2)	4 (1.2)	8 (1.5)
Male	86 (61.0)	44 (54.3)	177 (54.1)	307 (55.9)
Female	55 (39.0)	37 (45.7)	150 (45.9)	242 (44.1)
White	131 (92.9)	72 (88.9)	263 (80.4)	466 (84.9)
Non-White	10 (7.1)	3 (3.7)	50 (15.3)	63 (11.5)
Missing	0	6 (7.4)	14 (4.3)	20 (3.6)

[a] Total monotherapy: Pooled data from MOR208C201, MOR208C202, and XmAb5574-01 (Xencor) trials
[b] Includes 80 patients who received both tafasitamab and lenalidomide, and one patient who only received tafasitamab.
[c] Includes 327 patients who received tafasitamab with lenalidomide and rituximab.
Abbreviations: SD = standard deviation, Q1 = 1st quartile, Q3 = 3rd quartile
Data cut-offs: Xencor 28 MAR 2013; c202 29 JAN 2016; c201 30 NOV 2019; L-MIND 14 NOV 2022; inMIND 30 JUL 2024

An overview of duration of tafasitamab exposure in MOR208C203 (L-MIND), the pooled monotherapy trials and INCMOR 0208-301 (inMIND) is presented in Table Part II: Module SIII.3 and again by indication (DLBCL, FL, and non-DLBCL) in Table Part II: Module SIII.4.

Table Part II: Module SIII.3: Summary of Duration of Tafasitamab Exposure (Safety Analysis Set)

Exposure category (months)	Pooled Monotherapy[a] N = 141 n (%), SY	L-MIND[b] N = 81 n (%), SY	inMIND[c] N=327 n (%), SY	Overall N = 549 n (%), SY
<1	28 (19.9), 1.4	10 (12.3), 0.4	15 (4.6), 0.4	53 (9.7), 2.1
1-<3	99 (70.2), 17.9	15 (18.5), 2.3	18 (5.5), 3.6	132 (24), 23.8
3-<6	11 (7.8), 3.9	10 (12.3), 3.6	24 (7.3), 9.2	45 (8.2), 16.7
6-<12	3 (2.1), 1.5	12 (14.8), 8.1	270 (82.6), 229.8	285 (51.9), 239.4
12-<24	0 (0.0), 0	7 (8.6), 10.1	0 (0.0), 0	7 (1.3), 10.1
≥24	0 (0.0), 0	27 (33.3), 118	0 (0.0), 0	27 (4.9), 118
Total	141 (100.0), 24.7	81 (100.0), 142.5	327 (100.0), 242.9	549 (100.0), 410.2

[a] Total monotherapy: Pooled data from MOR208C201, MOR208C202, and XmAb5574-01 (Xencor) trials.
[b] Includes 80 patients who received both tafasitamab and lenalidomide, and one patient who only received tafasitamab.
[c] Includes 327 patients who received tafasitamab with lenalidomide and rituximab.
SY: Subject years = Sum of tafasitamab exposure duration [(Last treatment date of tafasitamab - First treatment date of tafasitamab)+1]/365.25 of all patients in the group.
Data cut-offs: Xencor 28 MAR 2013; c202 29 JAN 2016; c201 30 NOV 2019; L-MIND 14 NOV 2022; inMIND 30 JUL 2024

Table Part II: Module SIII.4: Summary of Duration of Tafasitamab Exposure by Indication (Safety Analysis Set)

Exposure in Months/ Category	Pooled Monotherapy[a] N = 141 n (%), SY	L-MIND[b] N = 81 n (%), SY	inMIND[c] N=327 n (%), SY	Overall N = 549 n (%), SY
<1 DLBCL	8 (5.7), 0.3	10 (12.3), 0.4	0 (0.0), 0	18 (3.3), 0.7
<1 non-DLBCL	20 (14.2), 1	-	15 (4.6), 0.4	35 (6.4), 1.4
<1 FL	3 (2.1), 0.1	-	12 (3.7), 0.3	15 (2.7), 0.5
1-<3 DLBCL	24 (17), 4.3	15 (18.5), 2.3	0 (0.0), 0	39 (7.1), 6.7
1-<3 non-DLBCL	75 (53.2), 13.6	-	18 (5.5), 3.6	93 (16.9), 17.2

Exposure in Months/ Category	Pooled Monotherapy[a] N = 141 n (%), SY	L-MIND[b] N = 81 n (%), SY	inMIND[c] N=327 n (%), SY	Overall N = 549 n (%), SY
1-<3 FL	29 (20.6), 6.2	-	14 (4.3), 2.9	43 (7.8), 9.1
3-<6 DLBCL	3 (2.1), 0.8	10 (12.3), 3.6	0 (0.0), 0	13 (2.4), 4.4
3-<6 non-DLBCL	8 (5.7), 3.1	-	24 (7.3), 9.2	32 (5.8), 12.3
3-<6 FL	2 (1.4), 0.5	-	20 (6.1), 8	22 (4), 8.5
6-<12 DLBCL	0 (0.0), 0	12 (14.8), 8.1	0 (0.0), 0	12 (2.2), 8.1
6-<12 non-DLBCL	3 (2.1), 1.5	-	270 (82.6), 229.8	273 (49.7), 231.3
6-<12 FL	0 (0.0), 0	-	228 (69.7), 193.9	228 (41.5), 193.9
12-<24 DLBCL	0 (0.0), 0	7 (8.6), 10.1	-	7 (1.3), 10.1
12-<24 non-DLBCL	0 (0.0), 0	-	-	0 (0.0), 0
12-<24 FL	0 (0.0), 0	-	-	0 (0.0), 0
≥24 DLBCL	0 (0.0), 0	27 (33.3), 118	-	27 (4.9), 118
≥24 non-DLBCL	0 (0.0), 0	-	-	0 (0.0), 0
≥24 FL	0 (0.0), 0	-	-	0 (0.0), 0
Total DLBCL	35 (24.8), 5.4	81 (100.0), 142.5	-	116 (21.1),148
Total non-DLBCL	106 (75.1), 19.3	-	327 (100.0), 242.9	433 (78.9), 262.2
Total FL	34 (24.1), 6.8	-	274 (83.8), 205.1	308 (56.1) , 211.9

[a] Total monotherapy: Pooled data from MOR208C201, MOR208C202, and XmAb5574-01 (Xencor) trials.
[b] Includes 80 patients who received both tafasitamab and lenalidomide, and one patient who only received tafasitamab.

[c] Includes 327 patients who received tafasitamab with lenalidomide and rituximab.
SY: Subject years = Sum of tafasitamab exposure duration [(Last treatment date of tafasitamab - First treatment date of tafasitamab)+1]/365.25 of all patients in the group.
Data cut-offs: Xencor 28 MAR 2013; c202 29 JAN 2016; c201 30 NOV 2019; L-MIND 30 OCT 2020; inMIND 30 JUL 2024

An overview of duration of tafasitamab exposure in MOR208C203 (L-MIND), the pooled monotherapy trials and INCMOR 0208-301 (inMIND) are presented by dose level in Table Part II: Module SIII.5.

