EU Risk Management Plan (Version 0.3)

Global Patient Safety
Signatory information is available on request.
Initial EU Risk Management Plan electronically approved by Lilly on date provided below.

Document ID: VV-PVG-107265

EU Risk Management Plan for Pirtobrutinib

RMP version to be assessed as part of the application: 0.3

Data lock point for this RMP: 31 January 2022

Date of final sign off: See cover page

Rationale for submitting an updated RMP: To address the Day 180 questions received from the Committee for Medicinal Products for Human use

Summary of significant changes in this RMP:

- Atrial fibrillation/atrial flutter has been upgraded to important identified risk
- Serious infections have been upgraded to important identified risk
- Second primary malignancies have been separated into two terms:
    - Second primary non-melanoma skin cancer
    - Second primary malignancies other than non-melanoma skin cancer
- Additional Pharmacovigilance activities have been added to characterize the risks of Second primary non-melanoma skin cancer second primary malignancies other than non-melanoma skin cancer

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP

Version number: Not applicable

Approved with procedure: Not applicable

Date of approval (opinion date): Not applicable

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

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Part I: Product Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Pirtobrutinib (LOXO-305; LY3527727)
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing authorisation Applicant	Eli Lilly Netherland B.V.
Medicinal products to which this RMP refers	Pirtobrutinib
Invented name(s) in the European Economic Area (EEA)	Jaypirca
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Pirtobrutinib is a highly selective ATP competitive small molecule inhibitor of the BTK.
	Summary of mode of action: Pirtobrutinib is a small molecule reversible, noncovalent inhibitor of BTK. BTK is a signalling protein of the BCR and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Pirtobrutinib binds to wild-type BTK as well as BTK harbouring C481 mutations leading to inhibition of BTK kinase activity. In nonclinical studies, pirtobrutinib inhibited BTK-mediated B-cell CD69 expression and inhibited malignant B-cell proliferation. Pirtobrutinib showed dose-dependent tumour growth inhibition and induced tumour regression in BTK wild-type and BTK C481S mutant mouse xenograft models.
	Important information about its composition: Empirical formula of pirtobrutinib is $C_{22}H_{21}F_4N_5O_3$. The chemical name is: (*S*)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1*H*-pyrazole-4-carboxamide.
Hyperlink to the Product Information	The proposed PI is provided in the submission for the initial marketing authorisation application (Module 1.3.1).
Indication in the EEA	**Proposed:** 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.
Dosage in the EEA	**Proposed:** The recommended dose is 200 mg orally once daily. Treatment should be continued until disease progression or unacceptable toxicity. Dose interruption is recommended for specific adverse events, depending on the CTCAE grade and associated symptoms.
Pharmaceutical form and strengths	**Proposed:** Pirtobrutinib is provided as 50 mg and 100 mg film-coated tablets

Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = Anatomical Therapeutic Chemical; EU = European Union; INN = International Nonproprietary Names; PI = package insert; RMP = risk management plan; SmPC = summary of medicinal product characteristics.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Mantle Cell Lymphoma

SI.1.1 Incidence

MCL accounts for 2% to 10% of all the cases of NHL in the North America and Western Europe (Sant et al. 2010; Dreyling et al. 2017; Jain and Wang 2019). In the US SEER database (1995 to 2013), the overall age-adjusted incidence of MCL was 1.01 in 100,000 persons per year (Fu et al. 2017). Several population-based studies in Europe (France, UK, Denmark, and Sweden), at various times between 1992 to 2012, reported annual incidence rates ranging from 0.42 to1.27 per 100,000 persons (Andersen et al. 2002; Abrahamsson et al. 2014; Leux et al. 2014; Smith et al. 2015).

Compared to the US and Europe, lower incidence of lymphoid malignancies, particularly mature B-cell NHL, has been reported in Asian countries (Lee et al. 2018; Chihara et al. 2014). According to data from the Singapore Cancer Registry (2008 to 2012), the annual age-standardised incidence of mature B-cell NHL was 8.5 per 100,000 population and MCL accounted for 2.4% of the incident cases (Lim et al. 2015). Similarly, MCL comprised 1.7% of the mature B-cell NHL in Korea (1999 to 2012), with an annual age-standardised incidence of 0.09 per 100,000 (Lee et al. 2018).

SI.1.2 Prevalence

Using data from the Global Cancer Incidence, Mortality and Prevalence, the overall complete prevalence of MCL, which is the proportion of patients alive with MCL, in the EU in 2020 was estimated to be approximately 0.61 per 10,000 people. In the US, the estimated number of patients with MCL was 18,414 in 2020, with the complete prevalence estimate of 0.56 per 10,000 people from the SEER data (1992 to 2016).

