14 November 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Minjuvi (tafasitamab)
Treatment of follicular lymphoma
EU/3/25/3027

Sponsor: Incyte Biosciences Distribution B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance	Tafasitamab
Other name	--
International Non-Proprietary Name	Tafasitamab
Tradename	Minjuvi
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 BP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Incyte Biosciences Distribution B.V.
COMP opinion	23 January 2025
EC decision	26 February 2025
EC registration number	EU/3/25/3027
Type II variation procedural history	
Rapporteur / Co-rapporteur	Boje Kvorning Pires Ehmsen / Alexandre Moreau
Applicant	Incyte Biosciences Distribution B.V.
Application submission	25 February 2025
Procedure start	22 March 2025
Procedure number	EMA/VR/0000255975
Invented name	Minjuvi
Proposed therapeutic indication	Minjuvi is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) (Grade 1-3a) after at least one line of systemic therapy. Further information on Minjuvi can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/minjuvi
CHMP opinion	13 November 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Jana Mazelova
Sponsor's report submission	10 July 2025
COMP discussion	7-8 October 2025
COMP opinion (adoption via written procedure)	14 November 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2024 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing tafasitamab was considered justified based on preliminary clinical data which showed increased progression free survival, and improved overall response rate in patients with previously treated Grade 1 – 3a follicular lymphoma;
- the condition is life threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma.
- the condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tafasitamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that tafasitamab in combination with lenalidomide and rituximab showed increased progression free survival and improved overall response rate in adult patients with previously treated Grade 1 – 3a follicular lymphoma compared to the authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing tafasitamab as an orphan medicinal product for the orphan condition: treatment of follicular lymphoma.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin's lymphoma (NHL) and the most prevalent indolent form of NHL (iNHL), accounting for approximately 20–25% of all new NHL cases in western countries (Swerdlow et al., 2017). In the fifth edition of the World Health

Organization (WHO) classification of haematolymphoid tumours, FL is categorized as a mature B-cell neoplasm within the group of lymphoid neoplasms (Alaggio et al., 2022). FL originates from germinal center (GC) B-cells and is composed of a mixture of centrocytes (small to medium-sized cleaved cells) and centroblasts (large non-cleaved cells). It typically displays a partially or completely follicular growth pattern in most cases (~85%) (Alaggio et al., 2022; Smith et al., 2013; Xerri et al., 2016).

FL is characterized by significant mutational and clinical heterogeneity, ranging from an indolent to a highly aggressive clinical course, often requiring multiple lines of treatment (Qualls et al., 2022). FL cells are immunophenotypically characterized by the expression of pan B-cell antigens (i.e., CD19, CD20, CD22, and CD79a) and germinal center markers (i.e., CD10 and BCL-6). A defining genetic feature of classic FL (cFL) is the t(14;18)(q32;q21) translocation, which leads to IGH::BCL2 fusion and overexpression of the anti-apoptotic B-cell leukaemia/ lymphoma 2 (BCL2) protein, driving disease pathogenesis (Alaggio et al., 2022; Relander et al., 2010). This subtype is distinct from two related subtypes, follicular large B-cell lymphoma (FLBL) and FL with uncommon features (uFL) (Alaggio et al., 2022).

The WHO classification previously adopted a grading system from 1-3, with grade 3 subdivided into grade 3a, in which centrocytes are present, and grade 3b, in which there are sheets of centroblasts (Ott et al., 2002). The clinical aggressiveness of FL increases with the number of centroblasts and subsequently with grade. FL grades 1-3a comprise the most prevalent indolent (low-grade) lymphoma subtype of iNHL. In contrast, FL grade 3b, which largely corresponds to the recently defined subtype of FLBL, is at an intermediate stage of large cell transformation and is typically treated as an aggressive (high-grade) lymphoma (aNHL) (Dreyling et al., 2021; Swerdlow et al., 2016). Of note, the grading of FL, which applies exclusively to cFL, is no longer considered mandatory in the latest WHO classification (Alaggio et al., 2022).

The aetiology of FL is poorly understood, but factors such as age, gender, and ethnicity are thought to influence the risk of the disease (Friedberg, 2023). FL is extremely rare in children and adolescents, with incidence increasing with age. The median age at diagnosis is around 60-65 years. Although the onset of FL can be gradual at the time of initial diagnosis, advanced FL is typically incurable, with lower response rates and shorter durations of response with successive lines of therapy (Jacobsen, 2022).

The approved extension of the therapeutic indication "MINJUVI is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) (Grade 1-3a) after at least one line of systemic therapy" falls within the scope of the designated orphan condition: Treatment of follicular lymphoma.

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

FL is a life-threatening and chronically debilitating condition that significantly impacts patients due to its incurable nature, symptom burden, and risk of transformation into aggressive lymphoma.