Table Part II: Module SIII.5: Summary of Duration of Tafasitamab Exposure by Dose Level (Safety Analysis Set)

Dose (in mg/kg)	Pooled Monotherapy[a] N = 141 n (%), SY	L-MIND[b] N = 81 n (%), SY	inMIND[c] N= 327 n (%), SY	Overall N = 549 n (%), SY
<12	11 (7.8), 1.4	0 (0.0), 0	0 (0.0), 0	11 (2.0) 1.4
12	130 (92.2), 23.3	81 (100), 142.5	327 (100), 242.9	538 (98.0), 408.8
>12	0 (0.0), 0	0 (0.0), 0	0 (0.0), 0	0 (0.0), 0
Total	141 (100.0), 24.7	81 (100.0), 142.5	327 (100.0), 242.9	549 (100.0), 410.2

[a] Total monotherapy: Pooled data from MOR208C201, MOR208C202, and XmAb5574-01 (Xencor) trials.
[b] Includes 80 patients who received both tafasitamab and lenalidomide, and one patient who only received tafasitamab.
[c] Includes 327 patients who received tafasitamab with lenalidomide and rituximab.
SY: Subject years = Sum of tafasitamab exposure duration [(Last treatment date of tafasitamab - First treatment date of tafasitamab)+1]/365.25 of all patients in the group.
Data cut-offs: Xencor 28 MAR 2013; c202 29 JAN 2016; c201 30 NOV 2019; L-MIND 14 NOV 2022; inMIND 30 JUL 2024

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

SIV.1.1 Diffuse large B-cell lymphoma (DLBCL):

Important exclusion criteria in MOR208C203 (L-MIND) were:

1. **Patients who had:**

   a) **any other histological type of lymphoma including primary mediastinal (thymic) large B-cell or Burkitt lymphoma**

   Reason for exclusion: Patients with other histological types of lymphoma were not included in the intended study population.

   Is it considered to be included as missing information?: No.

Rationale: Other histological types of lymphoma are not included in the proposed indication.

b) primary refractory DLBCL

Reason for exclusion: Patients with primary refractory DLBCL were to be excluded because a potential benefit for these patients could not be adequately predicted at the time of the trial design.

Is it considered to be included as missing information?: No.

Rationale: Patients with primary refractory DLBCL were to be excluded due to efficacy reasons, not safety. Primary refractory disease (defined as no response to or progression during or within 6 months after completion of frontline therapy for DLBCL) was reported for 18.8% of patients in the full analysis set (such patients were allowed to enter the trial initially, but were excluded subsequent to protocol amendment V2.0). The safety profile in these patients did not appear to differ from that of the total studied population.

c) a history of "double/triple-hit" genetics DLBCL characterised by simultaneous detection of MYC with BCL-2 and/or BCL-6 translocation(s) defined by fluorescence in-situ hybridisation. MYC, BCL-2, BCL-6 testing prior to study enrolment was not required

Reason for exclusion: Patients with a history of "double/triple-hit" genetics were excluded because a potential benefit for these patients could not be adequately predicted at the time of the trial design.

Is it considered to be included as missing information?: No.

Rationale: Patients with a known history of "double/triple-hit" genetics DLBCL were to be excluded for reasons of efficacy, however MYC, BCL-2, and BCL-6 testing was not required prior to study enrolment. Two enrolled patients were assessed after enrolment to have either a double-hit DLBCL or a triple-hit DLBCL, with no safety concerns raised. The safety profile is not expected to differ from that of the total studied population.

2. Patients who had, within the 14 days prior to Day 1 dosing:

a) not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anti-cancer therapy or other lymphoma-specific therapy

Reason for exclusion: This exclusion criterion was implemented to avoid confounding safety and efficacy factors.

Is it considered to be included as missing information?: Yes for B-cell depleting drugs and chemotherapy; otherwise no.

Rationale: not applicable for B-cell depleting drugs and chemotherapy (as included under missing information). With regard to radiotherapy and the broad exclusion criterion of other investigational therapies, these are standard for clinical trials to avoid confounding factors for safety and efficacy. The decision to treat with MINJUVI in combination with lenalidomide is to be made by the healthcare professional (HCP) after consideration of the patient's medical history/present medical condition and the product

information, and also considering the results of investigations to be performed before treatment.

b) undergone major surgery or suffered from significant traumatic injury

Reason for exclusion: This broad exclusion criterion is standard for clinical trials to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with MINJUVI in combination with lenalidomide is to be made by the HCP after consideration of the patient's medical history/present medical condition and the product information, and also considering the results of investigations to be performed before treatment.

c) received live vaccines

Reason for exclusion: Vaccines containing live organisms may cause severe infection in immunocompromised patients, due to extensive replication of the vaccine strain.

Is it considered to be included as missing information?: No.

Rationale: A warning that the safety of immunisation with live vaccines following tafasitamab therapy has not been investigated and that vaccination with live vaccines is not recommended concurrently with tafasitamab therapy is provided in Section 4.4 of the summary of product characteristics (SmPC). In addition, national health authorities have published guidelines for the use of live vaccines in immunocompromised persons/cancer patients receiving chemotherapy, and these guidelines are well-established in oncologic clinical practice. This is considered sufficient.

d) required parenteral antimicrobial therapy for active, intercurrent infections

Reason for exclusion: Patients with recent infections indicating that they are already immunocompromised may be at increased risk due to the B-cell depleting properties of MINJUVI.

Is it considered to be included as missing information?: No.

Rationale: The risk of infection is addressed in the warnings and precautions section of the SmPC for tafasitamab. The decision to treat with tafasitamab in combination with lenalidomide is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

3. Patients who:

a) had, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies

Reason for exclusion: This broad exclusion criterion is standard for clinical trials to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with MINJUVI in combination with lenalidomide is to be made by the HCP after consideration of the patient's medical history/present medical condition and the product information, and also considering the results of investigations to be performed before treatment.

b) were previously treated with CD19-targeted therapy or immunomodulatory drugs (IMiDs) (e.g., thalidomide, lenalidomide)

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for efficacy caused by prior use of other drugs with a mode of action similar to MINJUVI or lenalidomide.

Is it considered to be included as missing information?: No.

Rationale: This was due to avoid confounding factors for efficacy and not for safety.

c) had a history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs and/or the excipients contained in the study drug formulations

Reason for exclusion: Patients with a history of such hypersensitivities could have been at increased risk of hypersensitivity reactions to MINJUVI.

Is it considered to be included as missing information?: No.

Rationale: Use of MINJUVI is contraindicated in patients with hypersensitivity to the active substance or any of its excipients (SmPC Section 4.3). This is considered sufficient.

d) had undergone ASCT within the period ≤3 months prior to the signing of the Informed Consent Form. Patients who had a more distant history of ASCT had to exhibit full haematological recovery before enrolment into the study

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for efficacy and safety.

Is it considered to be included as missing information?: No.

Rationale: According to the proposed indication tafasitamab is to be used in patients who are not eligible for ASCT; for these patients there is a high medical need for an active treatment option.

The decision to treat with MINJUVI in combination with lenalidomide is to be made by the HCP after consideration of the patient's medical history/present medical condition and the product information, and also considering the results of investigations to be performed before treatment.

e) had undergone previous allogenic stem cell transplantation

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for efficacy and safety.