SI.1.3 Demographics of the Population in the proposed Indication – [age, gender, racial and/or ethnic Origin] and Risk Factors for the Disease

Age: MCL affects mainly older individuals. According to the US SEER database (2000 to 2013), median age at diagnosis was 67 years (Epperla et al. 2017). A slightly higher median age at diagnosis was reported from 2 European population-based studies: 71 years in Danish and Swedish population (Abrahamsson et al. 2014) and 72 years in French population (Leux et al. 2014).

Gender: Incidence of MCL is higher among men than in women. Age-adjusted incidence (per 100,000 person-years) was 1.58 in men and 0.57 in women in the US SEER database (1995 to 2013) (Fu et al. 2017). A similar gender difference has been reported in European studies, with a male-to-female ratio of 2.5 to 4:1 (Abrahamsson et al. 2014; Leux et al. 2014; Smith et al. 2015; Andersen et al. 2002).

Race/Ethnic origin: Racial/ethnic variation in the MCL incidence has been implied by higher rates in the US and Europe relative to those in Asian countries (Lim et al. 2015, Lee at al., 2018;). However, ethnic differences were also observed in the population within the same geographical regions. For example, in the US, the incidence rate (per 100,000 person-years) of MCL was highest among Whites (0.73), followed by 0.52 in Hispanics, 0.33 in Blacks and 0.29 in Asian/Pacific Islanders (Aschebrook-Kilfoy et al. 2013).

Risk Factors: According to a pooled analysis of 13 case-control studies from Europe, North America and Australia (557 cases and 13766 controls) in 2014, a haematological malignancy among first-degree relatives was associated with a 2-fold increased risk of MCL. The largest analysis, to date, has also reported a protective association with a history of hay fever and a positive association with living on a farm and select occupations characterized by exposure to engine exhausts, organic solvents and polychlorinated biphenyls, or electromagnetic fields. On the contrary, no statistically significant associations with MCL risk were found with autoimmune disorders, tobacco smoking, alcohol intake, body mass index, or ultraviolet radiation (Smedby et al. 2014).

Among genetic factors, *ATM*, *CCND1*, and *TP53* are the most common somatic mutations implicated in the development of MCL (Cheah et al. 2016), whereas no high-impact germline mutations have been identified for MCL or for mature B-cell neoplasms (Sud et al. 2019).

SI.1.4 Main Existing Treatment Options

MCL is a rare and aggressive subtype of NHL. While indolent subtypes of MCL have been characterised, the typical presentation of MCL is usually aggressive and incurable requiring treatment at diagnosis for most patients. Treatment is required for most patients to improve survival and quality of life. Heterogeneous disease behaviour dictates the indications and timing for therapy, although the specific treatment approach is generally the same. Median overall survival at diagnosis is estimated at only 3 to 5 years (Dreyling et al. 2018).

First-line treatment

At diagnosis, patients have a median age of 65 to 70 years, with associated comorbidities, which must be considered for appropriate treatment selection (Kluin-Nelemans et al. 2012). Frontline treatment selection is based on patient characteristics including age, with categorisation of patients as “younger than 65” or “older than 65” as a common key factor influencing treatment selection. More commonly, patients who are younger than 65 years and fit are candidates for intensive CIT approaches, often with SCT consolidation, followed by rituximab maintenance (Lenz et al. 2005; Flinn et al. 2014). In transplant-ineligible patients, commonly due to age and comorbidities, induction CIT followed by rituximab maintenance without transplant is an accepted alternate approach. Ultimately, none of these approaches are considered curative, and relapse is nearly universal. (Lenz et al. 2005; Flinn et al. 2014; Dreyling et al. 2017).

Relapsed and refractory treatment

For relapsed patients with MCL, the goals of treatment are focused on disease control. Standard prognostic features have less impact on treatment selection in this setting. Traditional approaches

to R/R MCL have typically included chemotherapy and CIT regimens; however, the standard of care is moving toward targeted therapies, primarily BTK inhibition.

Stem cell transplantation

Although SCT following multiagent intensive salvage chemotherapy is typically viewed as part of effective salvage for most other aggressive lymphomas, autologous SCT is less effective for MCL when used after relapse than when used to consolidate first remission (Cassaday et al. 2015). As in frontline settings, allogeneic SCT may be administered in relapse. Toxicity may be a limiting factor, thus, autologous and allogeneic SCT for treatment of MCL are complicated by toxicity concerns and are of limited benefit to a selected group of patients.

BTK inhibitors

Interruption of B-cell receptor signalling via BTK inhibition effectively limits cell growth via negative impact on downstream pathways mediated by NF-kB and phospholipase C-γ2 (Merolle et al. 2018). The importance of these pathways in the pathogenesis of MCL led to investigation of the first generation BTK inhibitor ibrutinib in advanced MCL. Patients with a median of 3 prior therapies had an overall response rate of 68%, complete responses in 21% and median duration of response of 17.5 months (Wang et al. 2013; Wang et al. 2015). These data led to the authorisation of ibrutinib for the treatment of relapsed MCL (Imbruvica summary of product characteristics). The BTK inhibitors acalabrutinib and zanubrutinib have recently received marketing authorisation in the US for R/R MCL and have a similar mechanism of action as ibrutinib by covalently inhibiting BTK and demonstrate similar efficacy (Brukinsa® package insert, 2019; Imbruvica® package insert, 2020; Calquence® package insert, 2022).