Patients with FL often present with asymptomatic lymphadenopathy, which may persist for years before diagnosis, with waxing and waning symptoms. Approximately 10% of patients have localized disease at diagnosis, and less than 20% present with B symptoms (fever, night sweats, and unintentional weight loss) or elevated serum lactate dehydrogenase (LDH) levels. Bone marrow involvement is frequent, occurring in approximately 40-70% of patients, whereas extra-nodal involvement of other organs is less common (Swerdlow et al., 2017; Freedman, 2020). Signs of bone

marrow involvement, such as anaemia, leukopenia, or thrombocytopenia, are rare at presentation but may develop during later stages of the disease.

Advanced-stage FL can cause debilitating symptoms and life-threatening complications. Patients may experience B symptoms, unexplained fatigue, and local effects of lymphadenopathy, such as abdominal pain, chest pain, cough, or dyspnoea. Bone marrow failure can lead to cytopenias, while other symptoms depend on the location of the lymphoma. For instance, gastrointestinal bleeding may occur due to gastrointestinal involvement, superior vena cava syndrome from vein compression, renal failure from ureter obstruction, and, rarely, spinal cord compression. These complications significantly impact patients' quality of life, particularly in cases of relapsed or refractory (r/r) disease.

A major life-threatening feature of FL is its potential for histologic transformation into a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). This transformation occurs in 10–30% of patients over time, with an annual risk of 2–3% (Al-Tourah et al., 2008; Link et al., 2013; Montoto et al., 2007; Sarkozy et al., 2016; Kridel et al., 2016; Freedman, 2018). Transformed FL is associated with poor prognosis and reduced survival outcomes which generally are inferior to those of de novo DLBCL (Davies et al., 2007; Sun et al., 2024).

FL is considered incurable with current therapies, as most patients experience multiple relapses requiring repeated courses of treatment. Each relapse becomes progressively harder to treat, with diminishing overall survival (OS) rates and worsening health and quality of life (Dreyling et al., 2021; Zucca et al., 2020; Kanters et al., 2023; Singh et al., 2023). Approximately one-third of r/r FL patients who have received two or more prior lines of therapy die within 24 months (Kanters et al., 2023). Patients with refractory disease to frontline therapy (~10%) or early relapse within 24 months of initial treatment (progression of disease within 24 months, POD24; ~20%) face particularly poor outcomes, including a higher risk of transformation (Casulo et al., 2015; Casulo et al., 2019; Sarkozy et al., 2019; Rodgers et al., 2021).

Although recent treatments have improved progression-free survival (PFS) for some subgroups, FL remains incurable, with a 5-year survival rate of 80–90%. Lymphoma is the leading cause of death, with a cumulative incidence of 10.3% after 10 years (Sarkozy et al., 2018). Other causes of death include treatment-related mortality (3.0%), other malignancies (2.9%), and non-lymphoma causes (2.2%). The chronic symptom burden, combined with the psychological impact of living with a relapsing illness, further underscores the debilitating nature of FL (Oerlemans et al., 2011).

The sponsor has not identified any significant changes in the seriousness of FL since the orphan designation was granted in 2024. The COMP acknowledged that the condition remains life-threatening and chronically debilitating due to its incurable nature, symptom burden of lymphadenopathy, splenomegaly, and bone marrow dysfunction, and the risk of transformation to aggressive lymphoma, with a progressive decline in prognosis after each relapse.

Number of people affected or at risk

At the time of the orphan designation in 2024, the COMP concluded that FL affected approximately 4.9 in 10,000 persons in the European Union (EU). To update the information submitted at the time of the initial orphan designation, the sponsor conducted a systematic literature review (SLR) and searches in real-world databases to incorporate the most recent and relevant epidemiological data available.

The SLR was conducted using PubMed, Embase®, and Evidence-Based Medicine (EBM) Reviews databases to retrieve publications reporting data on the incidence, prevalence, and survival outcomes of FL in the 27 EU member states (EU27). Eligible studies included all primary publication types, observational studies, retrospective analyses, systematic reviews, and meta-analyses, with a focus on

publications after 2010 that reflect the healthcare system during the relevant period. Abstracts from the European Haematology Association (EHA) and International Conference on Malignant Lymphoma (ICML; 2023) were also reviewed to complement the systematic searches. Additionally, data were gathered from population-based cancer registries and databases, including the European Cancer Information System (ECIS; 2022), the WHO Global Cancer Observatory (GCO, formerly GLOBOCAN; 2020), Orphanet, and the RARECARENet (2008), and national and regional registries such as the Netherlands Cancer Registry (Integraal Kankercentrum Nederland, IKNL; 2023), Slovenian Cancer Registry (SCR; 2021), German registry (Robert Koch Institute; 2022), Belgium Cancer Registry (2018), Italian Association of Cancer Registries (AIRTUM; 2015), the Spanish Network of Cancer Registries (REDECAN; 2025), and the Association of Nordic Cancer Registries (NORDCAN; 2021). Additional sources included EMA orphan designation reports and Google searches (results from the first three pages).