Is it considered to be included as missing information?: No.

Rationale: There is a high medical need for an active treatment option for patients with R/R DLBCL, including those who have previously undergone allogenic stem cell transplantation.

The decision to treat with MINJUVI in combination with lenalidomide is to be made by the HCP after consideration of the patient's medical history/present medical condition and the product information, and also considering the results of investigations to be performed before treatment.

f) had a history of deep venous thrombosis/embolism, threatening thromboembolism or known thrombophilia or were at a high risk for a thromboembolic event in the opinion of the investigator and who were not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period

Reason for exclusion: Lenalidomide is associated with an increased risk of thrombosis and the product information for lenalidomide recommends that prophylactic antithrombotic medicines be recommended, especially in patients with additional thrombotic risk factors (Revlimid 2024).

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with tafasitamab in combination with lenalidomide is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

g) concurrently used other anti-cancer or experimental treatments

Reason for exclusion: This broad exclusion criterion is standard for clinical trials to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with MINJUVI in combination with lenalidomide is to be made by the HCP after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide, and also considering the results of investigations to be performed before treatment.

4. Prior history of malignancies other than DLBCL, unless the patient had been free of the disease for ≥ 5 years prior to screening. Exceptions to the ≥ 5 year time limit included history of the following:

a) basal cell carcinoma of the skin

b) squamous cell carcinoma of the skin

c) carcinoma in situ of the cervix

d) carcinoma in situ of the breast

e) carcinoma in situ of the bladder

f) incidental histological finding of prostate cancer (Tumour/Node/Metastasis stage of T1a or T1b)

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors affecting efficacy and safety assessments. In addition, second primary malignancies has been identified as an important risk for lenalidomide (EU-RMP for Revlimid 2023).

Is it considered to be included as missing information?: No.

Rationale: The risk of second primary malignancies is described in the product information for lenalidomide (Revlimid 2024). The decision to treat with tafasitamab in combination with lenalidomide is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

5. Patients exhibiting:

a) positive hepatitis B and/or C serology

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for safety and efficacy. In addition, patients with positive hepatitis B and/or C serology may be at increased risk due to the B-cell depletion properties of MINJUVI.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat patients with MINJUVI in combination with lenalidomide is to be made by the HCP taking the patient's history and the present condition of the patient and the product information for both MINJUVI and lenalidomide into consideration. The SmPC for tafasitamab includes in section 4.4 that "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". Patients with positive hepatitis B serology (either hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

b) known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for safety and efficacy

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with tafasitamab in combination with lenalidomide is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide. The SmPC for tafasitamab includes in section 4.4 that "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".

c) central nervous system (CNS) lymphoma involvement – present or past medical history

Reason for exclusion: CNS lymphomas are a different type of lymphoma than DLBCL.

Is it considered to be included as missing information?: No.

Rationale: Not covered by the indication.

d) history or evidence of clinically significant cardiovascular, CNS and/or other systemic disease that in the investigator's opinion precluded participation in the study or compromised the patient's ability to give informed consent

Reason for exclusion: This broad exclusion criterion is standard for clinical trials to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with tafasitamab in combination with lenalidomide is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

e) history or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption

Reason for exclusion: Lenalidomide capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product (Revlimid 2024).

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with tafasitamab in combination with lenalidomide is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

f) gastrointestinal abnormalities including the inability to take oral medication, requiring intravenous alimentation, or prior surgical procedure affecting absorption

Reason for exclusion: Patients were to take lenalidomide, administered orally, as part of the treatment regimen.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with tafasitamab in combination with lenalidomide is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

g) history or evidence of severe hepatic impairment (total serum bilirubin > 3 mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion 6c[1])

Reason for exclusion: This exclusion criterion was implemented to avoid confounding efficacy and safety assessments; hepatic disorders have been described for concomitant lenalidomide.

Is it considered to be included as missing information?: No.

Rationale: The effect of renal or 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.

SIV.1.2 Follicular Lymphoma (FL):

Important exclusion criteria in INCMOR0208-301 (inMIND) were:

1. History of or current histology other than FL and MZL or clinical evidence of transformed lymphoma by INV assessment.

Reason for exclusion: Patients with different histological types of lymphoma were excluded from the target study population.

Is it considered to be included as missing information?: No.

Rationale: Other histological types of lymphoma are not included in the proposed indication.

2. History of radiation therapy to ≥ 25% of the bone marrow for other diseases.

Reason for exclusion: Radiation therapy affecting a large portion of the bone marrow can lead to prolonged recovery times between treatment sessions, also, patients become more susceptible to infections. Long-term effects may include chronic anemia, immunosuppression, and an increased risk of future malignancies like secondary leukemia.

Is it considered to be included as missing information?: No.

Rationale: Patients with a history of radiation therapy to ≥ 25% of the bone marrow for other conditions are excluded from the study.

[1] total serum bilirubin ≤ 2.5 × upper limit of normal (ULN) unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or with documented liver involvement by lymphoma may have been included if their total bilirubin was ≤ 5 × ULN (see exclusion criterion 5g)

3. Any systemic antilymphoma and/or investigational therapy within 28 days prior to the start of Cycle 1.

Reason for exclusion: This exclusion criterion was implemented to avoid confounding safety and efficacy factors.

Is it considered to be included as missing information: Yes for chemotherapy; otherwise No .

Rationale: With regard to systemic antilymphoma and/or investigational therapy, these are standard for clinical trials to avoid confounding factors for safety and efficacy. The decision to treat with MINJUVI in combination with lenalidomide and rituximab is to be made by the HCP after consideration of the patient's medical history/present medical condition and the product information, and also considering the results of investigations to be performed before treatment.

4. Major surgery (excluding lymph node biopsy) within 28 days prior to signing the ICF unless the participant is recovered at the time of signing the ICF.

Reason for exclusion: This wide exclusion criterion is commonly used in clinical trials to prevent confounding factors that could affect safety and efficacy outcomes.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with MINJUVI in combination with lenalidomide and rituximab should be made by the HCP after reviewing the patient's medical history, current condition, and product information, as well as taking into account the results of pre-treatment investigations.

5. Administration of a live vaccine within 28 days prior to the start of study treatment

Reason for exclusion: Live organism vaccines can lead to severe infections in immunocompromised patients because of the uncontrolled replication of the vaccine strain.

Is it considered to be included as missing information?: No.

Rationale: A warning that the safety of immunisation with live vaccines following tafasitamab therapy has not been investigated and that vaccination with live vaccines is not recommended concurrently with tafasitamab therapy is provided in Section 4.4 of the SmPC for tafasitamab. In addition, national health authorities have published guidelines for the use of live vaccines in immunocompromised persons/cancer patients receiving chemotherapy, and these guidelines are well-established in oncologic clinical practice. This is considered sufficient.

6. Active systemic infection (including SARS-CoV-2–positive test)

Reason for exclusion: Patients with recent infections, suggesting they are already immunocompromised, may face an elevated risk due to the B-cell depleting effects of MINJUVI and rituximab.

Is it considered to be included as missing information: No.

Rationale: The risk of infection is addressed in the warnings and precautions section of the SmPC for tafasitamab. The decision to treat with tafasitamab in combination with lenalidomide and rituximab is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI, lenalidomide and rituximab.