With these results, ibrutinib is increasingly supplanting other previously approved agents for relapsed MCL as it offers response rates and response durations better than reported with bortezomib (Goy et al. 2009), lenalidomide (Trněný et al. 2016), and temsirolimus (Hess et al. 2009). However, BTK inhibitor therapy is not curative, and patients continue to relapse. Of importance is the discontinuation rates of ibrutinib due to adverse events (AEs) which is reported in up to 25.6% of patients in some studies. Despite the superior benefits of BTK inhibition with ibrutinib over temsirolimus, salvage treatment with BTK inhibitors is still not curative and prospective studies evaluating therapy options specifically in the post-BTK inhibitor setting of relapsed MCL are rare (Dreyling et al. 2016). Available data demonstrate that following progression on BTK inhibitors, the survival of patients with MCL is very poor with median overall survival ranging from only 2.5 to up to 8.4 months (Martin et al. 2016; Cheah et al. 2015; Epperla et al. 2017). Thus, identifying agents that are effective and tolerable remains an unmet need for patients with relapsed MCL, particularly following BTK inhibitor therapy. Besides CAR-T, which has significant limitations as discussed below, currently, no other approved therapies are available specifically for the treatment of patients who have received a prior BTK inhibitor therapy, highlighting the unmet need in this area.

CAR-T

For patients who have failed prior BTK inhibitor the CAR-T cell therapy, Tecartus, has recently been made available for relapsed/refractory, heavily pre-treated MCL patients. Approval is based on a single-arm Phase 2 study, which predominantly enrolled patients who had received prior BTK inhibitor therapy (Tecartus SmPC). Despite an impressive ORR of 93% with CR rate of 67%, CAR-T treatment has associated considerations that limit its utility for many relapsed MCL patients. CAR-T toxicities, including severe cytokine release syndrome occurred in over 90% of patients, with Grade 3 or higher in 15% of patients. Neurologic events, occurred in 63% of patients, with Grade 3 or higher occurring in 31% of patients. Additionally, CAR-T is associated with significant toxicities with Grade ≥3 AEs occurring in 99% of patients (Wang et al. 2020). Prescribing CAR-T therapy requires successful leukapheresis, product manufacture, bridging chemotherapy, and conditioning therapy prior to cell infusion, all of which introduce additional logistical and clinical complexities given the specialised nature of treatment. Limitations due to safety concerns and treatment barriers are significant barriers for the larger population of relapsed MCL patients (Cerrano et al. 2020, Wang et al. 2020).

Bortezomib, lenalidomide and temsirolimus

Agents such as bortezomib (Goy et al. 2009), lenalidomide (Trněný et al. 2016), and temsirolimus (Hess et al. 2009) are less used in the modern era for patients with relapsed disease because of

- lower response rates (versus BTK inhibitors) ranging from 22% with temsirolimus to 40% with lenalidomide
- CRs being less than 10%
- PFS being shorter than 9 months, and
- preference to be combined with chemotherapy when using bortezomib or temsirolimus in first line (Dreyling et al 2017).

Marketing authorisation for these agents were granted in the EU for the treatment of relapsed MCL for lenalidomide in 2007 (Revlimid SmPC) and for temsirolomus in 2007 (Torisel SmPC). No prospectively published efficacy data for these agents are available in the post BTK inhibitor setting of relapsed MCL.

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

MCL results from a malignant transformation of a B lymphocyte in the outer edge of a lymph gastrointestinal (GI) tract. Typically, the first sign of MCL is the enlargement of lymph nodes, followed by digestive tract symptoms (loss of appetite, indigestion, bloating, nausea, and vomiting) and fatigue from anaemia. Approximately half of MCL patients also experience symptoms such as night sweats, fever, and weight loss, commonly referred to as B symptoms (Leukemia and Lymphoma Society, 2014, Wang and Ma 2014).

Although a small set of patients with MCL presents clinical features that do not need immediate treatment, the clinical behaviour of MCL is usually aggressive and most patients (approximately 70%) are diagnosed with advanced disease (Cheah et al. 2016; Fu et al. 2017). According to data from 404 patients with MCL managed at a tertiary hospital in the US (2000 to 2014), 22% (90 of

404) were initially observed, of which 20% (18 of 90) never received therapy and 80% (72 of 90) were subsequently treated. A total of 386 patients eventually received first-line treatment, and 58% (222 of 386) had R/R disease during a median follow-up of 74 months, requiring multiple lines of therapy. Treatment outcome shortened with each successive line of therapy, with the median PFS from 14 months after second line therapy to 3.3 months after 5 or more lines of therapy (Kumar et al. 2019).