The epidemiology of FL is not comprehensively characterised, with limited data available on direct prevalence estimates within the EU27. Existing population-based studies and epidemiological data sources predominantly report on haematological malignancies within broader classifications, such as NHL or B-cell malignancies. As a result, the prevalence estimates for FL have been derived using a combination of both direct and indirect methodologies.

Direct prevalence estimate

The SLR identified five publications reporting prevalence data for FL, including one new reference that was not included at the time of the initial orphan designation. Prevalence data from four European cancer registries (AIRTUM, SCR, IKNL, and the Belgian Cancer Registry) were directly retrieved from the registries.

The estimates from publications and population-based registries reported complete prevalence rates ranging from 1.65 per 10,000 in Germany in 2022 (DARWIN study, Burn et al., 2023) to 6.61 per 10,000 in Slovenia in 2021 (SCR, 2021). According to the sponsor, the prevalence rates reported in the SLR were comparable to those reported in national cancer registries and in the RARECARENet and Orphanet database. The complete prevalence rates obtained from the cancer registries (4.25 per 10,000) and the databases (2.75 per 10,000) were all below 5 per 10,000, as shown in Table 1.

To provide a direct estimate of FL prevalence, the sponsor combined the directly reported complete prevalence data from the SLR, the cancer registries and databases. The geometric mean of these rates resulted in a complete prevalence estimate of 3.17 per 10,000 persons in the European community.

Table 1. Summary of FL Prevalence Data Identified in the Literature, Cancer Registries and Databases

Prevalence per 10,000						
Source	**Country**	**Year (latest)**	**5 years**	**10 years**	**20 years**	**Complete**
SLR						
Kanas (2022)	Western Europe (FR, DE, IT, ES, and UK)	2024 (projected)		3.40		
Ekberg (2022)	Sweden	2016	1.69	2.84		
Lech-Maranda (2021)	Poland	2014	1.56			
Burn (2023)	Belgium	2022	1.47			2.61
	Germany	2022	0.90			1.65
	Spain	2022	2.83			5.52
Geometric mean			1.55	3.11		2.88
Cancer registries						
AIRTUM	Italy	2010				2.73
Slovenia Cancer Registry	Slovenia	2021				6.61
IKNL	Netherlands	2024	1.72	2.89	4.38	
Geometric mean			1.72	2.89	4.38	4.25
Databases						
RARECARENet	Europe	2008				2.04
Orphanet	Europe	2024				3.70
Geometric mean						2.75
Direct estimate of Complete prevalence				3.17		

Incidence Data

The SLR identified 15 publications reporting FL incidence data. Among these, eight sources were new compared to those included at the time of the orphan designation. Incidence rates varied significantly across EU countries, with crude rates ranging from 0.72 per 100,000 person-years in Poland (2000–2014; Szumera-Ciećkiewicz et al., 2020) to 5.15 per 100,000 person-years in Germany (2018–2021; IQWiG, 2022). The latter figure was based on data from the German statutory health insurance (GKV) routine database, as reported by the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the available data, the geometric mean of the age-standardised incidence rate per European population (ASRE) for FL was estimated to be 2.52 per 100,000 person-years. This estimate was derived from studies conducted in Poland, Italy, the Netherlands, and Spain, using data collected between 2000 and 2020 (Szumera-Cieckiewicz et al., 2020; Mangone et al., 2023; Dinnessen et al., 2021; Pla et al., 2022).

The sponsor also presented FL incidence data from five registries, as summarised in Table 2. Orphanet estimated the incidence of FL in 2024 at 2.192 per 100,000 person-years in Europe (Orphanet, 2024). NORDCAN, ECIS, and GLOBOCAN reported incidence data only for all NHL cases and did not provide specific data for FL. The ECIS database reported a crude incidence rate for NHL in 2022 of 20.8 per 100,000 person-years and an EU ASR of 19.3 per 100,000 person-years.

Table 2. Population-based Registries Review on FL Incidence

Cancer Registries Country	Time period	Patients with FL	Crude incidence per 100,000 (95% CI)	Age-standardised incidence per 100,000 (95% CI)
Netherlands Cancer Registry (IKNL)	2023	698	4.46	3.01
Slovenian Cancer Registry	2021	164	7.80	5.30
Robert Koch Institute Germany	2022	1,484 (male)	3.60	2.50
		1,507 (female)	3.50	2.20
Belgium Cancer Registry	2018	413	3.60	3.70
AIRTUM Italy	2015	1,849	2.85	NR

Proportion of FL patients among overall NHL population

The SLR identified eight studies reporting the proportion of FL patients among the overall NHL cohort, including four studies not discussed at the time of the initial orphan designation (Baastrup Nordsborg et al., 2013; Dotlic et al., 2015; Laurent et al., 2015; Wästerlid et al., 2013). The proportion of FL among all NHL cases, as reported in the included studies and population registries, ranged from 7.6% in Romania (2004–2006; Fetica et al., 2017) to 17% in Denmark (1999–2003; Baastrup Nordsborg et al., 2013) and Sweden (2000–2016; Ekberg et al., 2020). The WHO Classification, on the other hand, reported that FL accounts for 10–20% of all lymphomas, with the highest proportions reported in the USA and Western Europe, and the lowest in Eastern Europe.

