30 October 2023
EMA/OD/0000124200
EMADOC-1700519818-1160489
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Jaypirca (pirtobrutinib)
Treatment of mantle cell lymphoma
EU/3/21/2450

Sponsor: Eli Lilly Nederland 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	(S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide
Other name	--
International Non-Proprietary Name	Pirtobrutinib
Tradename	Jaypirca
Orphan condition	Treatment of mantle cell lymphoma
Sponsor's details:	Eli Lilly Nederland B.V. Papendorpseweg 83 3528 BJ Utrecht Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Eli Lilly Nederland B.V.
COMP opinion	12 May 2021
EC decision	21 June 2021
EC registration number	EU/3/21/2450
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Edward Laane
Applicant	Eli Lilly Nederland B.V.
Application submission	25 May 2022
Procedure start	16 June 2022
Procedure number	EMA/H/C/005863
Invented name	Jaypirca
Proposed therapeutic indication	Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor. Further information on Jaypirca can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/jaypirca
CHMP opinion	26 April 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Cécile Dop
Sponsor's report submission	21 December 2022
COMP discussion and adoption of list of questions	18-20 April 2023
Oral explanation	16 May 2023
COMP opinion	17 May 2023

Appeal to the COMP opinion procedural history	
COMP rapporteurs	Frauke Naumann-Winter / Karri Penttila
Appeal submission	15 August 2023
Scientific Advisory Group consultation	30 August 2023
Appeal oral explanation	5 September 2023
COMP final opinion	7 September 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2021 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide was considered justified based on durable and high overall response rates in late line treatment of mantle cell lymphoma patients, who were treated with the product as monotherapy;
- the condition is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss;
- the condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.
- 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 (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that show responses in a heavily pre-treated relapsed/refractory population. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

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

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin's lymphoma (NHL). It constitutes 5–7% of malignant lymphoma in Western Europe (Dreyling et al., 2017). The entity is divided in two major subgroups with distinct clinical and molecular features, specifically nodal MCL and leukaemic non-nodal MCL according to the 5th edition of the World Health Organisation (WHO) classification of haematological malignancies (WHO-HAEM5) of the type lymphoid neoplasms from 2022 (Alaggio et al., 2022). It is a B-cell malignancy with a broad spectrum of clinical, pathological, and biological features, affecting men and women with a ratio of around 3:1. Patients with MCL are

often diagnosed with advanced disease (Stage III/IV), characterized by an aggressive clinical course, and the median age at diagnosis is 68 years.

The approved therapeutic indication "*Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor"* falls within the scope of the designated orphan condition "Treatment of mantle cell lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

There is no change of the severity of the condition since the orphan designation was granted in 2021 that has been identified by the sponsor. The COMP has previously accepted that MCL is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, fatigue, and weight loss in the untreated state. The majority of patients will relapse, with median OS of around 10-13 months in patients who have progressed after chemotherapy and treatment with approved targeted agents. The severe nature of the condition earlier acknowledged by the COMP remains acceptable for this maintenance procedure.

Number of people affected or at risk

At the time of the orphan designation in 2021, the COMP concluded that the condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union (EU).

The sponsor conducted an updated literature and database search to determine the current prevalence of MCL in the European community. Published data from global and regional population-based cancer registries and other relevant sources including Global Cancer Incidence and Mortality (GLOBOCAN; 2020), European Cancer Information System (ECIS; 2022) and Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries (NORDCAN; 2012-2016) were searched. In addition, literature searches on PubMed/Medline (1950 to present) and Embase (1988 to present) for peer-reviewed articles reporting relevant data for a prevalence estimate of MCL in Europe were conducted. The Eurostat database (EC; 2020) was used as the source of total population data.

Both direct and indirect methods were applied to estimate the prevalence of MCL. For the direct methods, direct reporting of prevalence of MCL in peer-reviewed literature as well as web-based databases and registries was extracted. For the indirect methods, estimation of the prevalence for MCL was established indirectly using the standard formula P (point prevalence) = I (incidence) × D (mean duration), under the assumption of stable incidence and duration of the condition. Table 1 below recapitulates the different methodologies used as well as respective results.

Table 1. Prevalence of MCL Reported from Selected EU Populations

Methods	Source Data[a]	Geographies with Data Available	Estimated Prevalence (Per 10,000)
Estimation from direct reporting of NHL prevalence in Europe as a whole	1. GLOBOCAN report of a 5-year prevalence of NHL in 2020 2. Proportion of MCL out of all NHL (2% to 10%) 3. Population of the EU-27 on 01 January 2020 4. Ratio of complete/20-year prevalence to 5-year prevalence of MCL in Finland and Netherlands	27 EU member states	0.61
Direct reporting of MCL prevalence in the single population with highest prevalence	1. A web-based national cancer registry from Finland reporting a complete prevalence estimate of MCL in 2019 and 2020	Finland	1.12
Indirect prevalence estimation as a function of incidence and mean duration of disease	1. Incidence rate of MCL from the 44 European cancer registries[b] 2. A weighted average of the median OS (5.6 years)	48 European cancer registries operating in 20 countries[b]	0.27

Abbreviations: EU-27 = 27 member states of the European Union; GLOBOCAN = Global Cancer Incidence and Mortality; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; OS = overall survival.
a Andersen et al. 2002; Mitterlechner et al. 2006; Sant et al. 2010; Abrahamsson et al. 2014;
b The 48 cancer registries operated in Iceland, Norway, Sweden, Ireland, England, Northern Ireland, Scotland, Wales, Austria, France, Germany, Switzerland, the Netherlands, Italy, Malta, Slovenia, Spain, Czech Republic, Poland, and Slovakia.

Based on the results from the 3 different approaches applied and the epidemiological data found, the sponsor proposed a range for a 5-year prevalence estimate of 0.27-1.12 per 10,000 persons with a final estimate of 0.61 per 10,000 people in the EU. The proposed prevalence is based on an estimated 5-year prevalence for NHL in the 27 EU member states (EU27; GLOBOCAN and Eurostat, 2020 data) and the upper end of the reported proportion of MCL cases within all NHL cases in Europe and North America of 2-10% (Sant et al., 2010; Dreyling et al., 2017; Jain and Wang 2019). The data used for the estimates are representative of data available from the ECIS database.

The proposed prevalence is the same estimate as was concluded on at the time of the orphan designation and in line with the value accepted for MCL in the orphan maintenance procedure for Tecartus at the time of marketing authorisation (MA) in 2020 (EU/1/20/1492). The COMP concluded that no significant changes have occurred since then in the prevalence of MCL, and a final prevalence estimate of 0.6 per 10,000 persons in the EU was therefore considered acceptable.

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 described several EU approved therapies commonly used for treatment of MCL. Targeted therapies currently authorized in the community for treatment of MCL include bortezomib (Velcade and generics) for newly diagnosed patients not candidates for stem cell transplantation (SCT), and ibrutinib (Imbruvica), lenalidomide (Revlimid and generics), temsirolimus (Torisel), and the anti-CD19 chimeric antigen receptor (CAR)-modified T-cell product brexucabtagene autoleucel (Tecartus; hereinafter referred to as brexu-cel) for the treatment of patients with relapsed or refractory (r/r) disease. Several other medicinal products are also authorised either centrally or nationally in the community for the treatment of the proposed condition, including cyclophosphamide, doxorubicin, vincristine, prednisone, bendamustine, fludarabine, mitoxantrone, dexamethasone, methotrexate, cytarabine, carmustine, chlorambucil, bleomycin, etoposide, epirubicin, ifosfamide, melphalan, pixantrone, and vinblastin.

The latest ESMO clinical practice guidelines for diagnosis, treatment and follow-up of newly diagnosed and relapsed MCL describe the recommended treatment options available for these patients (Dreyling, Ann Oncol. 2017; 28(S4): iv62-71). In the r/r disease setting, where the sponsor's product will be used, an optimal sequence of treatments has not been established. The selection of a proper regimen in this setting is influenced by response duration to prior therapy, co-morbidities, tumour chemo-sensitivity, and overall risk-benefit evaluations. Both ibrutinib (Imbruvica), lenalidomide (Revlimid and generics), and temsirolimus (Torisel) are specifically authorised for patients with r/r MCL. Furthermore, brexu-cel (Tecartus) is indicated for the treatment of adult patients with r/r MCL after two or more lines of systemic therapy including a BTK inhibitor.

The sponsor's product Jaypirca (pirtobrutinib) is intended to treat adult patients with r/r MCL who have previously been treated with a BTK inhibitor. Since the therapeutic indication pertains explicitly to patients who had been previously treated with a BTK inhibitor, ibrutinib (Imbruvica) is not considered a satisfactory method. Additionally, it should be considered that ibrutinib is already at least a second-line treatment, as it is intended for patients with r/r MCL. This makes pirtobrutinib a treatment option in the third- and later lines setting. Considering this, lenalidomide, temsirolimus, and brexu-cel are the medicinal products considered satisfactory methods for the purpose of this orphan review procedure and relevant for a discussion on the significant benefit of pirtobrutinib in MCL.

Significant benefit

The sponsor did not seek any protocol assistance from EMA regarding the evidence needed to justify significant benefit of pirtobrutinib over existing methods of treatment for patients with r/r MCL who had received prior treatment with a BTK inhibitor.

The sponsor argued that pirtobrutinib is of significant benefit based on a clinically relevant advantage in terms of improved efficacy and safety in comparison to existing therapies for patients with r/r MCL in the post-BTK inhibitor setting. Ibrutinib is the only BTK inhibitor currently authorised in the EU for the treatment of MCL and is the preferred treatment option in the second line setting. Moreover, the sponsor claimed that pirtobrutinib also provides a significant benefit to MCL patients who have already received treatment with brexu-cel and for whom no approved therapy is available.

Pirtobrutinib (also called LOXO-305 or LY3527727) is a small molecule adenosine triphosphate (ATP)-competitive and reversible non-covalent inhibitor of BTK. BTK, which is a member of the TEC family of non-receptor tyrosine kinases, is predominantly expressed in B-cells. The kinase is an important B-cell receptor (BCR) signalling molecule and highly implicated in the development of lymphoproliferative disorders (Seiler and Dreyling, 2017). Pirtobrutinib has therefore the potential to prevent B-cell development and survival by targeting BTK and its underlying signalling.

The primary data supporting efficacy and safety of pirtobrutinib in r/r MCL in the conditional MA (CMA) application were obtained from the ongoing global multicentre, open-label, dose-escalation and dose-expansion first-in-human (FIH) phase 1/2 study 18001 (also called BRUIN). The study was designed to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of oral pirtobrutinib in adult patients with r/r B-cell NHL or chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) who have failed or are intolerant to standard of care. Patients with histologically confirmed diagnosis of MCL from the phase 1 and phase 2 parts, irrespective of starting dose, were pooled together to form the primary analysis set (PAS) of MCL patients who had previously been treated with a BTK inhibitor-containing regimen and received at least one dose of pirtobrutinib as monotherapy (N=90). The data cut-off (DCO) date for the efficacy and safety analyses provided was 29-Jul-2022.