Median overall survival of patients with MCL was 52 months in the US SEER database (1995 to 2013) (Fu et al. 2017). Older age was associated with worse survival, with the 5-year relative survival rates decreasing from 75.4% in age <50 years to 67.4% in 50 to 64 years; 56.6% in 65 to 74 years; and 36.2% in ≥ 75 years (Epperla et al. 2017). The MCL international Prognostic Index, formulated by the European MCL Network, is the prognostic model that incorporates age and other independent prognostic factors such as performance status, lactic acid dehydrogenase level and white blood cell count at diagnosis. Based on the MCL international Prognostic Index risk stratification, the median overall survival among patients with advanced MCL was 29 months and 51 months in the high and intermediate risk groups, respectively, and it was not reached in the low-risk group after a median follow-up of 32 months (Hoster et al. 2008; Vose 2017). Even with low-risk MCL, this disease is still considered incurable.

SI.1.6 Important Co-morbidities

- MCL mainly affects the elderly where the overall comorbidity burden is high. In a Swedish national registry-based cohort of MCL patients (2000 to 2014), 44% had at least 1 major comorbid condition at the time of diagnosis and 28% had 2 or more (Gilmelius et al. 2020).
- Table SI.1 summarizes the more common and/or important comorbidities in patients with MCL and expected comedications. Prevalence of comorbid conditions comes from a Swedish cohort of MCL patients (Glimelius et al. 2020), and US administrative claims-based data of MCL patients treated with acalabrutinib (Ryan et al. 2019).

Table SI.1. Comorbidities and Expected Comedications in Patients with MCL

Comorbidity	Prevalence (%) of Comorbid Conditions	Expected Comedications of Comorbidity
Acute myocardial infarction (including acute congestive heart failure)	13.9% [a]; ~11% [b]	Aspirin; Beta blockers; Calcium channel blockers; Diuretics; Digoxin; ACE inhibitors; Angiotensin II receptor blockers; Vasodilators (e.g., hydralazine); Statins
Peripheral vascular disease	3.7% [a]; 9.1% [b]	Antiplatelet agents (for example., aspirin, clopidogrel); Cilostazol; Statins; Anti-hypertensive drugs (for example., beta blockers, ACE inhibitors, angiotensin II receptor blockers); Anti-diabetic agents (e.g., insulin, metformin, sulfonylureas).
Cerebrovascular disease	6.8% [a]; 5.7% [b]	Antiplatelet agents (for example, aspirin, clopidogrel); Anticoagulants; Statins; Anti-hypertensive drugs (for example, beta blockers, ACE inhibitors, angiotensin II receptor blockers); Anti-diabetic agents (for example, insulin, metformin, sulfonylureas).
Pulmonary disease	7.0% [a]; 14.0% [b]	Bronchodilators; Corticosteroids; Theophylline; Phosphodiesterase-4 inhibitors; Leukotriene receptor antagonist (for example, montelukast)
Diabetes mellitus	9.2% [a]; 13.2% [b]	Insulin; Metformin; Sulfonylureas; Meglitinides; Thiazolidinediones; DPP-4 inhibitors; GLP-1 agonists; SGLT2 inhibitors
Atrial fibrillation	6.5% [a]; 12.1% [b]	Beta blockers; Calcium channel blockers; Digoxin; Antiarrhythmic agents (for example quinidine, disopyramide, flecainide, propafenone, amiodarone, dofetilide); ACE inhibitors; Angiotensin II receptor blockers; Anticoagulants
Hypertension	67.8% [b]	ACE inhibitors; Angiotensin II receptor blockers; Beta blockers; Calcium channel blockers; Diuretics; Other anti-hypertensive agents (for example, clonidine, hydralazine)
Coronary artery disease	12.1% [b]	Antiplatelet drugs (for example, aspirin, clopidogrel, ticagrelor); Beta blockers; ACE inhibitors; Angiotensin II receptor blockers; Aldosterone blockers; Nitrates; Statins; Anticoagulants

Abbreviations: ACE = Angiotensin-converting enzyme; DPP-4 = Dipeptidyl peptidase-4; GLP-1 = Glucagon-like peptide-1; MCL = Mantle cell lymphoma; SGLT1 = Sodium-glucose co-transporter-2

[a]Glimelius et al. 2020; [b]Ryan et al. 2019.

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Acute or repeat-dose toxicity

Pirtobrutinib was tested in rats and dogs for up to 3-month treatment duration at dose levels up to 500 mg/kg twice daily. Significant effects observed in repeat-dose studies in rats, dogs, or both consisted of

- lymphoid organ effects, such as decreased size, weight, or cellularity,
- decreases in B lymphocytes and other markers of immune system function,
- mortality in the 28-day dog study at clinically relevant exposure levels, and
- corneal lesions in the 3-month dog study

Effects on lymphoid organs and immune system function are consistent with the clinical safety profile of pirtobrutinib.