The included studies span a wide range of time periods (1989–2019), reflecting changes in diagnostic techniques and classification systems for NHL, including FL. Differences in study design, data sources, and classification criteria for FL likely contribute to the variability in the reported proportions. These findings highlight the heterogeneity in FL epidemiology, with higher proportions generally observed in Northern and Western Europe compared to Eastern Europe.

Survival data of incident FL and mean duration of the condition

Sixteen publications reporting survival outcomes for newly diagnosed FL patients were identified in the SLR. Median overall survival (mOS) varied substantially across the studies, ranging from 13 years in France (1980–2009; Dandoit et al., 2015) to 25 years in Italy (1982–2012; Tarella et al., 2014). The absence of FL grading in the latter study likely resulted in an overestimation of the survival duration. Similarly, Mozas and colleagues reported a mOS of 17.6 years for FL grades 1–3a diagnosed between 1989 and 2017 in Spain, though the exclusion of patients with FL grade 3b introduces bias, potentially increasing the survival estimate (Mozas et al., 2020). Rajamäki and colleagues observed a mOS of 15 years for patients with FL grades 1 and 2 diagnosed between 1997 and 2016 in Finland and Spain (Rajamäki et al., 2023). However, the focus on low-grade FL patients limits the generalizability of the findings to the broader FL population. Finally, a population-based registry study conducted in France reported a mOS of 13 years for FL patients of all grades diagnosed between 1980 and 2009 (Dandoit et al., 2015). These estimates, derived using Kaplan-Meier methods that accounted for loss to follow-up, strengthen the reliability of the findings.

Despite advancements in treatment, including the widespread adoption of rituximab, FL remains a fatal condition, particularly for elderly patients and those with advanced-stage disease (Dinnessen et al., 2021; Junlén et al., 2015; Mozas et al., 2020; Sarkozy et al., 2019). While significant improvements in survival were observed between 2000 and 2010, no demonstrable improvement in overall survival has been reported for FL patients in the past decade. Considering the median age at diagnosis of FL (60–65 years) and the survival data presented, the sponsor concluded that a mean disease duration of 15 years remains the most appropriate estimate for the prevalence calculations.

Indirect prevalence calculation

Indirect prevalence calculations were performed using the standard formula P = I x D, where (I) represents the incidence and (D) the mean disease duration. This equation assumes a stable incidence and duration of the disease. Using ECIS data for NHL, the ASR incidence rate was estimated at 1.93 per 10,000 in 2022. Assuming that FL accounts for 7.6–17% of all NHL cases, the incidence of FL was calculated to range from 0.15 to 0.33 per 10,000 persons. A mean disease duration of 15 years was applied in the estimate, as justified by the evidence outlined above. Using these parameters, the prevalence of FL in the EU27 was calculated to range between 2.25 and 4.95 per 10,000 persons.

The sponsor emphasised that the calculation using the ECIS NHL data can be considered to represent the upper range for the prevalence estimate. Based on the review of epidemiological data, the sponsor concluded that the overall prevalence of FL in the EU27 is approximately 4.95 per 10,000 persons, which confirms that FL continues to meet the prevalence criterion for orphan designation in the EU. This estimate is consistent with the prevalence accepted at the time of orphan designation in 2024.

COMP Discussion

The proposed prevalence estimate aligns with the figures accepted in orphan designations and maintenance procedures for FL in the EU in recent years. In these cases, the prevalence of FL was concluded to range between approximately 4.8 and 4.95 per 10,000 persons in the community. These estimates were based on ECIS data for the crude incidence of NHL, which is considered preferable to the ASR incidence rate, and a weighted average proportion of FL within all NHL cases of approximately 16.5–20%, consistent with the 17% applied in this calculation. A disease duration of 14.5–15 years was also used in most cases, aligning with the methodology applied in this procedure. Consequently, the COMP accepted that the same conclusion as for the initial orphan designation is supported by the data provided, confirming that FL affects approximately 4.9 in 10,000 persons in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor provided a list of medicinal products authorised in the EU for the treatment of patients with r/r FL and their therapeutic indications. Treatment for FL is initiated only upon the onset of lymphoma-related symptoms, such as B symptoms. The therapeutic approach is tailored based on clinical risk factors, symptoms, and patient preferences.