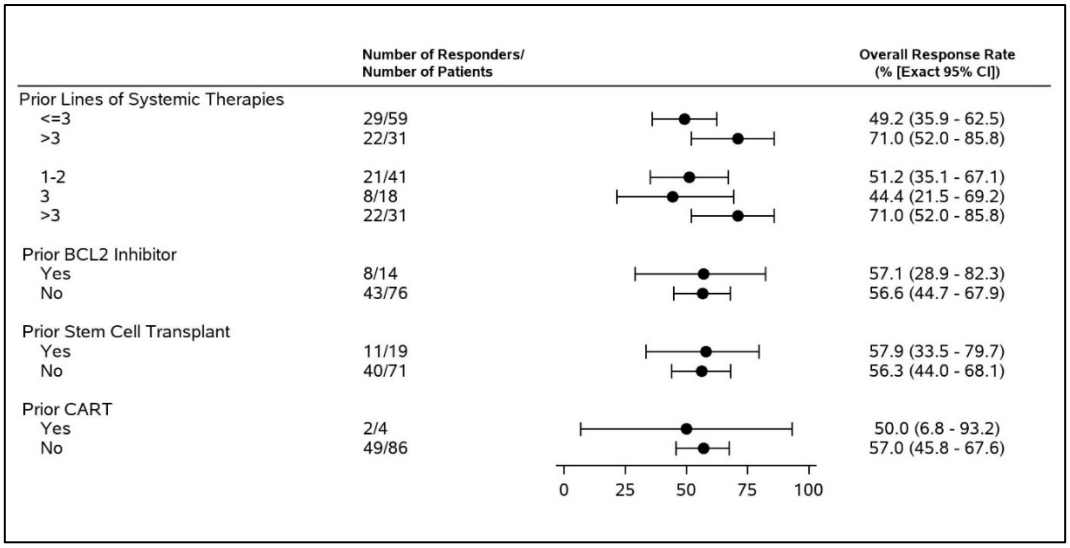
The primary objective for the phase 1 dose escalation and expansion was to determine the maximum tolerated dose (MTD)/ recommended phase 2 dose (RP2D) of oral pirtobrutinib, which was established at 200 mg once daily (QD) and no MTD was reached. The primary objective of the phase 2 part is to assess the preliminary antitumour activity of pirtobrutinib based on overall response rate (ORR) as assessed by an independent review committee (IRC) as per the IWG Lugano classification criteria (Cheson et al., 2014). Secondary efficacy endpoints included ORR by investigator assessment, best overall response (BOR), duration of response (DOR), time to any and best response, and progression-free survival (PFS) by IRC and investigator assessment, and overall survival (OS).

The median age of the patients with MCL in the PAS was 70.0 years (range: 46-87). In line with the usual distribution between men and women with MCL, a marked male predominance (80.0%; 72/90) relative to females (20.0%; 18/92) was observed. The majority of patients were white (84.4%) and had a baseline Eastern Cooperative Oncology Group (ECOG) performance score of either 0 (67.8%) or 1 (31.1%). Only one patient (1.1%) had an ECOG score of 2. The median number of prior therapies was 3 (range: 1-8). All patients had received a prior BTK inhibitor-based regimen, 95.6% (86/90) had received prior anti-CD20 therapy, and 87.8% (79/90) had previously been treated with chemotherapy. A total of 82.2% (74/90) of the patients had discontinued treatment with any prior BTK inhibitor due to progression, whereas 21.1% (19/90) of the patients had progressed following prior autologous- and/or allogeneic SCT. Only 4.4% (4/90) of the patients had previously received CAR-T cell therapy.

The median study follow-up time in the PAS at the DCO was 10.45 months (range: 0.5-34.4) and the median time on treatment for all patients in this cohort was 5.24 months (range: 0.2-33.7). The ORR by IRC assessment in the PAS was 56.7% (51/90; 95% CI: 45.8, 67.1), where 18.9% (17/90) of the patients achieved a complete response (CR) and 37.8% (34/90) obtained a partial response (PR). The responses to pirtobrutinib occurred rather quickly after initiation of treatment with a median time to response (TTR) among responding patients of 1.8 months by IRC assessment and they were durable with a median DOR of 17.6 months (95% CI: 7.3, 27.2) by IRC assessment. By KM analysis of the IRC assessment, an estimated 61.1% (95% CI: 44.1, 74.3) of the responders remained event-free (from disease progression or death) at 9 months and 58.0% (95% CI: 41.0, 71.7) remained event-free at 12 months. The median PFS and OS were 7.4 months (95% CI: 5.3, 13.3) by IRC assessment and 23.5 months (95% CI: 15.9, NE), respectively.

The efficacy of pirtobrutinib was evaluated in the PAS based on analyses of subgroups. Forest plots of ORR observed in relevant subgroups for the PAS based on the IRC assessment are shown in Figure 1.

Figure 1. ORR in subgroups based on IRC assessments - Primary Analysis Set (PAS)



Abbreviation: BCL2 = B-cell lymphoma 2; CART = chimeric antigen receptor-modified T cell; CI = confidence interval; IRC = independent review committee.

Significant benefit over existing non-CAR-T cell therapies

It was noted that the response rates to chemo-immunotherapy given as post-ibrutinib salvage therapy are as low as 27% (Jain et al., 2018). The regimen of rituximab-bendamustine-cytarabine (R-BAC) has been recently reported to have a promising ORR of 83% in relapsed MCL population, albeit in a small retrospective study of 36 patients who had not received a prior bendamustine-containing regimen. In current clinical practice, bendamustine-containing regimens, including R-BAC, are more commonly utilized in first line consistent with guidelines (McCulloch et al., 2020; NCCN 2022), and prospective studies of outcomes with R-BAC in relapsed patients previously exposed to bendamustine have not been reported or undertaken. Furthermore, R-BAC is associated with significant toxicities, such as high grade cytopenia, a high proportion of patients requiring dose reductions for toxicity (56% overall, 90% for patients aged at least 70 years) or blood transfusion support (68%), and a considerable number of patients requiring unplanned hospital admissions (50%, McCulloch et al., 2020). Overall R-BAC has limited utility and is not commonly used (Tisi et al., 2018; Bega et al., 2021).

The sponsor highlighted that available data from the pivotal study have shown that treatment with pirtobrutinib resulted in a clinically meaningful ORR with the lower bound of the 2-sided 95% CI of 45.8%, which exceeded that of 20 to 30% reported for the available monotherapy salvage therapies of lenalidomide, temsirolimus, and bortezomib, whose ORR results were generated in a BTK inhibitor-naive population. In addition, a DOR of 17.6 months by IRC assessment in response to pirtobrutinib compared favourably with the reported historical median DOR of 3 to 5.8 months with other commonly available approaches following prior ibrutinib therapy (Cheah et al. 2015; Epperla et al. 2017). Even when limiting evaluation of the efficacy of pirtobrutinib to patients with MCL who progressed on their most recent BTK inhibitor, the ORR of 48.6% (36/74; 95% CI: 36.9, 60.6) remained robust.

Consistent with the limited efficacy seen for targeted agents or chemo-immunotherapy following progression on BTK inhibitors, the survival of MCL patients who were pre-treated with a BTK inhibitor has been reported to be very poor, with median OS ranging from 2.5 to 8.4 months (Cheah et al.,

2015; Martin et al., 2016; Epperla et al., 2017). The OS observed for pirtobrutinib thus compared favourably to the OS results in the real-world patient populations in the post-BTK inhibitor setting. According to the sponsor, the data are particularly noteworthy in this heavily pre-treated patient population that received a median of 3 prior lines of therapy (including BTK inhibitors, anti-CD20 therapy, chemotherapy, immunomodulators, transplant, BCL2 inhibitor, and CAR-T cells), and that included patients with poor prognostic characteristics such as intermediate and high sMIPI, bulky disease, and blastoid/pleomorphic.

The COMP noted that the descriptive data presented indicated an improvement in ORR and DOR in patients with r/r MCL who were treated with pirtobrutinib in study 18001 compared to the monotherapy salvage therapies lenalidomide, temsirolimus, and bortezomib. Nevertheless, significant benefit based on improved efficacy of pirtobrutinib over lenalidomide and temsirolimus could not be established, since no methodologically sound indirect comparisons of the efficacy of pirtobrutinib versus lenalidomide and temsirolimus were provided by the sponsor to establish a clinically relevant advantage. Furthermore, no efficacy analyses for pirtobrutinib in relevant subgroups of patients with r/r MCL from the pivotal study who had progressed or relapsed after prior treatment with lenalidomide and temsirolimus has been presented by the sponsor.

The sponsor further argued that although results in study 18001 are not directly comparable to other studies, the safety profile of pirtobrutinib is arguably better than those reported for currently available therapies in the target patient population, including R-BAC, which as discussed above in the previous paragraphs, has unfavourable, life-threatening, and potentially fatal toxicities (McCulloch et al., 2020). This argument is not considered valid because of the lack of comparability between the clinical studies and based on immature data with the new product from a single-arm study with limited follow-up.

Significant benefit over the approved CAR-T-cell product

The CD19-directed CAR-T cell product brexu-cel (Tecartus) is the only medicinal product that has demonstrated efficacy in a BTK inhibitor pre-treated MCL population comparable to the one studied in study 18001. Tecartus was recently approved in the EU (CMA: 14/12/2020) based on data from an open-label, multicenter, single-arm phase 2 study called ZUMA-2, which was conducted in patients with MCL who had relapsed on a BTK inhibitor (N=74 ITT/68 mITT). Despite an impressive ORR of 93% (56/60) with a CR rate of 67%, this therapy is associated with significant toxicities with Grade ≥3 AEs occurring in 99% of the patients studied (Tecartus SmPC; Wang et al., 2020a).

The sponsor argued that CAR-T cell therapy carries significant logistical challenges as well as the potential severe toxicities of the therapy, which limits this treatment modality to those being fit and have slowly progressing disease to make it through the treatment. Successful leukapheresis, product manufacture, potential bridging chemotherapy, and conditioning therapy prior to cell infusion are all required to prescribe CAR-T cell therapy. In the single-arm study leading to approval of brexu-cel, 4% of the patients could not receive cell infusion due to complications and the product manufacture failed in another 4% of the patients (Wang et al., 2020a). In a community practice environment, where expertise may be lacking, CAR-T cell therapy may therefore be more challenging than described.