7. Participants in a severely immunocompromised state

Reason for exclusion: This exclusion criterion is applied to eliminate confounding factors related to safety and efficacy, considering the immunosuppressive effects of tafasitamab, lenalidomide, and rituximab.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with MINJUVI in combination with lenalidomide and rituximab is to be made by the HCP after consideration of the patient's medical history/present medical condition and the product information, and also considering the results of investigations to be performed before treatment.

8. Prior use of lenalidomide in combination with rituximab

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for efficacy caused by prior use of other drugs with a similar mode of action.

Is it considered to be included as missing information? No.

Rationale: This was due to avoid confounding factors for efficacy and not for safety.

9. History of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, immunomodulatory drugs, rituximab, other mAbs, and/or the excipients

Reason for exclusion: Patients with a history of such hypersensitivities could have been at increased risk of hypersensitivity reactions to MINJUVI.

Is it considered to be included as missing information? No.

Rationale: The use of MINJUVI is contraindicated in patients with hypersensitivity to the active ingredient or any of its excipients (refer to SmPC Section 4.3). This is deemed adequate.

10. History of prior nonhematologic malignancy except for the following:

a) Malignancy treated with curative intent and with no evidence of active disease for more than 2 years before screening.

b) Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.

c) Adequately treated carcinoma in situ without current evidence of disease.

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors affecting efficacy and safety assessments. In addition, second primary malignancies has been identified as an important risk for lenalidomide (EU-RMP for Revlimid 2023).

Is it considered to be included as missing information?: No.

Rationale: The product information for lenalidomide (Revlimid 2024) outlines the risk of second primary malignancies. The HCP should decide on the treatment with tafasitamab in combination with lenalidomide and rituximab after reviewing the patient's medical history, current condition, and the product information for both MINJUVI and lenalidomide.

11. Patients exhibiting:

a) Known positive test result for HCV (with anti-HCV serology testing) and a positive test for HCV RNA.

Known positive test result for chronic HBV infection (defined by HBsAg positivity).

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for safety and efficacy. In addition, patients with positive hepatitis B and/or C serology may be at increased risk due to the B-cell depletion properties of MINJUVI and rituximab.

Is it considered to be included as missing information? No.

Rationale: The decision to treat patients with MINJUVI in combination with lenalidomide amd rituximab is to be made by the HCP taking the patient's history and the present condition of the patient and the product information for both MINJUVI and lenalidomide into consideration. The SmPC for tafasitamab includes in section 4.4 that "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". Patients with positive hepatitis B serology (either hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

b) Known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)

Reason for exclusion: This exclusion criterion was implemented to avoid confounding factors for safety and efficacy.

Is it considered to be included as missing information?: No.

Rationale: The decision to treat with tafasitamab in combination with lenalidomide and rituximab is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide and rituximab. The SmPC for tafasitamab includes in section 4.4 that "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".

12. **Central nervous system (CNS) lymphoma involvement – present or past medical history.**

    Reason for exclusion: CNS lymphomas are different type of lymphoma than FL and MZL.

    Is it considered to be included as missing information? No.

    Rationale: Not covered by the indication.

13. **History or evidence of clinically significant cardiovascular, CNS, and/or other systemic disease that would, in the investigator's opinion, preclude participation in the study or compromise the participant's ability to give informed consent.**

    Reason for exclusion: This broad exclusion criterion is standard for clinical trials to avoid confounding factors for safety and efficacy.

    Is it considered to be included as missing information? No.

    Rationale: The decision to treat with tafasitamab in combination with lenalidomide and rituximab is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

14. **History or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption.**

    Reason for exclusion: Lenalidomide capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product (Revlimid 2024).

    Is it considered to be included as missing information?: No.

    Rationale: The decision to treat with tafasitamab in combination with lenalidomide and rituximab is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

15. **Congestive heart failure (left ventricular ejection fraction of < 50%, assessed by 2D-echocardiography or MUGA scan.**

    Reason for exclusion: This broad exclusion criterion is standard for clinical trials to avoid confounding factors for safety and efficacy.

    Is it considered to be included as missing information?: No.

    Rationale: The decision to treat with tafasitamab in combination with lenalidomide and rituximab is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for MINJUVI and lenalidomide.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme for MINJUVI in combination with lenalidomide is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

This section aims to present the size of the safety database in each of the populations that are under-represented.

Table Part II: Module SIV.6: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Pregnancy: There are no data on the use of tafasitamab in pregnant women. However, IgG molecules such as tafasitamab are known to cross the placenta and therefore tafasitamab may cause foetal B-cell depletion based on the mechanism of action. Tafasitamab is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-foetal harm and is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide pregnancy prevention programme are met. Breast-feeding: There are no data on the use of tafasitamab in breastfeeding women. It is not known whether tafasitamab is excreted in human milk. However, maternal IgG is known to be excreted in human milk. Because of the potential for adverse reactions to tafasitamab in nursing infants, advise women not to breast-feed during treatment with tafasitamab until at least 3 months after the last dose. Use in pregnancy and lactation is included as missing information in this RMP.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	Patients with hepatic and renal impairment: The effect of renal or hepatic 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) or 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

• Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	severe renal impairment to end-stage renal disease (CrCL < 30 mL/min) or of moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) is unknown. Patients with cardiovascular impairment: Patients with history or evidence of clinically significant cardiovascular disease were excluded from clinical trials. As tafasitamab is a human monoclonal antibody no dedicated thorough QT/QTc study was performed. Instead, periodic electrocardiogram (ECG) monitoring was implemented in all company-sponsored clinical studies to capture potential ECG changes. Results showed that tafasitamab did not have a clinically relevant effect on cardiac repolarization nor resulted in clinically significant cardiac AEs. Immunocompromised patients: Patients in the clinical development programme had all received prior treatment for DLBCL, meaning that they were at increased risk of being in an immunocompromised state prior to treatment. Some populations with an especially increased risk of being immunocompromised may have been excluded, however, due to the exclusion of patients with concomitant conditions, such as HIV, and/or some recent prior therapies (see Section Part II: Module SIV). Patients with a disease severity different from inclusion criteria in clinical trials: The disease severity studied is in agreement with the proposed indication, which is for the treatment of patients with R/R DLBCL, who are not eligible for, or refuse, ASCT. The clinical development programme included patients with DLBCL, who had relapsed after or were refractory to at least one but not more than three prior systemic therapies, including at least one CD20-targeting regimen, and who were not candidates for high-dose chemotherapy and ASCT. MOR208C203 (L-MIND) included patients ineligible for ASCT and the majority of patients had received 1 or 2 prior treatment lines (49.4% and 43.2%, respectively, for patients in the full analysis set). The majority of study participants had an ECOG performance status of 0 or 1 (35.8% and 55.6%, respectively) and 8.6% were ECOG grade 2. Primary refractory disease (defined as no response to or progression during or within 6 months after completion of frontline therapy for DLBCL) was reported for 18.5% of patients (such patients were allowed to enter the trial initially, but were excluded subsequent to protocol

	amendment V2.0). 36 (44.4%) patients were refractory to their last prior therapy and 34 (42.0%) were rituximab-refractory.
Population with relevant different ethnic origin	Exposure by race group is provided in Table Part II: Module SIII.4. The number of non-white patients in the clinical development programme was not large enough to determine the influence of race and ethnicity on the pharmacokinetics of tafasitamab.
Subpopulations carrying relevant genetic polymorphisms	MOR208C203 (L-MIND) excluded patients with known 'double/triple-hit' DLBCL at study entry.
Other	Not applicable.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

Monjuvi (tafasitamab-cxix) was first approved on 31 JUL 2020 in the US to be given in combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT). Since then, tafasitamab has been approved in 45 countries, including the EU-27, Australia, Brazil, Canada, Hong-Kong, Israel, the United Kingdom, and Switzerland under the tradename of MINJUVI. The precise wording of the indication may vary slightly by region. Worldwide exposure cumulatively since launch through 30 JUL 2024 is 8,376 patient-years.