For first-line treatment, the ESMO guidelines for FL recommend an anti-CD20 antibody, such as rituximab (R) or obinutuzumab (O), in combination with chemotherapy (e.g., cyclophosphamide, doxorubicin, vincristine and prednisone [CHOP], bendamustine [B], or cyclophosphamide, vincristine

and prednisone [CVP]), followed by optional anti-CD20 maintenance therapy (Eyre et al., 2025). Alternative options for low-risk patients or those in whom conventional chemotherapy is contraindicated include rituximab monotherapy or R-chlorambucil. Rituximab combined with lenalidomide, though off-label as combination in first line, may also be used in selected cases.

Minjuvi (tafasitamab) was granted a conditional MA in the EU (Product No. EMEA/H/C/005436) on 26-Aug-2021 in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with r/r DLBCL who are not eligible for autologous stem cell transplant (ASCT). This indication extension of tafasitamab is intended to include combination treatment with lenalidomide and rituximab (R^2) of adult patients with r/r FL grade 1-3a who have received at least one prior line of systemic therapy.

While most FL patients initially respond to systemic therapies, the disease is not curative, and many eventually experience relapse or refractory disease. Approximately 20% of patients with advanced FL progress within 24 months of initial treatment (POD24), a group associated with poor prognosis and diminished overall survival (Casulo et al., 2015; Rodgers et al., 2021). There is no standardized treatment for relapsed FL, and treatment decisions are guided by disease stage, tumour burden, as well as types and duration of response to prior therapies, and patient age and/or comorbidities. Options for r/r FL include immunochemotherapy regimens, non-chemotherapy approaches (e.g., R^2 or rituximab monotherapy), and, in selected cases and subject to eligibility, ASCT, radioimmunotherapy, idelalisib and duvelisib (double refractory), or allogenic stem cell transplantation (alloSCT).

Recently approved therapies include CD20-directed bispecific T cell engagers (e.g., mosunetuzumab, epcoritamab, odronextamab), anti-CD19-directed CAR T-cell therapies (e.g., axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel), and the BTK inhibitor zanubrutinib combined with obinutuzumab. Since the initial orphan designation of tafasitamab for treatment of FL, only one new treatment (lisocabtagene maraleucel [Breyanzi]) has been authorised for adult patients with r/r FL.

An overview of the medicinal products currently authorised for the treatment of r/r FL in the EU and whether these are considered satisfactory treatment methods relevant for a discussion of significant benefit of tafasitamab is provided in Table 3. In summary, the therapeutic indications for lenalidomide (Revlimid) in combination with rituximab (MabThera), and rituximab as monotherapy, overlap with the intended indication extension for tafasitamab and are considered satisfactory methods relevant for discussing its significant benefit in the target FL population. The other medicinal products have more restricted indications and will therefore not be further discussed.

Table 3. Overview of medicinal products authorised in the EU for the treatment of r/r FL and their relevance to the significant benefit of tafasitamab

INN (invented name)	**Approved Indication (as per SmPC)**	**Type of authorisation**	**Satisfactory Method of treatment**
Axicabtagene ciloleucel (Yescarta)	Treatment of adult patients with r/r FL after three or more lines of systemic therapy.	Centralized	**Non-satisfactory method**: • Indication limited to r/r FL patients after 3 or more prior lines of systemic therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2^{nd}) lines of therapy, where this product is not authorised.

INN (invented name)	Approved Indication (as per SmPC)	Type of authorisation	Satisfactory Method of treatment
Bendamustine	As monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.	National	**Non satisfactory method**: • Indication limited to patients with rituximab-refractory FL. • Clinical benefit of tafasitamab was also demonstrated in patients being non-refractory.
Duvelisib (Copiktra)	As monotherapy, for the treatment of adult patients with FL that is refractory to at least two prior systemic therapies.	Centralized	**Non-satisfactory method**: • Indication limited to patients being double refractory after 2 or more prior therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2nd) lines of therapy, where this product is not authorised.
Epcoritamab (Tepkinly)	As monotherapy, for the treatment of adult patients with r/r FL after two or more lines of systemic therapy.	Centralized	**Non-satisfactory method:** • Indication limited to r/r FL patients after 2 or more prior lines of systemic therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2nd) lines of therapy, where this product is not authorised.
Idelalisib (Zydelig)	As monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment.	Centralized	**Non-satisfactory method:** • Indication limited to patients being double refractory after 2 or more prior therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2nd) lines of therapy, where this product is not authorised.
Lenalidomide (Revlimid and generics)	In combination with rituximab (anti-CD20 antibody), for the treatment of adult patients with previously treated FL (Grade 1 – 3a).	Centralized	**Satisfactory method:** • The r/r FL indication of lenalidomide overlaps with the intended extension of indication for tafasitamab.
Lisocabtagene maraleucel (Breyanzi)	Treatment of adult patients with r/r FL after two or more lines of systemic therapy.	Centralized	**Non-satisfactory method:** • Indication limited to r/r FL patients after 2 or more prior lines of systemic therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2nd) lines of therapy, where this product is not authorised.