Safety concerns associated with CAR-T cell therapy, such as cytokine release syndrome (CRS) and neurological toxicity, have not been observed as safety risks for pirtobrutinib. Additionally, pirtobrutinib does not require the intensive logistical processes associated with CAR-T cell products, such as cell collection and processing, patient conditioning, and bridging chemotherapy for which 8% of clinical trial participants could not receive prescribed treatment as described. While CAR-T cell therapy is an option for selected patients, pirtobrutinib offers a meaningful therapeutic option for the larger population of

patients with MCL who have been pre-treated with a BTK inhibitor, including those unable to receive CAR-T cell therapy or for whom CAR-T cell therapy has been unsuccessful.

In study 18001, 13 patients with MCL were enrolled and treated following prior CAR-T cell therapy. A summary of the patient demographics from the DCO of 31-Jan-2022 showed that all 13 patients had received previous BTK inhibitor therapy, with a median number of prior lines of systemic therapy ranging from 5 to 6 (range: 4-8) across the analysis sets presented. A pooled ORR for patients with prior CAR-T cell therapy and prior BTK inhibitor therapy was 46.2% (6/13; all PR), which is clinically meaningful and generally comparable to the observed ORR in the overall PAS. In addition, 3 patients had a best response of stable disease (SD).

The claim of a better safety profile of pirtobrutinib over brexu-cel is difficult to conclude on based on immature data from a phase 1/2 study with a new product with limited follow-up, and without a head-to-head comparison. Nevertheless, the observation that 46.2% of the MCL patients who progressed after prior CAR-T cell therapy responded to pirtobrutinib in study 18001 may be considered a clinically relevant advantage if the patients who responded in the pooled population had received brexu-cel as prior CAR-T cell therapy and the responses in these patients were durable. No information on the pre-treatment history of those patients who had progressed or relapsed after prior treatment with brexu-cel before study entry in the pivotal study and their response data to pirtobrutinib has been provided, to further substantiate the claim of a significant benefit as compared to brexu-cel for patients with r/r MCL in the post-BTK inhibitor setting. Moreover, no indirect comparison of the efficacy outcomes of pirtobrutinib compared to brexu-cel has been provided to establish a clinically relevant advantage or a major contribution to patient care.

The argument that pirtobrutinib will confer a benefit to patients with r/r MCL who are unable or unfit to receive the approved CAR-T cell product due to selected eligibility criteria has not been sufficiently substantiated with relevant data. Efficacy data for pirtobrutinib from the subset of patients in the pivotal study 18001 who would be considered ineligible for CAR-T cell therapy, specifically brexu-cel, may be relevant for the COMP to evaluate such a claim.

Overall, the claim of significant benefit for pirtobrutinib over the satisfactory methods of treatment lenalidomide (Revlimid and generics), temsirolimus (Torisel), and brexu-cel (Tecartus) in patients with r/r MCL after failure with a BTK inhibitor was not considered established by the COMP based on the data provided. A list of questions on significant benefit has been adopted by the COMP.

4. COMP list of issues

Significant benefit

The sponsor is invited to detail the pre-treatment history and present an efficacy analysis for pirtobrutinib in relevant subgroups of patients from the pivotal study who had progressed or relapsed after prior treatment with each of the authorised satisfactory methods, specifically lenalidomide, temsirolimus, and brexucabtagene autoleucel.

In addition, a methodologically sound indirect comparison to the authorised satisfactory methods should be provided to establish a clinically relevant advantage or a major contribution to patient care.

Furthermore, efficacy data should be provided to support the argument that pirtobrutinib will confer a benefit to patients who would be considered ineligible for CAR-T cell therapy.

Comments on sponsor's response to the COMP list of issues

The sponsor further justified the claim of significant benefit for pirtobrutinib over the satisfactory methods lenalidomide, temsirolimus, and brexu-cel for the target MCL population in the post-BTK inhibitor setting based on efficacy data from the latest DCO of the pivotal study 18001 as requested.

Efficacy in patients previously treated with lenalidomide, temsirolimus, and brexu-cel

The sponsor presented the pre-treatment history and efficacy analyses of enrolled patients treated with pirtobrutinib in the pivotal study who have progressed or relapsed after previous therapy with lenalidomide, temsirolimus, or brexu-cel using the latest DCO date of 29-Jul-2022 (Table 2).

Table 2. Summary of Efficacy Results

Prior Treatment	**Lenalidomide**		**Temsirolimus**		**CAR-T**	
	PAS (N = 19)	Total (N = 26)	PAS (N = 2)	Total (N = 2)	PAS (N = 4)	Total (N = 13)
Overall Response Rate						
n (%)	13 (68.4)	14 (53.8)	2 (100)	2 (100)	2 (50.0)	6 (46.2)
95% Confidence Interval	43.4, 87.4	33.4, 73.4	15.8, 100	15.8, 100	6.8, 93.2	19.2, 74.9
Duration of Response (months)						
Median	25.26	7.46	12.52	12.52	9.2	9.2
95% Confidence Interval	6.47, NE	1.64, NE	7.29, NE	7.29, NE	NE, NE	1.28, NE
12-month Duration Rate	52.9	49.1	50	50	0	NE
95% Confidence Interval	20.3, 77.5	19.0, 73.7	0.6, 91.0	0.6, 91.0	NE, NE	NE, NE
Duration of Progression-free Survival (months)						
Median	9.07	5.55	14.32	14.32	9.33	5.32
95% Confidence Interval	3.45, NE	3.02, 27.01	9.07, NE	9.07, NE	5.32, NE	1.87, NE
Duration of Overall Survival (months)						
Median	NE	NE	NE	NE	NE	13.34
95% Confidence Interval	12.58, NE	8.28, NE	NE, NE	NE, NE	13.34, NE	4.70, NE

Abbreviations: CAR-T = chimeric antigen receptor-modified T cell; DoR = duration of response; N = number of participants; n = number of participants in the specified category; NE = not estimable; ORR = overall response rate; OS = overall survival; PAS = primary analysis set; PFS = progression-free survival; SAS = supplemental analysis set.

[a] Total is comprised of patients from the PAS, SAS1, and SAS2, data for SAS1 and SAS2 are provided in Appendix 1

Sources: Appendix 1 Table APP 2. (ORR), Table APP 3. (DoR), Table APP 4. (PFS), Table APP 5. (OS).

The analyses in the two supportive supplemental analysis sets (SAS1 and SAS2) were defined to investigate MCL patients pre-treated with covalent BTK inhibitor with either shorter follow-up time compared to the PAS (SAS1; N=48) or for those who did not meet the PAS criteria (such as CNS involvement and non-measurable disease at baseline; SAS2; N=14). While not part of the primary population, these SASs are supportive in the assessment of the benefit and increase the number of assessable patients who may have received one of the authorised satisfactory methods.

The 19 patients from the PAS who had previously been treated with lenalidomide, had received a median number of 5 (range: 2-8) prior lines of therapy and a median number of 1 (range: 1-3) prior lines of BTK inhibitors. The ORR by IRC assessment for patients in the PAS who had already received lenalidomide was 68.4% (95% CI: 43.4, 87.4), which was numerically higher than that reported for the overall population (56.7%; 95% CI: 45.8, 67.1). The median DOR among the responders was 25.3 months (95% CI: 6.47, NE), which was also longer than that observed in the full PAS (17.6 months; 95% CI: 7.3, 27.2). The sponsor noted there is uncertainty in the point estimates for DOR and minor data changes can be influential due to the limited number of responders, as shown by wide 95% CIs.

Among the 152 patients with MCL who were pre-treated with a BTK inhibitor in study 18001, only two patients had received prior treatment with temsirolimus. Both patients were in the PAS and responded to pirtobrutinib treatment. One patient received 6 lines of prior therapy including acalabrutinib and had a BOR of CR when treated with pirtobrutinib, which lasted for 17.7 months. The other patient received 7 lines of prior therapy including ibrutinib and obtained a PR when treated with pirtobrutinib that lasted for 7.3 months. The sponsor emphasised that the limited number of patients with prior treatment with temsirolimus reflects the limited use of this intravenously administered treatment option in clinical practice, which is largely due to tolerability issues, limited efficacy, and decrements to quality of life (Hess et al., 2017; Rule et al., 2018).

Among the 13 patients who received prior CAR-T cell therapy in study 18001, 7 of them specifically received brexu-cel, and none of these patients were in the PAS. One patient who received brexu-cel had also previously received a CAR-natural killer cell product. Of the remaining 6 patients, 2 patients had received an unknown CAR-T cell product type, 2 patients had prior axicabtagene ciloleucel (axi-cel), and other 2 patients had lisocabtagene maraleucel (liso-cel). The 13 patients who had already received CAR-T cell treatment had received a median number of 5 (range: 4-8) prior lines of therapy and a median number of 1 (range: 1-3) prior lines of BTK inhibitors. Efficacy data for the 7 patients who received brexu-cel are listed in Table 3. Three of the patients (42.9%) who had previously been treated with brexu-cel achieved a response (2 CR, 1 PR). The two patients who achieved a CR were still in response at 9.4 and 5.5 months from date of first response. The patient who achieved a PR to pirtobrutinib subsequently died 3.2 months from date of first response.

Table 3. List of patients who received prior brexu-cel and reported outcomes following pirtobrutinib

Patient	Number of Lines of Prior Systemic Therapy	Time on Pirtobrutinib Treatment (months)	Best Overall Response	Duration of Response (months)	Progression-free Survival (months)	Overall Survival (months)
1	5	12.3	CR	9.4+	11.0+	12.3+
2	5	9	CR	5.5+	7.3+	9.0+
3	4	3.5	PR	3.2	5.0	5.0
4	4	9	SD	NA	5.6	9.0+
5	5	1	SD	NA	1.0+	4.7
6	4	0.3	PD	NA	0.3	5.8
7	5	1.1	Other NEs	NA	0.0+	1.5+

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; NE = not estimable; + = censored observation

The COMP was of the opinion that due to the limited patient numbers in the subgroup of patients previously treated with brexu-cel or temsirolimus, a conclusion on a clinically meaningful benefit could

only be derived in the subgroup of patients who have progressed or relapsed after prior treatment with lenalidomide for adult patients with relapsed or refractory mantle cell lymphoma who have been previously treated with a Bruton's tyrosine kinase inhibitor.

In particular, the COMP pointed out that the efficacy data with Jaypirca in individual patients who have progressed or relapsed after prior treatment with brexu-cel before study entry were considered inconclusive in view of the low number of patients in this subset who responded to Jaypirca and the limited follow-up time in these patients, so that the clinical relevance of the responses observed could not be established.