SV.1.1 Method Used to Calculate Exposure

Commercial Use

The post-authorization exposure was calculated based on sales data, with assumptions as follows:

- Sales data are available for numbers of vials; each vial contains 200 mg of tafasitamab.
- The dosing regimen of tafasitamab is 12 mg/kg administered weekly in Cycles 1 to 3, with an additional dose at Day 4 in Cycle 1; and then every 2 weeks from Cycle 4 onwards; each treatment cycle consists of 28 days.
- Based on a sample of patient claims data in the US from IntrinsiQ (proprietary data on file) illustrating patient adherence with tafasitamab, the average number of vials per patient in the post-marketing setting is 64; it has been assumed that this average is the same worldwide.

SV.1.2 Exposure

The total number of patients dosed with tafasitamab up to 30 JUL 2024 is approximately 8,376 patients-year.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Based on its mechanism of action and safety profile, MINJUVI is not considered to have abuse potential.

Part II: Module SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

An evaluation of the safety concerns of MINJUVI was conducted in accordance with Revision 2 to the guideline on GVP Module V -Risk Management Systems (31 MAR 2017). A careful review of the available data was performed to determine if the identified risks and potential risks are in line with the guidance in the revised GVP Module V. Following this review, the following risks were not considered to have an important impact on the benefit-risk balance of the product:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised).

Identified risks

Myelosuppression (neutropenia, anaemia, thrombocytopenia)

Myelosuppression (neutropenia, anaemia, thrombocytopenia) was commonly observed during MINJUVI treatment and is a known safety concern in patients with haematologic malignancies under treatment. This risk is communicated in the product information for MINJUVI with specific advice on clinical management, including monitoring blood count assessments and dosing considerations. The frequency and severity of the established risk are considered to be understood in clinical practice. Currently no further characterisation of this risk is considered warranted as part of the pharmacovigilance plan. The marketing authorisation holder (MAH) considers this risk to be well-established and characterised for MINJUVI. This risk is being appropriately managed and does not have an important impact on the benefit-risk balance of the product. The MAH will continue to monitor myelosuppression (neutropenia, anaemia, thrombocytopenia) through routine ongoing safety surveillance.

Clinically severe infections

Infections were very commonly observed during MINJUVI treatment; while the majority were low grade and resolved, some were clinically severe. Clinically severe infections are a known safety concern for B-cell depleting therapies and an identified risk for MINJUVI. In order to minimise the risk posed by clinically severe infections, MINJUVI is to 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 are to be monitored appropriately. When following these precautions recommended in the SmPC, this risk is appropriately managed and therefore does not have an important impact on the benefit-risk balance of the product. The MAH will continue to monitor infections through routine ongoing safety surveillance.

Infusion-related reactions

Infusion-related reactions were generally mild or moderate in intensity and resolved without sequelae, however the potential for severe or life-threatening reactions must be considered. This risk is described in the section 4.4 Special warnings and precautions for use section of the SmPC, and section 4.2 Posology and Method of Administration provides specific advice on the clinical management of infusion-related reactions. When following the precautions recommended in the SmPC, the impact of infusion-related reactions on the risk-benefit balance is considered to be minimised in patients with R/R DLBCL who are not eligible for, or refuse, transplant and who have a poor prognosis. The frequency and severity of the established risk is considered to be understood. Currently no further characterisation of this risk is considered warranted as part of the pharmacovigilance plan. The MAH considers this risk to be well-established and characterised for MINJUVI. This risk is being appropriately managed and does not have an important impact on the benefit-risk balance of the product. The MAH will continue to monitor infusion-related reactions through routine ongoing safety surveillance.

The following are additional known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised).

Infections and infestations: Bacterial, viral and fungal infections, including opportunistic infections with fatal outcomes (e.g. bronchopulmonary aspergillosis, bronchitis, pneumonia and urinary tract infection), sepsis (including neutropenic sepsis)

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): Basal cell carcinoma

Blood and lymphatic system disorders: Febrile neutropenia, neutropenia, thrombocytopenia, anaemia, leukopenia, lymphopenia

Immune system disorders: Hypogammaglobulinaemia

Metabolism and nutrition disorders: Hypokalaemia, decreased appetite, hypocalcaemia, hypomagnesaemia

Nervous system disorders: Headache, paraesthesia, dysgeusia

Respiratory, thoracic and mediastinal disorders: Dyspnoea, cough, exacerbation of chronic obstructive pulmonary disease, nasal congestion

Gastrointestinal disorders: Diarrhoea, constipation, vomiting, nausea, abdominal pain

Hepatobiliary disorders: Hyperbilirubinaemia, transaminases increased (includes ALT and/or AST increased), gamma-glutamyltransferase increased

Skin and subcutaneous tissue disorders: Rash (different types of rash, e.g. rash, rash maculopapular, rash pruritic, rash erythematous)

Musculoskeletal and connective tissue disorders: Arthralgia, pain in extremity, musculoskeletal pain

Renal and urinary disorders: Blood creatinine increased

General disorders and administration site conditions: Asthenia (includes malaise), fatigue, oedema peripheral, pyrexia

Investigations: Weight decreased, C-reactive protein increased

Injury, poisoning and procedural complications: Infusion related reaction

The following is a potential risk that require no further characterisation and will be followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised).

Potential risks

Tumour lysis syndrome

Tumour lysis syndrome has been observed in patients treated with tafasitamab in clinical trials. Patients with high tumour burden and rapidly proliferative tumour may be at increased risk of tumour lysis syndrome. In patients with R/R DLBCL, tumour lysis syndrome during treatment with tafasitamab has been observed. Appropriate measures/prophylaxis in accordance with local guidelines should be taken prior to treatement with tafasitamab. Patients should be monitored closely for tumour lysis syndrome during treatement with tafasitamab. The MAH considers this risk to be well-established and characterized for tafasitamab. This risk is being appropriately managed and does not have an important impact on the benefit-risk balance of the product. The MAH will continue to monitor Tumour lysis syndrome through routine ongoing safety surveillance.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Potential Risk: Progressive multifocal leukoencephalopathy

Risk-benefit impact:

Progressive multifocal leukoencephalopathy (PML) has been reported for other agents that cause B-cell depletion. There were no treatment-emergent cases of progressive multifocal leukoencephalopathy in the clinical development programme for tafasitamab in combination with lenalidomide. A case of progressive multifocal leukoencephalopathy was received from an early access program, post marketing authorization application (MAA) approval. However, the case was heavily confounded by underlying disease (DLBCL), prior anti-lymphoma therapy and concomitant use of lenalidomide for which PML is reported in the Revlimid 2024. Therefore, the impact on the risk-benefit balance is estimated to be low in patients with R/R DLBCL who are not eligible for transplant and who have a poor prognosis. Progressive multifocal leukoencephalopathy will continue to be monitored as an important potential risk.