INN (invented name)	Approved Indication (as per SmPC)	Type of authorisation	Satisfactory Method of treatment
Mosunetuzumab (Lunsumio)	As monotherapy, for the treatment of adult patients with r/r FL who have received at least two prior systemic therapies.	Centralized	**Non-satisfactory method:** • Indication limited to r/r FL patients after 2 or more prior lines of systemic therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2nd) lines of therapy, where this product is not authorised.
Obinutuzumab (Gazyvaro)	In combination with bendamustine followed by obinutuzumab maintenance, for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.	Centralized	**Non satisfactory method:** • Indication limited to patients with rituximab-refractory FL. • Clinical benefit of tafasitamab was also demonstrated in patients being non-refractory.
Odronextamab (Ordspono)	As monotherapy, for the treatment of adult patients with r/r FL after two or more lines of systemic therapy.	Centralized	**Non-satisfactory method:** • Indication limited to r/r FL patients after 2 or more prior lines of systemic therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2nd) lines of therapy, where this product is not authorised.
Rituximab (MabThera and generics)	As monotherapy, for treatment of adult patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy.	Centralized	**Satisfactory method:** • The r/r FL indication of rituximab overlaps with the intended extension of indication for tafasitamab
Tisagenlecleucel (Kymriah)	Treatment of adult patients with r/r FL after two or more lines of systemic therapy.	Centralized	**Non-satisfactory method:** • Indication limited to r/r FL patients after 2 or more prior lines of systemic therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2nd) lines of therapy, where this product is not authorised.

INN (invented name)	Approved Indication (as per SmPC)	Type of authorisation	Satisfactory Method of treatment
Zanubrutinib (Brukinsa)	In combination with obinutuzumab, for the treatment of adult patients with r/r FL who have received at least two prior systemic therapies.	Centralized	**Non-satisfactory method:** • Indication limited to r/r FL patients after 2 or more prior lines of systemic therapies. • Clinical benefit of tafasitamab was demonstrated in earlier (2^{nd}) lines of therapy, where this product is not authorised.

Significant benefit

The sponsor did not seek protocol assistance from EMA to discuss the approach for justifying significant benefit over existing methods of treatment for patients with r/r FL who have received at least one prior line of systemic therapy.

Tafasitamab is an Fc-enhanced monoclonal antibody (mAb) targeting CD19, a key antigen involved in B-cell development and proliferation. The Fc modification enhances binding to Fc receptors on effector cells, particularly natural killer (NK) cells, thereby boosting antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and direct cytotoxic effects such as apoptosis and inhibition of proliferation.

The claim of significant benefit is based on results from the pivotal, global, randomized, double-blind, placebo-controlled, multicenter phase 3 study INCMOR 0208-301. This study provides the evidence required for the variation application, which seeks to expand the approved label of tafasitamab combined with lenalidomide and rituximab (R²) to adult patients (≥18 years) with r/r FL grade 1-3a who have received at least one prior systemic anti-CD20 immunotherapy or immunochemotherapy. The study enrolled 548 patients with histologically confirmed r/r FL grade 1-3a (FL Full Analysis Set [FAS] population) who were randomized 1:1 to receive tafasitamab plus R² (n=273) or placebo plus R² (n=275). Tafasitamab and rituximab were administered intravenously, while lenalidomide was administered orally. The data cut-off (DCO) date for the primary efficacy analysis was 23-Feb-2024.

The median age of enrolled patients was 64 years (range: 31–88), with 49.6% being ≥65 years of age. Most patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of either 0 (68.1%) or 1 (29.2%). All patients had documented CD19+ and CD20+ expression on their lymphoma cells and had received prior anti-CD20-containing immunotherapy, including 95.4% who previously received rituximab. The median number of prior systemic anti-cancer therapy lines was 1 (range: 1–10), with 39.2% of patients being refractory to rituximab and 54.4% relapsing after rituximab therapy.

The primary objective of the study was investigator-assessed PFS in the FL population, defined as the time from randomization to disease progression (per Lugano classification criteria; Cheson et al., 2014) or death from any cause. Key secondary endpoints included PET-compete response (CR) rate by investigator assessment in the FDG-avid FL population and overall survival (OS). Additional secondary endpoints included overall response rate (ORR), duration of response (DoR), by both investigator assessment and independent review committee (IRC) review, and other measures of response depth and duration, including minimal residual disease (MRD) negativity rate. Exploratory endpoints included time to next treatment (TTNT) and histological transformation rates.