Relative efficacy of pirtobrutinib versus lenalidomide, temsirolimus, and brexu-cel

The sponsor has conducted, as requested, indirect comparisons on the clinical benefit of pirtobrutinib compared to lenalidomide, temsirolimus, and brexu-cel based on a naïve (unadjusted) side-by-side comparison versus results from the registration studies. To further supplement this approach and investigate the benefit of pirtobrutinib in the post-BTK inhibitor population, methodologically sound adjusted comparative analyses were conducted of patients in study 18001 versus patient-level real-world data from the ConcertAI database and versus published data from SCHOLAR-2 (Hess G et al., 2022). However, the COMP is of the opinion that the real-world analyses are not considered relevant for evaluating significant benefit for pirtobrutinib in MCL because patients that had received CAR-T cell therapy were excluded and the outcome data for the individual therapies of lenalidomide and temsirolimus were insufficient to perform separate therapy-specific subgroup analyses.

The sponsor underscored that the pivotal studies for lenalidomide and temsirolimus reflected a different target patient population than that enrolled in study 18001 as they were conducted prior to the availability of covalent BTK inhibitors and had considerable differences in the studies regarding the outcome assessment (the pivotal study for temsirolimus utilized RECIST criteria from solid tumours to assess response/progression, whereas the others utilized hematologic criteria). "Unanchored" indirect comparisons to these products were thus not considered feasible to conduct since an assumption that all effect modifiers and prognostic factors could be accounted for was impossible to meet, and failure of this assumption would lead to an unknown amount of bias in the estimate (Phillippo et al., 2016).

In addition to the registration studies for lenalidomide and temsirolimus, a literature search and review of published studies in the MCL post-covalent BTK inhibitor setting was conducted. Five studies were identified for lenalidomide and no studies for temsirolimus. The feasibility assessment determined that none of the studies provided sufficient data for naïve side-by-side comparisons, unadjusted analyses, or adjusted comparative analyses given the small sample sizes of the three studies reporting outcomes related to lenalidomide (n=3, n=6, and n=30, respectively) and that no outcome data were reported specific to lenalidomide in the two remaining studies.

A summary of the registration studies and efficacy results for lenalidomide, temsirolimus, and brexu-cel for r/r MCL patients alongside that for the pivotal study for pirtobrutinib is presented in Table 4 and Table 5. Overall, these studies are relatively similar in terms of selected patient baseline characteristics (for example, sex and age) and were all conducted in the setting of r/r MCL. However, as noted above the temsirolimus and lenalidomide studies were quite different in several important aspects.

Table 4. Summary and baseline characteristics for pivotal studies of authorised products for r/r MCL

Authorized Treatment	**Lenalidomide**	**Temsirolimus 175/75 mg**	**Brexucabtagene Autoleucel**	**Pirtobrutinib**
Registrational trial	EMERGE[a] NCT00737529 N = 134	OPTIMAL[b] NCT00117598 N = 54	ZUMA-2[d] NCT02601313 N = 74	18001 NCT03740529 N = 90
Time period of study	Jan 2009 to Jul 2012	~May 2005 to Aug 2007	24 Oct 2016 to 16 Apr 2019	Mar 2019 - present
Key eligibility criteria	Relapsed/refractory disease, prior therapy with bortezomib	2 to 7 prior therapies that included anthracyclines, alkylating agents and rituximab; relapsed and/or refractory disease	Disease that was either relapsed or refractory to up to 5 previous regimens including anthracycline- or bendamustine-containing chemotherapy, anti-CD20, and cBTKi therapy.	Patients with B-cell malignancies who received at least 2 previous lines of therapy or at least one cBTKi as first-line therapy
Response assessment	modified International Workshop Lymphoma Response Criteria. CT scans every 2 cycles (± 7 days throughout treatment and every 90 days (± 14 days) after stopping lenalidomide until progression or initiation of subsequent therapy	Response Evaluation Criteria in Solid Tumors (RECIST). Assessment occurred every 8 weeks up to year 1, then every 12 weeks up to year 2, and then every 6 months until tumor progression or death (up to year 5)	Lugano Treatment Response Criteria 2014. Assessment occurred 4 weeks post-infusion, and at regular intervals during the posttreatment period	Lugano Treatment Response Criteria 2014 Assessment occurred 8 weeks for the first year, every 12 weeks for the second year, and every 6 months thereafter.
Prior therapies, median (range)	4 (2-10)	n (%) 1-2 prior: 34 (68) 3-6 prior: 19 (35) not reported: 1 (2)	3 (1-5)	3 (1-8)
Intermediate or high MIPI score, n (%)	90 (67.2)	39 (72.2)	Not reported	70 (77.8)
Age, median (range)	67 (43-83)	57.9% ≥ 65 years	65 (38, 79)	70 (46-87)

Male sex, n (%)	108 (81)	48 (84)	N not reported (84)	72 (80.0)
Prior cBTKi, n (%)	0 (0.0)	0 (0.0)[c]	74 (100)	90 (100.0)
Extranodal disease, n (%)	Three-fourths (exact number not reported)	Not reported	Not reported	35 (38.9)
Previous ASCT, n (%)	Bone marrow or ASCT, 30 (29)	17 (32)	N not reported (42)	17 (18.9)
Histology, classic/leukemic, n (%)	Not reported	Typical, 46 (85)	N not reported (54)	70 (77.8)
Stage III-IV, n (%)	124 (93)	54 (100)	Stage IV, 86%	77 (87.5)
Bone marrow involvement, n (%)	55 (41)	24 (44)	N not reported (51)	46 (51.1)
ECOG PS 0/1, n (%)	116 (87)	Karnofsky ≥80, 44 (81)	Not reported	89 (98.9)

Abbreviations: cBTKi: covalent Bruton's tyrosine kinase inhibitor; CD20 = cluster of differentiate 20; CT = computed tomography; ECOG = eastern cooperative oncology group; MCL = mantle cell lymphoma; MIPI = MCL international prognostic index; N = number of participants; n = number of participants in the specified category; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors; SCT = stem cell transplant.

[a] Goy et al. 2013; 2015.

[b] Torisel summary of product characteristics.

[c] Hess et al. 2009.

[d] Tecartus summary of product characteristics.

Based on the naïve comparison both lenalidomide and temsirolimus have substantially lower ORR and overall lower DOR reported in their registrational studies in a covalent BTK inhibitor naïve population than that observed with pirtobrutinib in the post-covalent BTK inhibitor setting. The reported ORR for pirtobrutinib was 56.7% (95% CI: 45.8, 67.1) and its lower bound of 45.8% far exceeded not only the point estimate, but even the upper bound of the confidence intervals for ORR for temsirolimus (ORR 22.2% [95% CI: 11.1, 33.3]) or lenalidomide (ORR 28% [95% CI: 20, 36]), highlighting the strength and confidence in efficacy of pirtobrutinib compared to these therapies. From the naïve comparison, CAR-T cell therapy demonstrated superior efficacy in terms of ORR and durability to that observed for pirtobrutinib, which was expected, and a further matched comparison was therefore not pursued.

Table 5. Clinical outcomes summary for pivotal studies of authorised products for r/r MCL

Authorized Treatment	**Lenalidomide**	**Temsirolimus 175/75 mg**	**Brexucabtagene Autoleucel**	**Pirtobrutinib**
Registrational trial	EMERGE[a] NCT00737529 N = 134	OPTIMAL[b] NCT00117598 N = 54	ZUMA-2[c] NCT02601313 N = 74	18001 NCT03740529 N = 90
ORR, % (95% CI)	28 (20-36)	22.2 (11.1-33.3)	84 (73.4-91.3)	56.7 (45.8-67.1)
Median DOR, months (95% CI)	16.6 (7.7-26.7)	Not reported	28.2 (13.5, 47.1)	17.6 (7.3-27.2)
Median PFS, months (95% CI)	4.0 (3.6-5.6)	4.8 (3.1-8.1)	24.0 (10.1, 48.2)	7.4 (5.3-13.3)
Median OS, months (95% CI)	19.0 (12.5-23.9)	12.8 (8.6-22.3)	47.4 (24.6, NE)	23.5 (15.9-NE)

Abbreviations: CI: confidence interval; DoR = duration of response; N = number of participants; NE: not estimable; ORR: overall response rate; PFS: progression-free survival; OS: overall survival.

[a] Goy et al. 2013; 2015.

[b] Torisel summary of product characteristics.

[c] Tecartus summary of product characteristics.

The COMP was of the opinion that the clinical study data (descriptive side-by-side comparison) showed improved efficacy of Jaypirca, with sustained overall responses, as compared to lenalidomide and temsirolimus but suggested inferior efficacy of Jaypirca in comparison to Tecartus.

Efficacy of pirtobrutinib in subset of patients who would be ineligible for CAR-T cell therapy

To evaluate the efficacy of pirtobrutinib in patients that would be considered ineligible for CAR-T cell therapy, the sponsor compared the eligibility criteria and available baseline characteristic data of patients enrolled in the registration study ZUMA-2 for brexu-cel versus those enrolled in study 18001. Based on this assessment, the criteria outlined in Table 6 were used to identify patients potentially ineligible for CAR-T cell therapy among MCL patients pre-treated with a BTK inhibitor in study 18001.

The sponsor stressed that the ineligibility criteria used were expected guides and ultimately whether a patient would be selected in the real world setting for CAR-T cell therapy would depend on the overall benefit-risk assessment made by the treating healthcare professional (HCP).

Table 6. Selection criteria and rationale for determining potential ineligibility for CAR-T cell therapy for patients enrolled in study 18001

Selection Criteria for Potentially Ineligible Patients	Rationale for Selection Criteria	Number of Patients that met each Selection Criteria
Age >= 80	• While no specific exclusion or contraindication highlighted in clinical trials or Tecartus SmPC, patients generally must be considered fit enough to undergo procedure. Patients of 80 years or older are often considered more frail with other significant comorbidities that can be limiting. • Note in CAR-T trials, no patients greater than 79 years old were enrolled.	17
Received prior CAR-T cell therapy	• Patients were excluded from CAR-T trials, and thus, there are no data to support. • The Tecatus SmPC indicates that the benefit risk has not been established in patients with CNS involvement. • The Tecartus SmPC indicates that there is no experience with manufacturing Tecartus for patients with hepatitis B and there is a warning and precaution for such patients.	13
With CNS involvement at baseline		5
With medical history of hepatitis B		5
With medical history of multiple sclerosis	• Patients were excluded from CAR-T trials likely due to known neurological toxicity concerns and thus there are no data to support.	1
With grade >= 2 WBC decrease at baseline based on CTCAE 5.0	• Patients must have sufficient bone marrow reserve to undergo conditioning and collection.	12

Based on the selected ineligibility criteria, 40 patients were identified across PAS, SAS1, and SAS2 to be likely ineligible for CAR-T cell therapy at the time on enrolment into study 18001, with 16 patients specifically from the PAS. A summary of pirtobrutinib efficacy for these patients are given in Table 7.