Dogs have generally been less tolerant of exposure to pirtobrutinib than humans. The relevance of this finding to human usage is not believed to be significant, as humans have been treated for longer durations than dogs, and pirtobrutinib is well-tolerated in humans at efficacious exposure levels.

Minimal to mild corneal lesions were observed in 2 dogs treated with pirtobrutinib for 3 months at clinically relevant exposure levels. Eye effects were not observed in rats treated for 3 months. It is not clear if this finding will translate to an effect in humans; however, it has not been identified as a risk in humans to date. If it were to translate to a human effect, it would have limited impact on the risk-benefit profile of pirtobrutinib since such lesions are readily detectable in humans and clinically manageable.

Genotoxicity

Pirtobrutinib has been tested in a complete battery of genotoxicity studies. It is an aneugenic genotoxicant based on the finding of predominantly centromere-positive micronuclei in *in vitro* micronucleus studies. However, this is not a significant clinical risk, as exposure levels in the clinic at 200 mg once daily are approximately 12-fold lower than the no effect level for micronucleus formation in a rat micronucleus study. Therefore, at clinical exposures pirtobrutinib is not expected to cause aneugenic genotoxic effects.

Pirtobrutinib was negative in all other genotoxicity studies.

Carcinogenicity

Studies to assess the carcinogenicity of pirtobrutinib have not been conducted.

Reproductive/developmental toxicity

Fertility risks of pirtobrutinib were assessed in repeat-dose toxicity studies. No effects on male or female reproductive organs were observed in any animal study. There are no data on the effect of pirtobrutinib on human fertility.

Pirtobrutinib caused embryo-foetal toxicity and malformations in pregnant rats treated during the period of embryogenesis in the absence of significant maternal toxicity. These effects occurred at clinically relevant exposure levels. Female patients of reproductive potential are advised to use effective contraception in accordance with product labelling.

Local tolerance

Local tolerance studies are not warranted or applicable for the oral route of delivery.

Phototoxicity

Pirtobrutinib is not phototoxic.

SII.2 Safety Pharmacology

Minor QTc prolongation was observed at the mid-dose in the 28-day repeat-dose dog study at the end of the study. The increase was minimal and was not considered physiologically important. In contrast, no QTc prolongation was observed at a higher dose level in a Good Laboratory Practice dog cardiovascular safety pharmacology study. Unbound or free human pirtobrutinib C_{max} at 200 mg is approximately 56-fold lower than the hERG IC_{50} measured in an in-vitro hERG study (see Module 2.6.2.4.1). Thus, QTc prolongation is not considered a significant risk to humans.

There were no effects on central nervous system or respiratory safety pharmacology endpoints in repeat-dose toxicology studies.

SII.3 Other Toxicity-Related Information or Data

Other findings in nonclinical studies that were minor, with little relevance to human safety, included:

- bone marrow toxicity in the 28-day dog study,
- GI toxicity in the 28-day dog study,
- lung inflammation in the 28-day dog study,
- decreased red cell mass in rats and dogs, and
- a rat-specific pancreatic effect.

Bone marrow toxicity, GI toxicity, and lung inflammation occurred only in dogs at dose levels that were not tolerated. Decreases in red cell mass were minor, not adverse, and clinically monitorable. The pancreatic effects were consistent with a well-known rat-specific effect that has been documented (Erickson et al 2017; Bhaskaran et al 2018). This effect is not known to translate to a clinical effect. Therefore, the effects listed above are not considered to be a clinical risk.

Table SII.1. Key Safety Findings from Nonclinical Studies and their Relevance to Usage of Pirtobrutinib in Humans

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Lymphoid organ effects, such as decreased size, weight, or cellularity	The nonclinical data indicate that there is a risk for negative effects in lymphoid organs, which may translate to immune suppression. Patients should be advised of the risk of infections and prophylaxis is considered in patients who are at increased risk for opportunistic infections. Based on the grade of infection and whether it occurs with neutropenia, dose adjustment may be required.
Decreases in B lymphocytes and other markers of immune system function	The nonclinical data indicate that there is a risk for immune suppression. Patients should be advised of the risk of infections and prophylaxis is considered in patients who are at increased risk for opportunistic infections. Based on the grade of infection and whether it occurs with neutropenia, dose adjustment may be required.
Mortality in the 28-day dog study at clinically relevant exposure levels	Humans tolerate pirtobrutinib treatment better than dogs; thus, there is no relevance to human usage.
Corneal lesions	The nonclinical data indicate that there is a risk for eye lesions. There were no reported clinical observations of corneal lesions in Study 18001.
Aneugenic genotoxicity	Aneugenic genotoxicity does not occur at clinically relevant exposure levels; thus, there is no relevance to human usage.
Embryofetal toxicity and malformations	The nonclinical data indicate that there is a risk for reproductive and developmental toxicities in women exposed to pirtobrutinib during pregnancy. Women of childbearing potential should be advised to use highly effective contraception according to product labelling.

