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.

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® SmPC 2021). Cases of progressive multifocal leukoencephalopathy have also been reported with lenalidomide (Revlimid® SmPC 2020).
Risk factors and risk groups	Progressive multifocal leukoencephalopathy in general occurs in patients with suppressed cellular immunity. Cases of progressive multifocal leukoencephalopathy reported in patients taking

	lenalidomide were generally in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy (Revlimid® SmPC 2020). 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: 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

Missing information: Use in pregnancy and lactation	
Risk minimisation measures	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 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 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: Study MOR208C204 (B-MIND) is a Phase II/III Randomised, Multicentre Study of MOR00208/tafasitamab with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) Who Are Not Eligible for High Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT).

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 (Study TBD): 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

Study MOR208C204 (B-MIND) is a Phase II/III Randomised, Multicentre Study of MOR00208/tafasitamab with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) Who Are Not Eligible for High Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT).

In Study MOR208C204, treatment with study drugs (tafasitamab with bendamustine or rituximab with bendamustine) is offered in 28-day cycles at specified time points at protocol-prescribed dose levels for a maximum of six cycles. Thereafter, patients with at least partial response at the end of Cycle 6, as per local disease response assessment, continue antibody monotherapy treatment until disease progression. Thus, the antibody treatment may vary individually. Treatment may be stopped due to recurrence/disease progression, unacceptable toxicity, death or discontinuation for any other reason, whichever comes first.

Rationale and study objectives:

This is a randomised, open-label clinical trial to compare the safety and efficacy of MOR00208 with bendamustine versus rituximab with bendamustine, an accepted standard of care for this patient population.

Primary Objective:

- To determine the efficacy of a combination of MOR00208 with bendamustine versus a combination of rituximab with bendamustine in terms of progression-free survival in:
    - Adult patients with R-R DLBCL (overall population)
    - A subgroup of adult patients with R-R DLBCL with low baseline peripheral blood NK-cell count, defined as 100 or less NK cells per µl blood at baseline.

Secondary Objectives:

- To determine and compare both study arms, MOR00208 with bendamustine versus rituximab with bendamustine, for the overall population and NKCC-low subgroup in terms of:
    a) best objective response rate based on the best response achieved at any time during the study
    b) duration of response
    c) overall survival
    d) disease control rate
    e) time to progression
    f) time to next treatment
    g) safety, based on the frequency, incidence and severity of adverse events
    h) quality of life
- To assess the potential immunogenicity of MOR00208 (anti-MOR00208 antibody formation)

- To assess the pharmacokinetic profile of MOR00208

Study design:

Study MOR208C204 is a randomised, two-arm, multicentre, open-label phase II/III efficacy and safety study of MOR00208 in combination with bendamustine versus rituximab in combination with bendamustine given to adult patients who have relapsed after or are refractory to at least one but no more than three prior systemic therapies and have failed, or are not candidates for HDC and ASCT, and have thus exhausted their therapeutic options of demonstrated clinical benefit. At least one prior therapy line must have included a CD20-targeted therapy (e.g. rituximab).

Treatment with study drugs (MOR00208 with bendamustine or rituximab with bendamustine) will be offered in 28-day cycles at specified time points at protocol-prescribed dose levels for a maximum of six cycles.

Thereafter, patients with a response of at least partial response at the end of Cycle 6, as per local disease response assessment, will continue antibody monotherapy treatment (MOR00208 or rituximab) in accordance with their original treatment allocation until disease progression. Treatment may be stopped due to recurrence/disease progression, unacceptable toxicity, death or discontinuation for any other reason, whichever comes first.

In the case of local confirmation of disease recurrence/progression, it is up to the investigator to decide according to the individual risk/benefit ratio if the patient should continue further antibody treatment (rituximab or MOR00208) in accordance with the initial treatment allocation for up to 24 months in total.

MOR00208 dose: 12 mg/kg intravenously (IV) Cycle 1-3: MOR00208 will be administered on Day 1, Day 8, Day 15 and Day 22 of each cycle. Additionally, a loading dose will be administered on Day 4 of Cycle 1. Cycle 4-until disease progression: MOR00208 will be administered on Day 1 and Day 15 of each cycle.

Rituximab dose: 375 mg/m2 IV

Rituximab will be administered on Day 1 of each cycle, with a pre-planned treatment interval of at least 28-days to the subsequent rituximab administration.

Bendamustine dose: 90 mg/m2 IV

Bendamustine will be administered on Days 2+3 of Cycle 1. Bendamustine administration will be repeated on Days 1+2 or Days 2+3 of the subsequent cycles, with a pre-planned treatment interval of at least 28-days between the commencements of two succeeding cycles.

Study population:

Patients with DLBCL who have relapsed after or are refractory to at least one but no more than three prior systemic therapies and have failed, or are not candidates for HDC and ASCT, and have thus exhausted their therapeutic options of demonstrated clinical benefit.

Milestones:

First Patient First Visit – August 2016

Enrollment completion – June 2021

Primary analysis results – September 2024

Final clinical study report – March 2025

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no other studies required for tafasitamab.