Patients enrolled in study 18001 who would be considered ineligible for CAR-T cell therapy across all analysis sets had received a median number of 4 (range: 1-8) prior lines of therapy and a median number of 1 (range: 1-3) prior lines of BTK inhibitors. This subgroup thus appeared to have similar prior treatment history and obtained similar benefit as the overall MCL population pre-treated with a BTK inhibitor. The sponsor pointed out that the potential CAR-T cell ineligible population from study 18001 constitute a significant proportion of patients enrolled in the study, representing over 25% of the overall MCL population which was pre-treated with a BTK inhibitor. According to the sponsor, this is likely an underestimate of the true proportion of patients in clinical practice that would be ineligible for

CAR-T cell therapy but would still be appropriate for pirtobrutinib. Furthermore, retrospective analyses support a higher proportion with 35-58% of patients being considered ineligible for CAR-T cell therapy (Smith et al., 2019; Puckrin et al., 2022).

Table 7. Summary of efficacy results for patients who would be ineligible for CAR-T cell therapy

	PAS (N = 16)	**SAS1 (N = 18)**	**SAS2 (N = 6)**	**Total (N = 40)**
Overall Response Rate				
n (%)	7 (43.8)	7 (38.9)	2 (33.3)	16 (40.0)
95% Confidence Interval	19.8, 70.1	17.3, 64.3	4.3, 77.7	24.9, 56.7
Duration of Response (months)				
Median	14.82	NE	NE	14.82
95% Confidence Interval	6.47, NE	3.22, NE	NE, NE	6.47 NE
Duration of Progression-free Survival (months)				
Median	8.28	5.59	5.55	5.59
95% Confidence Interval	1.58, 16.59	1.87, NE	1.87, NE	3.25, 16.59
Duration of Overall Survival (months)				
Median	8.57	NE	NE	13.34
95% Confidence Interval	2.83, NE	4.70, NE	2.60, NE	5.82, NE
Rate of Duration of Overall Survival				
At 12 months (%)	49.6	53.8	60.0	53.9
95% Confidence Interval	21.8, 72.4	25.9, 75.2	12.6, 88.2	35.9, 68.9

Abbreviations: CAR-T = chimeric antigen receptor-modified T cell; N = number of participants; n = number of participants in the specified category; NE = not estimable; PAS = primary analysis set; SAS = supplemental analysis set.
Sources: Appendix 1 Table APP 7. (ORR), Table APP 8. (DoR), Table APP 9. (PFS), Table APP 10. (OS)

Overall, the sponsor has provided supplementary data as requested to further substantiate the claim of significant benefit for pirtobrutinib over the satisfactory methods lenalidomide, temsirolimus, and brexu-cel for the target MCL population in the post-BTK inhibitor setting.

The efficacy analyses in the subsets of patients in the pivotal study 18001 who had previously received lenalidomide, temsirolimus, or brexu-cel before study entry showed that pirtobrutinib offered a benefit for patients who had previously been treated with lenalidomide as those patients in the PAS who had progressed following this therapy achieved an ORR of 68.4% (13/19; 95% CI: 43.4, 87.4), which was numerically higher than that reported for the overall PAS population (56.7%; 95% CI: 45.8, 67.1). The median DOR among the responders previously treated with lenalidomide was 25.3 months (95% CI: 6.47, NE), which was also somewhat longer than that observed in the full PAS (17.6 months; 95% CI: 7.3, 27.2). The responses observed in the subgroup of patients who had failed prior treatment with lenalidomide is hence considered to constitute a clinically relevant advantage for patients with r/r MCL in the post-BTK inhibitor setting although data on the time-dependent endpoints were immature.

The anti-tumour responses observed in patients who had previously been treated with temsirolimus (n=2) or brexu-cel (n=7) could in principle also be considered to constitute a clinically relevant advantage for patients with r/r MCL. However, the numbers of patients recorded to have been exposed to these two products prior to enrolment in the pivotal study for pirtobrutinib were very limited and the data also immature. In addition, only three of the patients (3/7; 42.9%) who had previously been treated with brexu-cel were reported to have achieved a response to pirtobrutinib. The two patients who achieved a CR were still in response at 5.5 and 9.4 months from date of first response, while the

patient who obtained a PR subsequently died 3.2 months from date of first response. Both patients who had received prior treatment with temsirolimus in the PAS responded to pirtobrutinib. One of the two patients had received prior acalabrutinib and obtained a CR when treated with pirtobrutinib, which lasted for 17.7 months, whereas the other patient had previously been treated with ibrutinib and obtained a PR to pirtobrutinib that lasted for 7.3 months.

The justification provided by the sponsor as to why "unanchored" indirect comparisons of the clinical benefit of pirtobrutinib compared to lenalidomide, temsirolimus, and brexu-cel were not considered feasible are endorsed. The sponsor has therefore conducted indirect comparisons to these products based on a descriptive (unadjusted) side-by-side comparison versus results from the registration studies. The efficacy outcomes reported in the naive comparison indicated that more r/r MCL patients in study 18001 achieved a sustained ORR to pirtobrutinib in the post-covalent BTK inhibitor setting compared to those treated with lenalidomide or temsirolimus in a covalent BTK inhibitor naïve setting. Specifically, the ORR for pirtobrutinib in study 18001 was >2 times higher than that reported for both temsirolimus and lenalidomide in OPTIMAL and EMERGE (56.7% vs. 22.2% and 28%, respectively). In addition, the lower bound of the 95% CI for ORR of 45.8% far exceeded not only the point estimate, but even the upper bound of the CIs for temsirolimus (95% CI: 11.1, 33.3) and lenalidomide (95% CI: 20, 36). As expected, brexu-cel showed superior efficacy in terms of ORR (84% vs. 56.7%) and durability (median DOR: 28.2 months vs. 17.6 months) to that observed for pirtobrutinib in study 18001, and matched comparison was therefore not pursued.

The descriptive indirect side-by-side comparison of results from the pivotal studies for temsirolimus and lenalidomide versus that for pirtobrutinib provided adequate evidence to support the claim of a clinically relevant advantage of pirtobrutinib based on improved efficacy in terms of higher and sustained ORR compared to that obtained with temsirolimus and lenalidomide in r/r MCL patients.

The efficacy results from the analyses conducted in the subset of patients who would be considered ineligible for CAR-T cell therapy based on eligibility criteria and available baseline characteristic data from patients enrolled in the comparator study ZUMA-2 for brexu-cel versus the pivotal study 18001 for pirtobrutinib were not taken into consideration because none of the sponsor-defined ineligibility criteria are reflected in the therapeutic indication wording or are contraindications for the treatment with Tecartus. Furthermore, there are currently no published consensus guidelines defining specific (in)eligibility criteria for CAR-T cell therapy.

The COMP did not consider the efficacy results with Jaypirca from this subgroup analysis in selected patients deemed potentially ineligible for treatment with Tecartus as none of the sponsor-defined ineligibility criteria are reflected in the therapeutic indication wording of Tecartus and none of these ineligibility criteria are contraindications for the treatment with Tecartus. Furthermore, there are currently no published consensus guidelines defining specific (in)eligibility criteria for CAR-T cell therapy.

COMP conclusion

The claim of significant benefit for pirtobrutinib compared to lenalidomide and temsirolimus for the target MCL population in the post-BTK inhibitor setting can be considered established based on the data provided. However, the sponsor failed to provide sufficient evidence to demonstrate significant benefit for pirtobrutinib over brexu-cel (Tecartus). The data provided are consequently not considered satisfactory to support the maintenance of the orphan designation.

5. COMP position adopted on 17 May 2023

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 mantle cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, fatigue, and weight loss in the untreated state;
- the sponsor's claim that pirtobrutinib (Jaypirca) is of significant benefit to those affected by the orphan condition does not hold since the sponsor could only establish the existence of a clinically relevant advantage over two of the authorised satisfactory methods of treatment, specifically lenalidomide (Revlimid and generics) and temsirolimus (Torisel), but not over the third authorised satisfactory method brexucabtagene autololeucel (Tecartus).
    - Clinical study data showed improved and sustained overall responses with Jaypirca as compared to lenalidomide and temsirolimus and a clinically meaningful benefit in a subgroup of patients who have progressed or relapsed after prior treatment with lenalidomide for adult patients with relapsed or refractory mantle cell lymphoma who have been previously treated with a Bruton's tyrosine kinase inhibitor.
    - A descriptive side-by-side comparison of the efficacy outcomes from the pivotal studies for Jaypirca and Tecartus suggested inferior efficacy of Jaypirca in comparison to Tecartus.
    - The efficacy data with Jaypirca in individual patients who have progressed or relapsed after prior treatment with Tecartus before study entry were considered inconclusive in view of the low number of patients in this subset who responded to Jaypirca and the limited follow-up time in these patients, so that the clinical relevance of the responses observed could not be established.
    - The efficacy results with Jaypirca from the subgroup analysis in selected patients considered potentially ineligible for treatment with Tecartus were not taken into consideration because a) none of the sponsor-defined ineligibility criteria are reflected in the therapeutic indication wording of Tecartus and b) none of these ineligibility criteria are contraindications for the treatment with Tecartus. Furthermore, there are currently no published consensus guidelines defining specific (in)eligibility criteria for CAR-T cell 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 not satisfied.

The Committee for Orphan Medicinal Products has recommended that Jaypirca, (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide, pirtobrutinib for treatment of mantle cell lymphoma (EU/3/21/2450) is removed from the Community Register of Orphan Medicinal Products.

6. Appeal to the negative opinion adopted on 17 May 2023

Grounds for appeal

The sponsor presented detailed grounds for appeal on 15 August 2023.

Please refer to the sponsor's appeal documents in the case *Input from Industry* folder.

Ground 1. *Pirtobrutinib offers a significant therapeutic benefit by offering a clinically relevant advantage to patients who are ineligible for brexucabtagene autololeucel or who have progressed after receiving brexucabtagene autololeucel*

According to the sponsor, based upon the CHMP-endorsed indication of pirtobrutinib, a patient with relapsed or refractory MCL is eligible for treatment with pirtobrutinib if previously treated with a BTKi. Thus, pirtobrutinib offers a treatment for those patients that received a BTKi in the first line. In contrast, brexucabtagene autololeucel is not available in the second line, as it is only authorised for those patients who have received at least 2 lines of prior therapy. According to the sponsor, pirtobrutinib will be authorised for the subset of patients that received brexucabtagene autololeucel and progressed; therefore, this represents a patient population with a significant unmet medical need where no realistic treatment options remain.

Thus, pirtobrutinib offers a clinically relevant advantage in at least 2 specific subsets of patients with MCL, namely patients:

1. treated in the first line with a BTKi and requiring further treatment, and
2. patients previously treated with a BTKi and brexucabtagene autololeucel and who have subsequently progressed.