Module SIII - Clinical Trial Exposure

Table SIII.1. Duration of Exposure

Cumulative for All Cancer Types Studied[a]		
Duration of exposure	**Persons**	**Person-time (months)**
Pirtobrutinib single agent		
1 month (≥1 to ≤30 days)	56	33.12
3 months (≥31 to ≤90 days)	118	225.08
6 months (≥91 to ≤180 days)	124	531.06
>6 months (≥181 days)	427	6240.00
Total	725	7029.26
MCL		
Pirtobrutinib single agent		
1 month (≥1 to ≤30 days)	20	14.29
3 months (≥31 to ≤90 days)	37	70.31
6 months (≥91 to ≤180 days)	40	168.77
>6 months (≥181 days)	67	854.21
Total	164	1107.58

Abbreviations: MCL = Mantle cell lymphoma.

Data Cut-off: 31-Jan-2022

[a] All cancer types include only the B-cell malignancies

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Table SIII.2. Age Group and Gender

Cumulative for All Cancer Types Studied[a]				
Age group	**Persons**		**Person-time (months)**	
Pirtobrutinib single agent				
	Male	**Female**	**Male**	**Female**
<65 years	164	90	1574.37	832.49
≥65 years and <75 years	205	89	1982.39	922.58
≥75 years and <85 years	99	54	969.95	568.41
≥85 years	14	10	99.58	79.47
Total	482	243	4626.30	2402.96
MCL				
Age group	**Persons**		**Person-time (months)**	
Pirtobrutinib single agent				
	Male	**Female**	**Male**	**Female**
<65 years	37	10	279.03	53.88
≥65 years and <75 years	54	16	383.44	69.16
≥75 years and <85 years	30	9	191.34	81.02
≥85 years	7	1	48.46	1.25
Total	128	36	902.28	205.31

Abbreviations: MCL = Mantle cell lymphoma

Data Cut-off: 31-Jan-2022

[a] All cancer types include only the B-cell malignancies

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Table SIII.3. Dose

Cumulative for All Cancer Types Studied[a]		
Dose of exposure	**Patients**	**Person-time (months)**
Pirtobrutinib single agent		
Phase 1 dose escalation and expansion[b]		
25 mg QD	5	115.15
50 mg QD	6	150.74
100 mg QD	9	146.53
150 mg QD	20	296.15
200 mg QD	113	1595.53
250 mg QD	25	360.77
300 mg QD	20	278.64
Phase 2[b]		
200 mg QD	527	4085.75
Total	725	7029.26
MCL		
Pirtobrutinib single agent		
Phase 1 dose escalation and expansion[b]		
25 mg QD	3	64.49
50 mg QD	0	0
100 mg QD	3	33.31
150 mg QD	1	1.84
200 mg QD	24	323.78
250 mg QD	3	31.67
300 mg QD	6	59.27
Phase 2[b]		
200 mg QD	124	593.22
Total	164	1107.58

Abbreviations: MCL = Mantle cell lymphoma; QD = once daily.

Data Cut-off: 31-Jan-2022

a All cancer types include only the B-cell malignancies

b Patients are summarised based on the planned starting dose.

Source: /lillyce/prd/ly3527727/j2n_ox_jzna/intrm2/output/shared/03212022/t_exdurdos.rtf
/lillyce/prd/ly3527727/j2n_ox_jzna/intrm2/output/shared/03212022/t_exdurdosdis.rtf

Table SIII.4. Ethnic Origin

Cumulative for All Cancer Types Studied[a]		
Ethnic/racial origin	**Persons**	**Person-time (months)**
Pirtobrutinib single agent		
White	628	6234.41
Black or African American	22	215.89
Asian	42	254.89
American Indian or Alaska Native	3	4.21
Native Hawaiian or Other Pacific Islander	3	27.99
Unknown	1	24.31
Other	26	267.53
Total	725	7029.26
MCL		
Pirtobrutinib single agent		
White	129	877.60
Black or African American	3	9.03
Asian	20	129.41
American Indian or Alaska Native	2	2.50
Native Hawaiian or Other Pacific Islander	0	0
Unknown	0	0
Other	10	89.03
Total	164	1107.58

Abbreviations: MCL = mantle cell lymphoma.

Data Cut-off: 31-Jan-2022

a All cancer types include only B-cell malignancies

Source: /lillyce/prd/ly3527727/j2n_ox_jzna/intrm2/output/shared/03212022/t_exdurrace.rtf
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Module SIV - Populations Not Studied in Clinical Trials

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

In the pirtobrutinib clinical development programme, the primary population studied comprised patients with histologically confirmed B-cell malignancies failed or intolerant to either at least 2 prior standard of care regimens given in combination or sequentially, or who have received 1 prior BTK inhibitor-containing regimen when a BTK inhibitor was utilised as first-line therapy. Key exclusion criteria were intended to ensure safety and minimise risk in a research setting.