Missing Information 1: Use in pregnancy and lactation

Pregnant and breastfeeding women were excluded from clinical trials.

Risk-benefit impact: There are no data on the use of tafasitamab in pregnant women. However, IgG is known to cross the placenta and tafasitamab may cause foetal B-cell depletion based on the mechanism of action.

Tafasitamab is not recommended during pregnancy and in women of childbearing potential not using contraception. Advise patients to notify their doctor if they become pregnant or intend to become pregnant during tafasitamab therapy, as it may cause harm to the unborn baby.

Tafasitamab is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-foetal harm and is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide pregnancy prevention programme are met.

It is not known whether tafasitamab is excreted in human milk. However, maternal IgG is known to be excreted in human milk. Because of the potential for adverse reactions in nursing infants

from tafasitamab, advise women not to breast-feed during treatment with tafasitamab until at least 3 months after the last dose.

Missing information 2: Use in patients with recent use of B-cell depleting drugs or chemotherapy

Patients with recent use of CD20 targeted therapy or chemotherapy (within ≤14 days) were excluded from clinical trials.

Risk-benefit impact: Patients with recent use of B-cell depleting drugs or chemotherapy are in need of further characterisation to determine whether the safety profile differs in these patients.

Missing information 3: Long-term safety

Limited information is available for long-term use of tafasitamab (e.g., 12-24 cycles, > 24 cycles).

Risk-benefit impact: Additional data are needed to assess the safety profile of tafasitamab with long-term treatment to determine if the safety profile differs from that characterised so far.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no newly identified or reclassified safety concerns since the last RMP version 2.0.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Potential Risk: Progressive multifocal leukoencephalopathy

PT: Progressive multifocal leukoencephalopathy

Potential mechanisms:

Progressive multifocal leukoencephalopathy, caused by reactivation of the John Cunningham (JC) virus, classically occurs in patients with severe immunodepression and has been linked to therapeutic monoclonal antibodies which deplete B-cells (Durali et al 2015).

Evidence source(s) and strength of evidence:

There were no cases of treatment-emergent progressive multifocal leukoencephalopathy in the clinical development programme for tafasitamab in combination with lenalidomide. One case of worsening of progressive multifocal leukoencephalopathy was reported, and progressive multifocal leukoencephalopathy due to reactivation of the JC virus has been reported for other B-cell depleting therapies (eg, MabThera 2024). In addition, a post-marketing case of progressive multifocal leukoencephalopathy was received from an early access program, however the case was heavily confounded. Furthermore, cases of progressive multifocal leukoencephalopathy have also been reported with lenalidomide (Revlimid 2024).

Characterisation of the risk:

As of the data lock point for this report, one case of worsening of progressive multifocal leukoencephalopathy had been reported in the clinical development programme:

A 79-year-old, male patient experienced a worsening of progressive multifocal leukoencephalopathy which was treatment-emergent (on-treatment; Study Day 09) with first, unspecific neurological symptoms occurring 10 days prior to initiation of study treatment. The patient received in total 4 infusions of tafasitamab, and lenalidomide daily for 15 days, and the patient died 68 days after end of treatment. The event was assessed as not related to any study drug, but was likely a result of the patient's prolonged immunocompromised state due to multiple prior lymphoma treatments (immunochemotherapies) during the preceding 2 years.

An analysis of serious adverse events, including deaths, to the data lock point of 30 JUL 2024 revealed one case of progressive multifocal leukoencephalopathy due to John Cunningham (JC) virus in the INCMOR 0208-301 (inMIND) study. The event of PML was experienced by a participant in the FL safety population receiving placebo + rituximab + lenalidomide. The event was assessed as related to lenalidomide and rituximab. In addition, review of adverse event data received to this date provided no additional pertinent knowledge on the potential risk of progressive multifocal leukoencephalopathy.

As of the data lock point for this report, a case of progressive multifocal leukoencephalopathy in an elderly R/R DLBCL patient treated with tafasitamab and lenalidomide was received from an early access program. The assessment of the case led to the conclusion that there was insufficient evidence of a causal association between tafasitamab and this single event of PML. The assessment of causality was confounded by concomitant use of lenalidomide, previous history of treatment with immunosuppressive regimens including rituximab, underlying DLBCL and medical history of Hodgkin lymphoma, any of which could offer a plausible alternative explanation for the onset of PML.

Risk factors and risk groups:

Progressive multifocal leukoencephalopathy occurs generally in patients with suppressed cellular immunity. Cases of progressive multifocal leukoencephalopathy reported in patients taking lenalidomide were generally confounded by patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy (Revlimid 2024).

There are currently no known risk groups or risk factors for the development of progressive multifocal leukoencephalopathy whose consideration would lead to practicable preventative measures.

Preventability:

There are no known, practical steps to specifically avoid this risk. However, patients are followed up for changes in neurologic signs or symptoms as per standard of care.

Impact on the risk-benefit balance of the product:

Progressive multifocal leukoencephalopathy has been reported for other agents that cause B-cell depletion. As of the data lock point of this RMP, there were no treatment-emergent cases of progressive multifocal leukoencephalopathy in the clinical development programme for tafasitamab in combination with lenalidomide. Therefore, the impact of the potential risk of

progressive multifocal leukoencephalopathy on the risk-benefit balance is estimated to be low in patients with R/R DLBCL who are not eligible for transplant and who have a poor prognosis. The MAH will continue to monitor progressive multifocal leukoencephalopathy through routine ongoing safety surveillance and as an important potential risk.

Public health impact:

Progressive multifocal leukoencephalopathy would affect the individual only; no public health impact is expected.

SVII.3.2 Presentation of the Missing Information

Missing Information: Use in pregnancy and lactation

Evidence source:	Pregnant and breastfeeding women were excluded from clinical trials.
Anticipated risk/consequence of the missing information:	There are no data on the use of tafasitamab in pregnant women. However, IgG is known to cross the placenta and tafasitamab may cause foetal B-cell depletion based on the mechanism of action. Tafasitamab is not recommended during pregnancy and in women of childbearing potential not using contraception. Advise patients to notify their doctor if they become pregnant or intend to become pregnant during tafasitamab therapy, as it may cause harm to the unborn baby. Tafasitamab is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-foetal harm and is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide pregnancy prevention programme are met. It is not known whether tafasitamab is excreted in human milk. However, maternal IgG is known to be excreted in human milk. Because of the potential for adverse reactions in nursing infants from tafasitamab, advise women not to breast-feed during treatment with tafasitamab until at least 3 months after the last dose. As pregnant and breastfeeding women were excluded from clinical trials and as tafasitamab may cause foetal harm, pregnant and breastfeeding women have been included under missing information.