The sponsor concludes on a line independent anti-MCL activity and provided updated overall response rate and duration of response by number of prior lines of therapy primary analysis set (Table 8).

Table 8. Overall response rate and duration of response by number of prior lines of therapy primary analysis set (All Patients Received Prior BTKi) Data Cutoff Date: 05 May 2023

	1-2 Prior Lines (N = 41)	**1 Prior Line, BTKi-Containing Therapy (N = 7)**	**3 Prior Lines (N = 18)**	**>3 Prior Lines (N = 31)**
Overall Response Rate				
% (n)	51.2% (21)	28.6% (2)	44.4% (8)	71.0% (22)
95% Confidence Interval	35.1, 67.1	3.7, 71.0	21.5, 69.2	52.0, 85.8
Duration of Response, months				
Median	NE	NE	25.26	7.29
95% Confidence Interval	4.01, NE	NE, NE	1.71, NE	3.71, 21.59
Follow-Up, months				
Median	20.11	10.66	31.34	20.01
Interquartile Range	7.85, 23.62	0.03, 21.29	5.78, 31.64	3.71, 38.83

Abbreviations: BTKi = Bruton tyrosine kinase inhibitor; NE = not evaluable.

The sponsor provided also updated analyses of the primary analysis population (5 May 2023 data cutoff date, Table 9).

Table 9. Efficacy endpoints-primary analysis set-data cutoff date: 05 May 2023

	July 2022	**May 2023**
Overall Response Rate		
% (n/N)	56.7% (51/90)	56.7% (51/90)
95% Confidence Interval	45.8%, 67.1%	45.8%, 67.1%
Duration of Response, months		
Median	17.61	17.74
95% Confidence Interval	7.46, 27.24	7.46, 27.24
Follow-Up, months		
Median	12.68	20.11
Interquartile Range	5.78, 25.82	5.78, 31.34

Abbreviations: n = number of participants in the specified category; N = number of participants.

Furthermore, the sponsor provided updated data on the 7 patients who had previously been treated with brexucabtagene autololeucel (Table 10).

Table 10. Outcomes for patients treated with pirtobrutinib after a prior line of CAR-T therapy

Patient	**Number of Lines of Prior Systemic Therapy**	**Time on Pirtobrutinib Treatment (months)**	**BoR**	**DoR (months)**	**PFS (months)**	**OS (months)**
Brexucabtagene Autololeucel (Tecarctus)						
1	5	21.5	CR	17.6+	19.3+	21.5+
2	5	18.2	CR	14.7+	16.6+	18.2+
3	4	3.5	PD	NA	1.8	5.0
4	4	9.0	SD	NA	5.6	18.2+
5	5	1.0	SD	NA	1.0+	4.7
6	4	0.3	PD	NA	0.3	5.8
7	5	1.1	Other NEs	NA	0.0+	1.5+
CAR-T Product Not Specified						
8	7	3.3	PR	1.3+	3.0+	6.3
9	5	1.5	Other NEs	NA	0.0+	1.6+
Axicabtagene Ciloleucel						
10	4	12.4	PR	9.2	13.3	13.3
11	8	5.5	SD	NA	5.3	28.2+
Lisocabtagene Maraleucel						
12	6	6.0	PR	1.9+	3.7+	32.0+
13	6	3.5	PD	NA	1.9	4.3

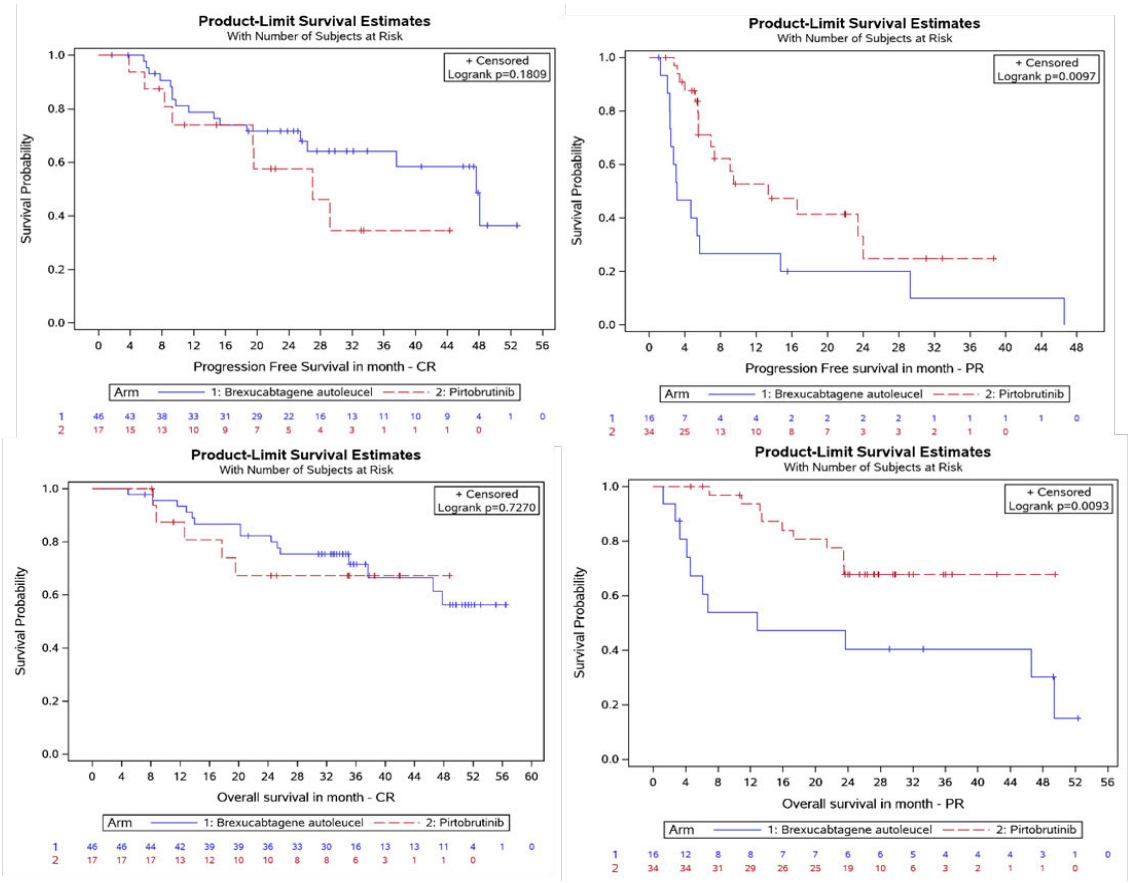
Abbreviations: + = alive without documented PD at time of data cutoff; BoR = best overall response; CAR-T = chimeric antigen receptor therapy; CR = complete response; DoR = duration of response; NA = not applicable; NE = not evaluable; PD = progressive disease; PFS = progression-free survival; OS = overall survival; SD = stable disease.

Ground 2: *Pirtobrutinib delivers significant therapeutic benefit by offering a major contribution to patient care*

The sponsor argued that pirtobrutinib offers an alternate efficacy and superior safety profile to brexucabtagene autololeucel that reflects a similar benefit-risk profile to brexucabtagene autololeucel. In significant contrast to brexucabtagene autololeucel, pirtobrutinib offers an oral, non-hospital self-administered treatment that can be initiated immediately upon diagnosis. Pirtobrutinib, through ease of oral administration, provides a major contribution to the care of patients with MCL that cannot be addressed by brexucabtagene autololeucel.

Regarding the claim on alternate efficacy, the sponsor argued on the durability of PR induced by pirtobrutinib (ORR 56.7%, CR 18.9%; 37.8 PR) which contrasts to a very short duration of partial response induced by brexucabtagene autololeucel (ORR was 91%, including 68% of patients with an observed CR and 24% with an observed PR) which is also associated with prolonged survival. There is also a scientific rationale for the difference of the prognosis of a partial response for an immune-mediated treatment (non-recognised clones continue to grow) vs a signalling interfering agent (not sufficient to eliminate bulk tumour).

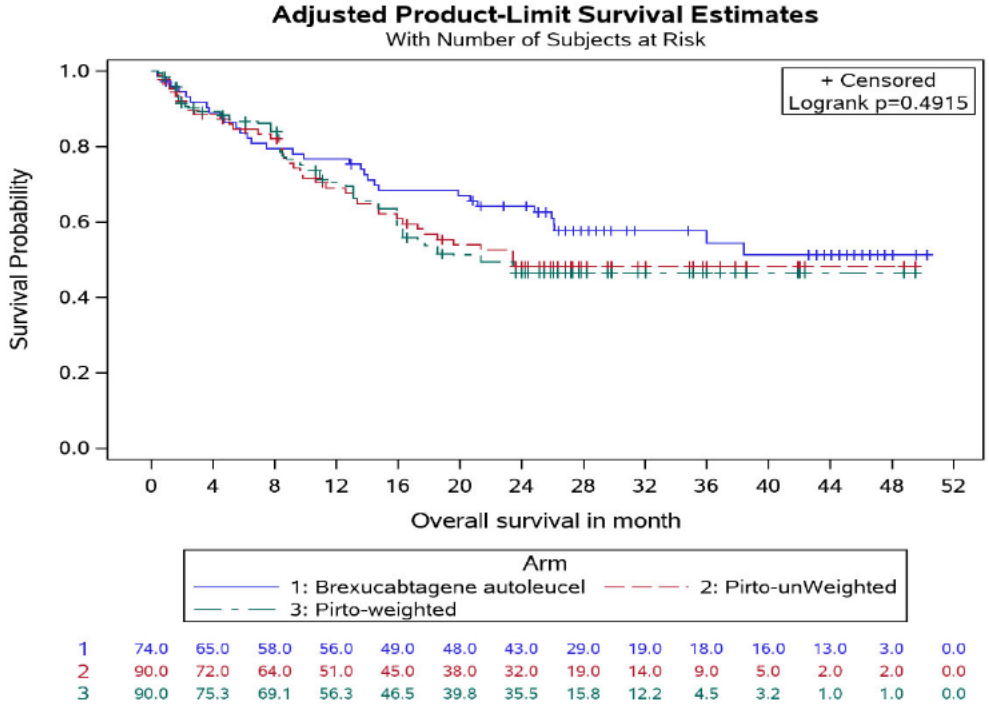
Figure 2. KM plots for progression-free survival and overall survival of patients with CR and PR. Indirect, unadjusted comparison of brexucabtagene autololeucel to pirtobrutinib



A: KM plots progression-free survival of patients with R/R MCL who achieved CR and were treated with pirtobrutinib or brexucabtagene autololeucel.B: KM plots progression-free survival of patients with R/R MCL who achieved PR and were treated with pirtobrutinib or brexucabtagene autololeucel.C: KM plots for overall survival of patients with R/R MCL who achieved CR and were treated with pirtobrutinib or brexucabtagene autololeucel.
D: KM plots for overall survival of patients with R/R MCL who achieved PR and were treated with pirtobrutinib or brexucabtagene autololeucel.
Abbreviations: CR = complete response; KM = Kaplan-Meier; MCL = mantle cell lymphoma; PR = partial response; R/R = relapsed/refractory.