Specific and relevant exclusion criteria that are important to pirtobrutinib are addressed below.

Criterion: Patient is pregnant or a lactating woman

Reason for exclusion: Pirtobrutinib caused embryo foetal toxicity and malformations in pregnant rats treated during the period of embryogenesis in the absence of significant maternal toxicity. These effects occurred at clinically relevant exposure, therefore, risks to new-borns or infants cannot be excluded. It is unknown whether pirtobrutinib is excreted in human milk.

Is it considered to be included as missing information? No

Rationale: Labelling information will clearly indicate that women of childbearing potential should use highly effective contraception during treatment with pirtobrutinib and for 5 weeks after the last dose. In addition, patients will be instructed through labelling that they should not breastfeed during treatment with pirtobrutinib and for 1 week after the last dose.

Criterion: Patients with significant cardiovascular disease

Reason for exclusion: As a class, BTK inhibitors have exhibited cardiotoxic AEs. To mitigate this known class risks, patients meeting the following criteria were excluded from Study LOXO-BTK-18001 (18001):

- unstable angina
- history of myocardial infarction within 6 months prior to planned start of pirtobrutinib
- previously documented left ventricular ejection fraction (LVEF) by any method of not more than 45% in the 12 months prior to planned start of pirtobrutinib; assessment of LVEF via echocardiogram or multigated acquisition (MUGA) scan during Screening should be performed in selected patients as medically indicated
- any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification
- uncontrolled or symptomatic arrhythmias, or
- prolongation of the QT interval corrected for heart rate (QTcF).

Additionally, electrocardiograms (ECGs) were required to be administered at regular intervals to detect any potential cardiac issues.

Is it considered to be included as missing information? No

Rationale: Patients with significant cardiac diseases were excluded from Study 18001 as per the exclusion criteria; however, patients presenting with other subtypes and severities of cardiac conditions were allowed in the study. In the overall monotherapy safety analysis set (OMTSAS) population, 184 (25.4%) patients had history of cardiovascular disease. The most common conditions were atrial fibrillation (11.3%) and coronary artery disease (4.3%).

A comparison of incidence of cardiovascular events in patients with underlying cardiac disease (n=184) against all patients in OMTSAS (n=725) showed a significant numerical imbalance in the incidence of atrial fibrillation: 6.5% in patients with underlying cardiac disease and 2.3% in the OMTSAS.

The risk of atrial fibrillation and atrial flutter in patients with cardiovascular conditions is recognised and a warning statement is included in the Summary of Product Characteristics (SmPC). The following is mentioned in Section 4.4 of SmPC:

Atrial fibrillation and atrial flutter have been observed in patients treated with pirtobrutinib, particularly in patients with a history of atrial fibrillation and/or multiple cardiovascular comorbidities. Monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an electrocardiogram as medically indicated. Based on the grade of atrial fibrillation/atrial flutter, dose interruption may be required (see section 4.2).

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

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

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

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	Patients with severe hepatic impairment were excluded from entering Study 18001. In a population pharmacokinetic analysis of patients enrolled in the Study 18001, mild hepatic impairment (per NCI criteria) had no effect on the exposure of pirtobrutinib. Data from the clinical pharmacology Study LOXO-BTK-20012, in participants with mild, moderate, and severe hepatic impairment, systemic exposure of pirtobrutinib was similar between subjects with mild hepatic impairment and normal hepatic function and was approximately 15% and 21% lower in subjects with moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. Hepatic function has no effect on the C_{max} of pirtobrutinib. No adjustment of the dose of pirtobrutinib is required for patients with mild to severe hepatic impairment. Patients with severe renal impairment and patients on dialysis were excluded from entering Study 18001. Data from the clinical pharmacology study in patients with severe renal impairment (eGFR <30 mL/min) did not show clinically meaningful differences in exposure. In a population pharmacokinetic analysis of patients enrolled in Study 18001, mild (60 mL/min /1.73m^2≤ eGFR<90 mL/min/1.73m^2) and moderate (30 mL/min /1.73m^2≤ eGFR <60 mL/min/1.73m^2) renal impairment had no effect on the exposure of pirtobrutinib.
Patients with relevant comorbidities: • Patients with clinically significant, uncontrolled cardiovascular disease • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme

Population with relevant different ethnic origin	No restrictions concerning ethnic origin was outlined in the clinical protocol. The distribution of patients according to race can be found in Table SIII.4. Although the number of Asian and Black/African American enrolled in Study 18001 are limited (42 and 22 patients, respectively), no clinically significant differences were observed in relation to overall incidence of TEAEs, TEAEs leading to dose reduction or treatment discontinuation in these populations when compared to the white patient population (n = 628). Of note, no fatal TEAE were reported in the Asian or Black/African American population.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

No significant exposure information is available yet.