Significant Benefit of Tafasitamab over Lenalidomide (R²)

The sponsor argued that tafasitamab plus R² provides a significant benefit over lenalidomide (in combination with rituximab; R²) based on improved efficacy in patients with r/r FL in the second- and later lines setting. Approval of lenalidomide in combination with rituximab (R²) was based on clinical data from the AUGMENT study, which demonstrated a significant clinical benefit of R² versus rituximab monotherapy for patients with previously treated FL.

The claim of significant benefit over lenalidomide is supported by efficacy results from the primary analysis of INCMOR 0208-301. Tafasitamab plus R² significantly improved PFS compared to placebo plus R² with a median PFS of 22.37 months versus 13.93 months (HR: 0.434; p<0.0001), representing a 57% reduction in the risk of progression/relapse or death. The primary outcome was further supported by the findings that tafasitamab plus R² improved PET-CR rates (49.4% vs. 39.8%; OR: 1.5; p=0.0286), ORR (83.5% vs. 72.4%; p=0.0014), and DOR (median DOR: 21.19 months vs. 13.60 months; HR: 0.473; p<0.0001). Subgroup analyses showed statistically significant benefits across prognostic factors, including POD24 status and refractoriness to prior anti-CD20 therapy. Quality of life outcomes, as measured by validated scales such as EORTC QLQ-C30, EQ-5D, and FACT-Lym, were similar between the two treatment groups. TTNT was longer in the tafasitamab plus R² group, and no histological transformations were reported, compared to 3.3% in the placebo plus R² group. This suggests that tafasitamab plus R² may delay the need for subsequent therapy and reduce the risk of disease progression to more aggressive forms.

The sponsor also noted that safety data demonstrated that tafasitamab plus R² was tolerable, with the majority of treatment-emergent adverse events (TEAEs) being Grade 1 or 2 in severity and manageable with dose modifications, concomitant medications, or supportive care as per institutional guidelines. Slightly higher rates of Grade 3 or 4 infections were reported in the tafasitamab plus R² group compared to the placebo plus R² group (25.7% vs. 17.2%), primarily driven by pneumonia (8.3% vs. 4.9%) and COVID-19 infections, which likely reflect the additional immunosuppressive effect of tafasitamab. Importantly, no new potentially important risks were identified, and the safety profile was consistent with prior knowledge of the individual study medicines.

COMP Discussion

The clinical data from the pivotal comparative study demonstrated that tafasitamab plus R² provided clinically meaningful and statistically significant improvements in PFS compared to R² alone. Patients treated with tafasitamab plus R² achieved a higher ORR, with responses that were longer-lasting and deeper. The COMP agreed that these findings provide robust evidence to support the significant benefit of tafasitamab plus R² compared to R² alone, offering extended disease-free intervals and improved treatment outcomes for patients with r/r FL in the second- and later lines setting.

Significant Benefit of Tafasitamab over Rituximab Monotherapy

The sponsor argued that tafasitamab plus R² provides a significant benefit over rituximab monotherapy based on improved efficacy, particularly in difficult-to-treat patient populations with r/r FL, such as the early-relapse (POD24) population and the population refractory to prior anti-CD20 therapy. The clinical efficacy outcomes of tafasitamab plus R² was compared to those reported for rituximab monotherapy using data from the pivotal study and historical data from pivotal studies on rituximab.

The initial EU approval of rituximab for r/r FL was based on results from a pivotal phase 2 study of 166 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL receiving 375 mg/m² rituximab intravenously weekly over 4 weeks (MabThera SmPC). The ORR in the ITT population was 48% (95% CI: 41, 56), with a CR rate of 6% and a partial response (PR) rate of 42%. The median

time to progression (TTP) was 11.6 months. Notably, these data were generated in patients not previously exposed to rituximab and/or anti-CD20 therapy. In contrast, patients enrolled in the inMIND study were required to have received prior systemic therapy, including anti-CD20 therapy. More recently, published data from the CHRONOS-3 study provided efficacy and safety outcomes for rituximab monotherapy in a subgroup of patients with relapsed FL (Matasar et al., 2021). In this study, 91 patients with relapsed FL were randomized to the rituximab plus placebo arm. The ORR was 54% (95% CI: 43, 64), the CR rate was 21%, and the median PFS (after a median follow-up time of 19.2 months) was 18.7 months (95% CI: 5.5, 27.9).

The efficacy results of tafasitamab plus R² from study INCMOR 0208-301 demonstrated superior outcomes compared to rituximab monotherapy, with a median PFS of 22.37 months (investigator-assessed) and NE (IRC-assessed) versus 13 months (historical data). The ORR was 83.5% (investigator-assessed) and 85.7% (IRC-assessed) for tafasitamab plus R², compared to 48% (95% CI: 41, 56) for rituximab monotherapy. Similarly, the CR rate was 52.0% (investigator-assessed) and 52.4% (IRC-assessed) for tafasitamab plus R², compared to 6% for rituximab monotherapy.