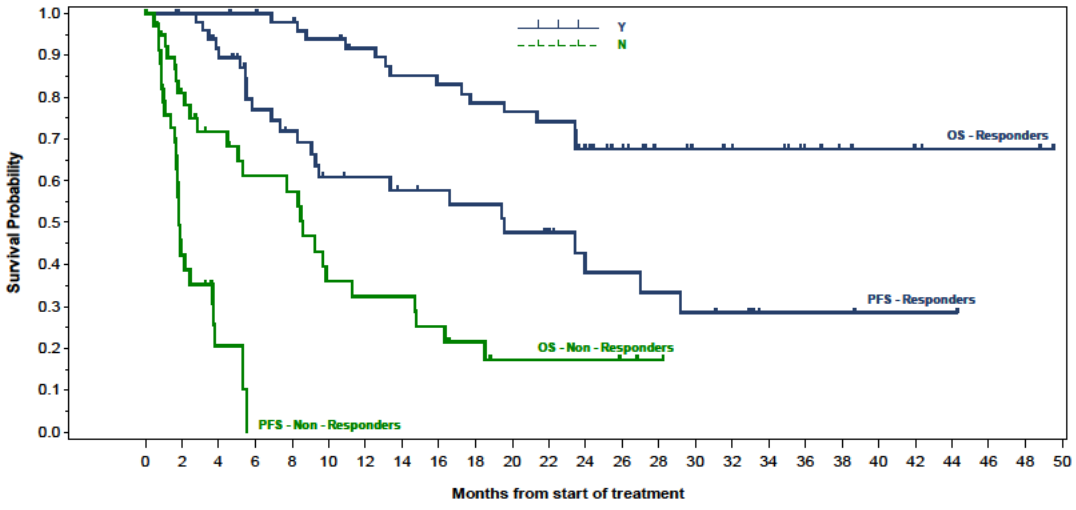
In addition, an unanchored MAIC of brexucabtagene autololeucel OS in the ZUMA-2 trial to pirtobrutinib OS in Study 18001 was presented (Figure 3).

Figure 3. MAIC of overall survival



Furthermore, the sponsor highlighted the impact on OS of the high number of patients who progressed rapidly following their inclusion into the trial (Figure 4).

Figure 4. PFS and OS of pirtobrutinib-treated patients (PAS) with CR, PR (responders) and patients with SD, PD, NE (non-responders)



Abbreviations: CR = complete response; NE = not evaluable; OS = overall survival; PAS = Primary Analysis Set; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

Regarding the more favourable safety profile of pirtobrutinib compared to brexucabtagene autololeucel the sponsor presented a comparison of the safety profiles observed in MCL clinical trials of pirtobrutinib (n = 166 Study 18001 treated) and brexucabtagene autololeucel (n = 68 ZUMA-2 treated) (Tables 11 and 12).

Table 11. Summary of Adverse Events for Study 18001 and ZUMA-2

AE Category, n (%)	**Pirtobrutinib Study 18001 (N = 166)**	**Brexucabtagene Autololeucel ZUMA-2 (N = 68)**
Any AE	151 (91%)	68 (100%)
All Grade ≥3	82 (49.4)	67 (99%)
All SAE	62 (37.3)	46 (68%)
All fatal events due to an AE	11 (6.6)[a]	2 (3%)
Treatment discontinuation due to an AE	9.6%	NA

Abbreviations: AE = adverse event; n = number of participants in the specific category; N = number of participants;
NA = not applicable; SAE = serious adverse event.

a Fatal AEs not related to pirtobrutinib.

Table 12. Summary of Major Safety Risks for Study 18001 and ZUMA-2

PT, n (%)	**Pirtobrutinib (N = 166)**		**Brexucabtagene autololeucel (N = 68)**	
	Any	Grade ≥3	Any	Grade ≥3
CRS	0	0	62 (91%)	10 (15%)
Neurologic toxicity	44 (26.5)	NA	43 (63%)	21 (31%)
Encephalopathy	0		21 (31%)	13 (19%)
Cytopenia				
Neutropenia	26 (15.7)	25 (15.1)	59 (87%)	58 (85%)
Febrile neutropenia	2 (1.2)	2 (1.2)	5 (7.35%)	5 (7.35%)
Thrombocytopenia	30 (18.1)	16 (9.6)	50 (74%)	35 (51%)
Infection[a]	67 (40.4)	32 (19%)	38 (56%)	32%
Opportunistic infections				
CMV infection	0	0	2 (3%)	0
Herpes Zoster	4 (2.4)	1 (0.6)	3 (4%)	0
Oral candidiasis	0	0	4 (6%)	0

Abbreviations: CMV = cytomegalovirus; CRS = cytokine release syndrome; n = number of participants in the specific category; N = number of participants; NA = not available; PT = preferred term.

a Occurring in at least 2 patients.

The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 5 September 2023.

7. Scientific Advisory Group consultation of 30 August 2023

1. **The SAG is invited to comment on the following grounds for negative opinion on the orphan medicinal product designation:**

   – **A descriptive side-by-side comparison of the efficacy outcomes from the pivotal studies for Jaypirca and Tecartus suggested inferior efficacy of Jaypirca in comparison to Tecartus.**

Both trials are small non-randomized controlled trials, and any conclusions are difficult from such indirect comparison. In particular, it is difficult to ascertain whether the populations are comparable. Furthermore, patient selection and delays prior to CAR-T treatment start may favor CAR-T group in indirect comparisons from start of treatment due to the long lead time to receive treatment. Thus, the apparent suggested inferior efficacy cannot be confirmed.

The suggested inferior efficacy of Jaypirca in comparison to Tecartus remains an interesting clinical question that is open and warrants further investigation.

On a different note, CAR-T treatment is a good option with frequent long remissions in patients with mantle-cell lymphoma who are eligible for treatment, but the treatment is complex and severe toxicity is frequent. About 40% to 50% are not eligible for CAR-T therapy mainly due to disease and patient characteristics based on current practice (see below). There is currently an unmet medical need in this population as there are few established options with limited activity.

   – **The efficacy data with Jaypirca in individual patients who have progressed or relapsed after prior treatment with Tecartus before study entry were considered inconclusive in view of the low number of patients in this subset who responded to Jaypirca and the limited follow-up time in these patients, so that the clinical relevance of the responses observed could not be established (data cut-off July 2022).**

The SAG agreed that it is difficult to draw strong conclusions about the objective response rate in the data in patients whose disease progressed after CAR-T therapy, due to the small data set. However, responses were observed, and the results should be confirmed in a larger data set with sufficient follow-up to assess duration of response.

   – **The efficacy results with Jaypirca from the subgroup analysis in selected patients considered potentially ineligible for treatment with Tecartus were not taken into consideration because a) none of the sponsor-defined ineligibility criteria are reflected in the therapeutic indication wording of Tecartus and b) none of these ineligibility criteria are contraindications for the treatment with Tecartus. Furthermore, there are currently no published consensus guidelines defining specific (in)eligibility criteria for CAR-T cell therapy.**

The SAG considered that there is a clear unmet medical need in the population of patients that are not eligible for CAR-T therapy, and that the activity of Jaypirca consisting of high durable objective response rate in patients not eligible for CAR-T therapy is of high clinical importance given the limited available options.

- The population of patients with mainly rapid progression, important co-morbidities, older age (>80), is currently not indicated for CAR-T treatment and corresponds to about 40%-50% of patients based on current practice, despite these options being available. Although published international guidelines are currently lacking, there is a wide consensus based on expert opinion

and published series, fully acknowledging that the field of optimising CAR-T treatment continues to progress.

- Available alternative treatment options that are established consist of lenalidomide and temsirolimus and the activity is considered to be less than 20%-25% objective response rate.
- The available data for Jaypirca (study 18001) indicate a much higher activity in terms of durable objective response rate (ORR: 56.7%; median duration of response: 17.6 months), compared to available established options.
- The activity has been observed consistently across different subgroups and it is reasonable to assume it will apply to the population of patients not eligible for CAR-T therapy. The activity is of such magnitude that it is likely that it will translate in a favourable effect in terms of clinical endpoints such as progression-free survival, health-related quality of life (QOL), and possibly overall survival. QOL data presented at the meeting looked promising in this respect.
- The safety profile is considered acceptable in this setting, where patients ineligible for CAR-T therapy may be of older age and have multiple co-morbidities, not to mention the convenience of oral treatment.
- In summary, Jaypirca is a clinically important therapeutic option in patients not eligible for CAR-T therapy, and the benefits of Jaypirca against available treatment are high activity, oral administration, and acceptable toxicity. Given the magnitude of effects, the differences compared to available established treatments are clear.

2. **Are there patients who are refractory to or relapse after Bruton's tyrosine kinase (BTK) treatment that would not be eligible to be treated with conditioning and Tecartus in clinical practice, despite these options being available? Please describe the extent and characteristics of such patient population. Please also describe the benefits of pirtobrutinib against available treatment options in this population, also taking into account the toxicity profile of other treatment options and the impact of partial response on overall outcome.**

The SAG considered that there is a clear unmet medical need in the population of patients that are not eligible for CAR-T therapy, and that the activity of Jaypirca consisting of high durable objective responses in patients not eligible for CAR-T therapy is of high clinical importance given the current limited use of CAR-T therapy (see answer to the previous question).

8. Comments on the grounds of appeal

COMP position on Ground #1

The COMP took note of the sponsor's argument that Jaypirca (pirtobrutinib) is intended to treat adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) who have previously been treated with a BTK inhibitor. Ibrutinib is the only BTK inhibitor which is authorised in the EU for the treatment of MCL patients; it should be noted that ibrutinib is authorised in the EU only in the r/r setting. This means that no BTK inhibitor (including ibrutinib) is authorised in the EU for use as first-line treatment in MCL patients.

In view of the fact that treatment for MCL patients with a BTK inhibitor is authorised in the EU as a second line treatment, and in view of the fact that Jaypirca is authorised in the EU for use after (failed) treatment with a BTK inhibitor, this would qualify Jaypirca as a third line treatment for MCL patients.

For completeness, Tecartus is also authorised in the EU as a third line treatment for MCL patients.

On balance, Jaypirca and Tecartus are authorised in the EU for the same line of treatment in patients with MCL.