Missing Information: Use in patients with recent use of B-cell depleting drugs or chemotherapy

Evidence source:	Patients with recent (≤14 days) use of CD20 targeted therapy and/or chemotherapy were excluded from clinical trials. Pre-existing neutropenia and other toxicities are concerns that are to be investigated before treatment. Use in patients with recent prior use of

	B-cell depleting drugs or chemotherapy has been added as missing information.
Population in need of further characterisation:	Patients with recent (≤14 days) use of B-cell depleting drugs or chemotherapy.

Missing Information: Long-term safety

Evidence source:	Limited information is available for long-term use of tafasitamab (e.g., 12-24 cycles, > 24 cycles).
Population in need of further characterisation:	Patients treated with tafasitamab for 12-24 cycles and > 24 cycles.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of 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

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

There are currently no specific adverse reaction follow-up questionnaires being used for tafasitamab.

Other forms of routine pharmacovigilance activities:

There are currently no other forms of routine pharmacovigilance activities for tafasitamab.

III.2 Additional Pharmacovigilance Activities

None

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: 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				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Study	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
Study INCMOR 0208-305 (firmMIND): A Phase 3, Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of Tafasitamab Plus Lenalidomide in Participants With Relapsed or Refractory Diffuse Large B-Cell Lymphoma	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 shall 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.	Efficacy and Safety	Clinical study report	December 2026
Study MOR208C310 (front-MIND): A phase 3, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of 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 the efficacy and re-confirm the safety profile of tafasitamab in combination with lenalidomide the applicant shall submit the results of a phase 3, multicentre, randomized, 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).	Confirm the efficacy and re-confirm the safety of 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)	First Patient First Visit	May 2021
			Enrollment completion	June 2023
			Primary analysis results	June 2026
			Clinical study report	December 2026

Part V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Progressive multifocal leukoencephalopathy	Routine risk communication: SmPC Section 4.4 Patient Leaflet (PL) Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: PML has been reported during combination therapy with tafasitamab. Patients should be monitored for new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing of tafasitamab must be immediately suspended. Referral to a neurologist should be considered. Appropriate diagnostic measures may include MRI scan, cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments. If PML is confirmed, tafasitamab must be permanently discontinued (SmPC section 4.4). Progressive multifocal leukoencephalopathy (PML) is a very rare and life-threatening infection in the brain. Tell your doctor straight away if you have symptoms such as memory loss, trouble speaking, difficulty walking, or problems with your eyesight. If you had any of these symptoms before or during treatment with MINJUVI , or you notice any changes, tell your doctor straight away (PL section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Use in pregnancy and lactation	Routine risk communication: SmPC sections 4.6, 5.3

Safety concern	Routine risk minimisation activities
	PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Treatment with tafasitamab in combination with lenalidomide should not be initiated in female patients unless pregnancy has been excluded (SmPC Section 4.6). Advise females of reproductive potential to use effective contraception during treatment with tafasitamab and for at least 3 months after end of treatment (SmPC Section 4.6). Advise patients to notify their doctor if they become pregnant or intend to become pregnant during tafasitamab therapy as may it may cause harm to the unborn baby (SmPC section 4.6 and PL Section 2). In case of exposure during pregnancy, which may cause B-cell depletion in the fetus, 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 (SmPC section 4.6). Tafasitamab is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-foetal harm and is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide pregnancy prevention programme are met (SmPC Section 4.6). Use of effective contraception during treatment with tafasitamab and for at least 3 months after end of treatment is recommended for women of reproductive potential (PL Section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
Use in patients with recent use of B-cell depleting drugs or chemotherapy	Routine risk communication: SmPC sections 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Monitor complete blood counts throughout treatment and prior to administration of each treatment cycle. Cytopenia may require a delay, dose reduction, or discontinuation of lenalidomide and/or a delay or discontinuation of tafasitamab (SmPC, Section 4.4).

Safety concern	Routine risk minimisation activities
	Advise patients to report signs or symptoms of fever or other evidence of potential infection, such as chills, cough or pain on urination, or signs or symptoms of bruising or bleeding immediately (SmPC Section 4.4). Patients are advised to inform their doctor immediately of a fever of 38 degrees Celsius or above, chills, cough or pain on urination, or any signs of any signs of bruising or bleeding (PL Section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription
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

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Table Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.2: 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: SmPC section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Progressive multifocal leukoencephalopathy (PML) has been reported during combination therapy with	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	tafasitamab. Patients should be monitored for new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing of tafasitamab must be immediately suspended. Referral to a neurologist should be considered. Appropriate diagnostic measures may include MRI scan, cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments. If PML is confirmed, tafasitamab must be permanently discontinued (SmPC section 4.4). Progressive multifocal leukoencephalopathy (PML) is a very rare and life-threatening infection in the brain. Tell your doctor straight away if you have symptoms such as memory loss, trouble speaking, difficulty walking, or problems with your eyesight. If you had any of these symptoms before or during treatment with MINJUVI , or you notice any changes, tell your doctor straight away (PL section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription Additional risk minimisation measures: None	None
Use in pregnancy and lactation	Routine risk communication: SmPC sections 4.6, 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Treatment with tafasitamab in combination with lenalidomide should not be initiated in	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	female patients unless pregnancy has been excluded (SmPC Section 4.6). Advise females of reproductive potential to use effective contraception during treatment with tafasitamab and for at least 3 months after end of treatment (SmPC Section 4.6). Advise patients to notify their doctor if they become pregnant or intend to become pregnant during tafasitamab therapy as may it may cause harm to the unborn baby (SmPC section 4.6 and PL Section 2). In case of exposure during pregnancy, which may cause B-cell depletion in the fetus, 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 (SmPC section 4.6). Tafasitamab is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-foetal harm and is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide pregnancy prevention programme are met (SmPC Section 4.6). Use of effective contraception during treatment with tafasitamab and for at least 3 months after end of treatment is recommended for women of reproductive potential (PL Section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Use in patients with recent use of B-cell depleting drugs or chemotherapy	Routine risk communication: SmPC sections 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Monitor complete blood counts throughout treatment and prior to administration of each treatment cycle. Cytopenia may require a delay, dose reduction, or discontinuation of lenalidomide and/or a delay or discontinuation of tafasitamab (SmPC Section 4.4). Advise patients to report signs or symptoms of fever or other evidence of potential infection, such as chills, cough or pain on urination, or signs or symptoms of bruising or bleeding immediately (SmPC Section 4.4). Patients are advised to inform their doctor immediately of a fever of 38 degrees Celsius or above, chills, cough or pain on urination, or any signs of any signs of bruising or bleeding (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: None

Part VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR MINJUVI (TAFASITAMAB)

This is a summary of the risk management plan (RMP) for MINJUVI. The RMP details important risks of MINJUVI, how these risks can be minimised, and how more information will be obtained about MINJUVI 's risks and uncertainties (missing information).

MINJUVI 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how MINJUVI should be used.