A descriptive, cross-study comparison of tafasitamab plus R² efficacy versus rituximab monotherapy is presented in Table 4. As always, comparisons of efficacy outcomes across studies must be interpreted with caution due to differences in patient population, trial methodology, and other factors.

Table 4. Efficacy of Tafasitamab plus R² versus Rituximab Monotherapy

	Tafasitamab+ R² INCMOR 0208-301 (inMIND) CSR	**Rituximab in relapsed or chemoresistant low-grade FL (MabThera EU SmPC; (Younes et al 1998)**	**CHRONOS-3 study (Matasar et al 2021)**
Number of FL participants	273	166	91
Study population			
Median age (range)	64 (36-88) 50.2% < 65 years old	58 (22-79)	62 (53–70)[a]
Prior therapy, median (range)	1 (1-10)	3 (1-10)	2 (IQR 1–3)[b]
Prior anti-CD20 therapy**	100%	None (0%)	99% [a]
Rituximab refractory**	25.9%	None (0%)	None
ECOG 0-1 2	 97.4% 2.6%	NR	 99% [a] 1% [a]
Ann Arbor III-IV	81.0%	NR	81% [a]
% FLIPI high-risk	50.2%	NR	NR

Clinical efficacy results			
Median PFS, months	INV assessment: 22.37 (19.22, NE) IRC assessment: NE (19.29, NE)	N/R (Projected median time to progression [in responding patients]): 13 months	IRC assessment: 18·7 (IQR: 5·5–27·9)
ORR, % CR Rate, %	INV assessment: ORR: 83.5% CR rate: 52.0% IRC assessment: ORR: 85.7% CR rate: 52.4%	48% (95%CI: 41 - 56) CR: 6% PR: 42%	ORR: 54% (95%CI: 43–64) CR: 21% PR: 33%
Median DOR, months	INV assessment: 21.19 (19.48, NE) IRC assessment: NE (19.2, NE)		17·3 months (11·8–25·3) for the overall population

According to the sponsor, subgroup analyses demonstrated consistent benefit for tafasitamab plus R² across prognostic factors, including POD24 status and refractoriness to prior anti-CD20 therapy. The benefit of tafasitamab when added to R² also appeared consistent regardless of the type and number of prior lines of therapy, including in patients pre-treated with rituximab alone or in combination with chemotherapy. Importantly, the clinical benefit of tafasitamab plus R² compared with R² was maintained for participants with anti-CD20-refractory disease (HR: 0.444 [95% CI: 0.302, 0.652]), addressing a critical need in this patient population where resistance to anti-CD20–based therapies is an increasing concern due to the widespread use of anti-CD20 antibodies and the heterogeneity of CD20 surface expression.

COMP Discussion

While the indirect comparison of tafasitamab plus R² with historical data for rituximab suggests improved efficacy, differences in patient populations limit the comparability of the presented data. Nonetheless, rituximab combined with lenalidomide (R²) serves as the comparator arm in the pivotal study INCMOR 0208-301, a regimen previously shown in the registrational AUGMENT study to be superior to rituximab monotherapy in patients with previously treated FL. The COMP determined that these findings confirm that tafasitamab plus R² offers significant benefits over both the established R² regimen, as demonstrated in the pivotal study with improved PFS, as well as higher, deeper, and more durable responses, and rituximab monotherapy.

COMP Conclusion

The claim of significant benefit, based on a clinically relevant advantage for tafasitamab (Minjuvi) over lenalidomide (in combination with rituximab) and rituximab as monotherapy for the target patient population, is considered established based on the evidence provided. This conclusion is supported by the head-to-head comparison of efficacy outcomes from study INCMOR 0208-301, demonstrating the significant benefit of tafasitamab plus R² compared to R² alone in adult patients with r/r FL in the second- and later lines setting.

The data presented are considered sufficient by the COMP to support the maintenance of the orphan designation for Minjuvi (tafasitamab) for the orphan condition, treatment of follicular lymphoma.

4. COMP position adopted on 14 November 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of follicular lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to its incurable nature, symptom burden of lymphadenopathy, splenomegaly, and bone marrow dysfunction, and the risk of transformation to aggressive lymphoma, with a progressive decline in prognosis after each relapse;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Minjuvi is of significant benefit to those affected by the orphan condition is established. The sponsor provided clinical efficacy data from the pivotal study demonstrating significant benefit of tafasitamab combined with lenalidomide and rituximab compared to lenalidomide and rituximab alone, with improved progression free survival and a greater proportion of patients achieving more durable responses in adult patients with relapsed or refractory follicular lymphoma after at least one line of systemic therapy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Minjuvi, tafasitamab for treatment of follicular lymphoma (EU/3/25/3027) is not removed from the Community Register of Orphan Medicinal Products.