Further to the above, the sponsor's claim that the r/r MCL population after first line BTK treatment may only benefit from Jaypirca, and not from Tecartus, is not valid from a regulatory perspective; and should therefore be rejected.

In addition, the sponsor claimed that Jaypirca (pirtobrutinib) is intended to treat adult patients who have progressed after previous treatment with a BTK inhibitor and Tecartus. In connection to this claim, the COMP assessed all data submitted by the sponsor, including the data after the adoption of the opinion of 17 April 2023 (namely, including data with a cut-off point of 5 May 2023).

The COMP maintained its position that efficacy of Jaypirca could not be established in the subgroup of patients who have progressed or relapsed after prior treatment with Tecartus due to the very limited number of studied patients (7 patients were followed; with only 2 of them having complete responses). The duration of the responses was prolonged by 9 months with the new data cut-off point, but the clinical relevance of the limited responses in this small subgroup remains unclear. In this respect, the COMP agrees with the SAG conclusion "*that it is difficult to draw strong conclusions about the objective response rate in the data in patients whose disease progressed after CAR-T therapy, due to the small data set. However, responses were observed, and the results should be confirmed in a larger data set with sufficient follow-up to assess duration of response*".

On balance, COMP maintains its position that there is no conclusive evidence of a clinically relevant advantage of Jaypirca over Tecartus in the subset of patients that have progressed after treatment with Tecartus due to the limited responses of this small subset of patients.

In relation to the first ground of appeal, the COMP considers that the presented data is not sufficient to establish that Jaypirca offers a clinically relevant advantage in the following two specific subsets: 1) in adult patients with r/r MCL who have previously been treated with a BTK inhibitor in the first line setting; and 2) in patients that are r/r to Tecartus.

COMP position on Ground #2

Under the second ground of appeal, the sponsor essentially claims that Jaypirca offers an alternate efficacy and superior safety profile to that of Tecartus that ultimately results in a similar risk-benefit balance. On the basis of that claim, the sponsor proceeds to claim that Jaypirca should qualify as a

major contribution to patient care on that basis that Jaypirca "*offers an oral, non-hospital self-administered treatment that can be initiated immediately upon diagnosis*".

Regarding the claim of an alternate efficacy profile, the COMP agreed with the SAG that "*available alternative treatment options that are established consist of lenalidomide and temsirolimus and the activity is considered to be less than 20%-25% objective response rate. The available data for Jaypirca (BRUIN study) indicate a much higher activity in terms of durable objective response rate (ORR: 56.7%; median duration of response: 17.6 months), compared to available established options".* However, in the most recent update of ZUMA-2 (Wang et al. 2023), among all the patients who received Tecartus (n = 68), the ORR was 91% with a median duration of response of 28.2 months. The secondary endpoint, duration of response, is also considered of importance, in order to confirm the clinical benefit of a response rate.

The COMP took note of the sponsor's argument regarding the difference between Jaypirca and Tecartus in terms of partial responses (37.8% versus 24% respectively) and the impact of partial responses on PFS and OS. However, the COMP considered the primary efficacy endpoint of overall response rate (for the studies submitted for both Tecartus and Jaypirca) as the most relevant and highlighted the considerable difference between Jaypirca and Tecartus in that respect (56.7% versus 91%, respectively). This difference was driven by the much higher proportion of patients on Tecartus with complete responses (68% versus 18.9 % in Tecartus and Jaypirca, respectively). The single arm design of the pivotal studies and the lack of a comparator leads in uncertainties especially in relation to interpretation of time to event endpoints such as PFS and OS.

The sponsor also provided MAIC analyses on OS. However, the effective sample size after weighting is 44.2 (approximately 50%). In addition, the 95% CIs of the hazard ratios from the MAIC analysis comparing pirtobrutinib to brexucabtagene autololeucel did not demonstrate a statistically significant difference; the hazard ratios and 95% CIs are 1.29 (0.809, 2.057) for the unweighted pirtobrutinib group and 1.35 (0.777, 2.340) for the weighted pirtobrutinib group.

Regarding the claim of a superior safety profile of Jaypirca over Tecartus, this cannot be established due to the limitations of the submitted data. In particular, the submitted data comes from a small single-arm study, with limited follow-up, and cannot substantiate in any conclusive way the claimed better safety of Jaypirca over Tecartus, also in view of the major difference in their respective treatment schedules (continuous vs unique administration).

During the SAG meeting and at the oral explanation, the sponsor argued that Jaypirca will address an unmet medical need in patients with rapid disease progression as it is an "off-the-shelf" medicinal product for immediate administration. The COMP took note of these arguments but highlighted that there are no specific criteria at present which would allow to predefine a specific patient population not benefiting from CAR-T cell therapy but benefitting instead from Jaypirca; and that choice of treatment is at the individual discretion of the treating physician. In addition, as it is mentioned above, the efficacy of Jaypirca in patients with rapid disease progression and/or who cannot receive CAR-T cell therapy has not been demonstrated.

The responder analysis also showed that early progression occurred in the BRUIN study in a relevant subgroup of patients.

The sponsor was asked to provide more data on patients with rapidly progressing disease in their pivotal trial; however, this data was not presented before and during the oral explanation at the COMP. Currently, no robust data on the efficacy of Jaypirca as bridging therapy to CAR-T or allogeneic SCT are available. In addition, it is not known whether the activity of Jaypirca as observed in the phase 1/2 trial (including the durable responses in 2 patients failing CAR-T therapy) can be extrapolated to the

subgroup of patients considered ineligible for CAR-T treatment either due to unfavourable baseline or disease characteristics.

The COMP agreed with the SAG that "*the activity has been observed consistently across different subgroups and it is reasonable to assume it will apply to the population of patients not eligible for CAR-T therapy"*. However, this argument cannot be taken into consideration as none of the factors identified to representing ineligibility for CAR-T cell therapy are contraindications for this class of products and, as also recognised by the sponsor and the SAG, that eligibility criteria for CAR-Ts therapy are still developing and *published international guidelines are currently lacking*.

During the SAG and at the oral explanation, the sponsor also provided an analysis of QoL data in MCL patients in which QoL appears to have been maintained over time. The COMP agreed with the SAG that "*the data looked promising"* but highlighted the limitations of an unblinded assessment in a single-arm study.

However, it should be recalled that a claim of major contribution to patient care may only be assessed once the equivalence of the candidate orphan product and the authorised product under comparison has been established in terms of efficacy, safety and benefit/risk balance. To that effect, reference is made to the "Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products" (available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN).

On balance, the COMP considers that the presented data is insufficient to establish that Jaypirca has equivalent efficacy (and risk-benefit balance) when compared with Tecartus. In the absence of such demonstration, it is not possible to accept a claim of major contribution to patient care.

Based on the above, and after taking note of the SAG advice, the COMP considered that for the purpose of the European orphan designation, the arguments presented were not sufficient to establish the existence of a significant benefit of Jaypirca over Tecartus.

In relation to the first and second grounds of appeal, the COMP considers that the presented data is not sufficiently robust to conclude that Jaypirca provides a clinically relevant advantage or a major contribution to patient care for any (subsets of) r/r MCL patients vis-à-vis the authorised CAR-T cell product Tecartus.

9. COMP final position on review of criteria for orphan designation adopted on 7 September 2023

Based on the assessment of the detailed grounds for appeal and the argumentations presented by the sponsor during the oral explanation, 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 mantle cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, fatigue, and weight loss in the untreated state;
- in the context of the first opinion, the COMP concluded that the data the sponsor's claim that pirtobrutinib (Jaypirca) is of significant benefit to those affected by the orphan condition does not hold since the sponsor could only establish the existence of a clinically relevant advantage over two of the authorised satisfactory methods of treatment, specifically lenalidomide (Revlimid and generics) and temsirolimus (Torisel), but not over the third authorised satisfactory method brexucabtagene autololeucel (Tecartus).

  Clinical study data showed improved and sustained overall responses with Jaypirca as compared to lenalidomide and temsirolimus and a clinically meaningful benefit in a subgroup of patients who have progressed or relapsed after prior treatment with lenalidomide for adult patients with relapsed or refractory mantle cell lymphoma who have been previously treated with a Bruton's tyrosine kinase inhibitor.

  - A descriptive side-by-side comparison of the efficacy outcomes from the pivotal studies for Jaypirca and Tecartus suggested inferior efficacy of Jaypirca in comparison to Tecartus.
  - The efficacy data with Jaypirca in individual patients who have progressed or relapsed after prior treatment with Tecartus before study entry were considered inconclusive in view of the low number of patients in this subset who responded to Jaypirca and the limited follow-up time in these patients, so that the clinical relevance of the responses observed could not be established.
  - The efficacy results with Jaypirca from the subgroup analysis in selected patients considered potentially ineligible for treatment with Tecartus were not taken into consideration because a) none of the sponsor-defined ineligibility criteria are reflected in the therapeutic indication wording of Tecartus and b) none of these ineligibility criteria are contraindications for the treatment with Tecartus. Furthermore, there are currently no published consensus guidelines defining specific (in)eligibility criteria for CAR-T cell therapy.

- In the context of the appeal, the sponsor presented evidence and arguments to the COMP to substantiate the claim of the existence of significant benefit of Jaypirca over Tecartus. The appeal comprises two grounds. Under the first ground of appeal, the sponsor claims that Jaypirca offers a clinically relevant advantage to patients who are ineligible for Tecartus or who have progressed after receiving Tecartus. Under the second ground of appeal, the sponsor claims that Jaypirca qualifies as a major contribution to patient care in view of its ease of administration.
- In relation to the first ground of appeal, the COMP considers that the presented data remains insufficient to establish that Jaypirca offers a clinically relevant advantage over Tecartus. In

particular, the sponsor's claim that the population who failed after first line ibrutinib treatment may only benefit from Jaypirca and not from Tecartus, which is specifically authorised in more than 2 prior lines of treatments, is not valid from a regulatory perspective as ibrutinib is currently authorised as second line treatment. In addition, the COMP maintained its position that the efficacy data with Jaypirca in individual patients who have progressed or relapsed after prior treatment with Tecartus before study entry were considered inconclusive in view of the limited number of patients who responded to Jaypirca.

- In relation to the second ground of appeal, the COMP considers that the presented data is insufficient to establish that Jaypirca has equivalent efficacy (and risk-benefit balance) when compared with Tecartus. In the absence of such demonstration, it is not possible to accept a claim of major contribution to patient care.

Therefore, the sponsor has not established that Jaypirca is of significant benefit to those affected by the condition.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data 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 not satisfied.

The COMP recommends that Jaypirca, (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide, pirtobrutinib for treatment of mantle cell lymphoma (EU/3/21/2450) is removed from the Community Register of Orphan Medicinal Products.