This summary of the RMP for MINJUVI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of MINJUVI's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

MINJUVI is authorised in combination with lenalidomide followed by MINJUVI monotherapy for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), who are not eligible for autologous stem cell transplant (ASCT) (see SmPC for the full indication). It contains tafasitamab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of MINJUVI’s benefits can be found in MINJUVI’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of MINJUVI together with measures to minimise such risks and the proposed studies for learning more about MINJUVI's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of MINJUVI is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of MINJUVI are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of MINJUVI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of Important Risks and Missing Information	
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

II.B Summary of Important Risks

Important Potential Risk: Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	There were no cases of treatment-emergent progressive multifocal leukoencephalopathy reported in the clinical development programme for tafasitamab in combination with lenalidomide. One case of worsening of progressive multifocal leukoencephalopathy was reported, and progressive multifocal leukoencephalopathy due to reactivation of the JC virus has been reported for other B-cell depleting therapies (eg, MabThera 2024). A case of progressive multifocal leukoencephalopathy was received from an early access program, however the case was heavily confounded. Cases of progressive multifocal leukoencephalopathy have also been reported with lenalidomide (Revlimid 2024).
Risk factors and risk groups	Progressive multifocal leukoencephalopathy in general occurs in patients with suppressed cellular immunity. Cases of progressive

Important Potential Risk: Progressive multifocal leukoencephalopathy	
	multifocal leukoencephalopathy reported in patients taking lenalidomide were generally in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy (Revlimid 2024). There are currently no known risk groups or risk factors for the development of progressive multifocal leukoencephalopathy whose consideration would lead to practicable preventative measures.
Risk minimisation measures	Routine risk communication: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Progressive multifocal leukoencephalopathy (PML) has been reported during combination therapy with tafasitamab. Patients should be monitored for new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing of tafasitamab must be immediately suspended. Referral to a neurologist should be considered. Appropriate diagnostic measures may include MRI scan, cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments. If PML is confirmed, tafasitamab must be permanently discontinued(SmPC section 4.4). Progressive multifocal leukoencephalopathy (PML) is a very rare and life-threatening infection in the brain. Tell your doctor straight away if you have symptoms such as memory loss, trouble speaking, difficulty walking, or problems with your eyesight. If you had any of these symptoms before or during treatment with MINJUVI , or you notice any changes, tell your doctor straight away (PL section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription

Missing information: Use in pregnancy and lactation	
Risk minimisation measures	Routine risk communication: SmPC sections 4.6, 5.3

Missing information: Use in pregnancy and lactation	
	PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Treatment with tafasitamab in combination with lenalidomide should not be initiated in female patients unless pregnancy has been excluded (SmPC Section 4.6). Advise females of reproductive potential to use effective contraception during treatment with tafasitamab and for at least 3 months after end of treatment (SmPC Section 4.6). Advise patients to notify their doctor if they become pregnant or intend to become pregnant during tafasitamab therapy as may it may cause harm to the unborn baby (SmPC section 4.6 and PL Section 2). In case of exposure during pregnancy, which may cause B-cell depletion in the fetus, 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 (SmPC section 4.6). Tafasitamab is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-foetal harm and is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide pregnancy prevention programme are met (SmPC Section 4.6). Use of effective contraception during treatment with tafasitamab and for at least 3 months after end of treatment is recommended for women of reproductive potential (PL Section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription Additional risk minimisation measures: None

Missing information: Use in patients with recent use of B-cell depleting drugs or chemotherapy	
Risk minimisation measures	Routine risk communication: SmPC sections 4.4

Missing information: Use in patients with recent use of B-cell depleting drugs or chemotherapy	
	PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Monitor complete blood counts throughout treatment and prior to administration of each treatment cycle. Cytopenia may require a delay, dose reduction, or discontinuation of lenalidomide and/or a delay or discontinuation of tafasitamab (SmPC Section 4.4). Advise patients to report signs or symptoms of fever or other evidence of potential infection, such as chills, cough or pain on urination, or signs or symptoms of bruising or bleeding immediately (SmPC Section 4.4). Patients are advised to inform their doctor immediately of any signs of a fever of 38 degrees Celcius or above, chills, cough or pain on urination, or any signs of bruising or bleeding (PL Section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription Additional risk minimisation measures: None

Missing information: Long-term safety	
Risk minimisation measures	Routine risk communication: None 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
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

Single-arm study of tafasitamab in combination with lenalidomide in DLBCL (StudyfirmMIND; INCMOR0208-305): 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 shall 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.

Study MOR208C310 (front-MIND): A phase 3, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of 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).

Rationale and study objectives:

To compare the efficacy and safety of tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP in previously untreated, high-intermediate and high-risk patients with newly-diagnosed DLBCL.

Primary Objective:

- To compare the efficacy of tafasitamab plus lenalidomide in addition to R-CHOP versus tafasitamab placebo, lenalidomide placebo and R-CHOP.

Secondary Objectives:

- To compare the efficacy (additional parameters) of tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP.
- To compare the safety of tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP.
- To compare the efficacy of tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP in DLBCL subtypes of COO assessed by Hans-classifier and gene expression profiling (GEP).
- To compare the efficacy of tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP in DLBCL subtypes: DLBCL not otherwise specified (NOS) versus HGBL versus other.
- To compare the incidence of central nervous system (CNS) relapse in patients receiving tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP.
- To assess patient-reported outcomes (PRO) in patients receiving tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP.
- To assess the pharmacokinetic (PK) profile of tafasitamab.
- To assess the potential immunogenicity of tafasitamab.

- To assess the role of baseline NK cell count (NKCC) as a predictor of response.

Study design:

This is a parallel arm, double-blind, placebo controlled, multi-center, randomized, phase 3 study to investigate the efficacy and safety of tafasitamab plus lenalidomide as add-on therapy to R-CHOP (experimental arm) vs. R-CHOP (control arm). The stratification factors are:

- International Prognostic Index (IPI): IPI status 3 (IPI 3) (> 60 years old)/age-adjusted (aa) IPI 2 (≤ 60 years old) vs. IPI 4-5 (> 60 years old)/aaIPI 3 (≤ 60 years old).
- Geographic Regions (Europe, United States, Canada, Australia and New Zealand versus Asia versus the Rest of World [3 groups]). The total expected duration of the study from first patient's first visit (FPFV) to last patient's last visit (LPLV) is approximately 5 years.

Study population:

Patients with newly diagnosed, previously untreated, high-intermediate or high-risk DLBCL.

Milestones:

First Patient First Visit – April 2021

Enrollment completion – June 2023

Primary analysis results – June 2025

Final clinical study report – December 2025

II.C.1 Other Studies in Post-Authorisation Development Plan

There are no other studies required for tafasitamab.

PART VII ANNEXES

LIST OF ANNEXES

Pages 66-69 have been removed per EMA guidance on the preparation and redaction of risk management plans (body and annexes 4 and 6)

- ANNEX 1 EUDRAVIGILANCE INTERFACE
- ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME
- ANNEX 3 PROTOCOLS FOR PROPOSED, ONGOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

Page 71 has been removed per EMA guidance on the preparation and redaction of risk management plans (body and annexes 4 and 6)

- ANNEX 5 PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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Pages 79-85 have been removed per EMA guidance on the preparation and redaction of risk management plans (body and annexes 4 and 6)

- ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Signature Page for VV-PVG-000232 v15.0

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