SV.1.1 Method Used to Calculate Exposure

Not applicable

SV.1.2 Exposure

Not applicable

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Pirtobrutinib has not been studied systematically in humans for its potential for abuse, tolerance, or physical dependence. While the current clinical trial programme did not reveal any tendency for any drug seeking behaviour, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which an anticancer drug will be misused, diverted, and/or abused once marketed. If stolen, like any drug, pirtobrutinib has a potential for misuse.

Module SVII - Identified and Potential Risks

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

The primary safety analysis set of Study 18001 is the OMTSAS (n = 725) and includes patients with CLL/SLL, MCL and other NHL (including diffuse large B-cell lymphoma, marginal zone lymphoma, Richter´s Transformation, follicular lymphoma and Waldenstrom's macroglobulinemia), who received at least 1 dose of pirtobrutinib as monotherapy, at any dose level, as of the data cut-off of 31 January 2022. Separate analyses for the patient populations with MCL (MCL safety analysis set [MSAS]; n = 164) and CLL/SLL (CLL safety analysis set [CSAS]; n = 311) were also performed to investigate whether there were any notable differences in the safety profile of pirtobrutinib in these individual tumour types compared to the OMTSAS. No notable differences in the safety profile of pirtobrutinib between the OMTSAS and MSAS were identified, hence, OMTSAS is the primary analysis set utilised for the determination of pirtobrutinib's risks.

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

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated): fatigue, diarrhoea, contusion, nausea, abdominal pain, headache, arthralgia, petechiae and rash.

These events will be categorised as adverse drug reactions (ADRs) for pirtobrutinib and further included in Section 4.8 of the SmPC.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- **Lymphocytosis**: Lymphocytosis is a recognised effect of treatment with covalent BTK inhibitors and has been observed in patients treated with pirtobrutinib. Lymphocytosis will be included as an ADR for pirtobrutinib and included in Section 4.8 of the SmPC. While lymphocytosis is a known, on-target drug class effect of BTK inhibitor therapy, it is also a manifestation of disease in this patient population. Severe lymphocytosis due to progressive or active disease that could lead to complications such as leukostasis that may have resultant clinical complications (for example cardiopulmonary events) and/or require procedural intervention (for example, leukapheresis), is distinctly separate from lymphocytosis that may result from treatment with BTK inhibitor therapies, including pirtobrutinib. In Study 18001, 35 patients (4.8%) had lymphocytosis (20 patients had events assessed by the investigator as related, 2.8%) with a median time of first onset of 1.86 weeks. The majority of patients (22 patients, 3.0%) had Grades 3/4 events and no Grade 5 events were reported. One patient required dose reduction due to lymphocytosis (0.1%). No patient discontinued from pirtobrutinib due to lymphocytosis.
  At baseline, prior to initiating study drug therapy, history of lymphocytosis or lymphocyte count increased had been reported (OMTSAS: 0.8% and 0.3%, respectively), mainly in CLL patients (CSAS: 1.6% and 0.3%, respectively; MSAS: 0.6% and 0,

respectively). In addition, prior to initiating study treatment, 36.9% of OMTSAS patients had a Grade ≥2 elevated lymphocyte counts based on laboratory tests (257/696 patients assessed). Lymphocytosis is manageable without aggressive intervention and can be resolved despite ongoing therapy, which is reflected in the low-dose reduction rate and absence of events leading to treatment discontinuation. Thus, lymphocytosis is not considered to have a significant impact on the risk-benefit balance.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- Not applicable

Known risks that do not impact the risk-benefit profile:

- **Cytopenia (thrombocytopenia, neutropenia and anaemia):** Thrombocytopenia, neutropenia and anaemia are considered ADRs for pirtobrutinib and addressed in Sections 4.2, 4.4 and 4.8 of the SmPC. AEs of ≥Grades 3 were seen in 6.6% patients for thrombocytopenia, 19.7% for neutropenia and 7.9% for anaemia. Cytopenias are a common part of the disease state and complete blood count monitoring is a known practice for management. Frequent monitoring of haematology laboratory values, together with the implementation of a dose modification strategy when the decreases occurred, allowed the vast majority of patients with cytopenia to stay on study, and discontinuation from study due to cytopenia occurred in only 3 patients (0.4%) due to neutropenia, 1 patient (0.1%) due to anaemia. No patient discontinued due to thrombocytopenia. Of note, at baseline, it is notable that 13.7%, 23.8%, and 19.9% of patients in the OMTSAS had Grade ≥2 decreased laboratory values for ANC, haemoglobin, and platelets, respectively. Cytopenia-related outcomes do not translate into significant impact to the risk-benefit balance of pirtobrutinib, therefore cytopenias will not be considered important risks. Instruction on dose interruption for selected cytopenia-related events are outlined in Section 4.2 of the SmPC.

Other reasons for considering the risks not important:

- Not applicable

Risks reported for other members of this pharmacological class but not considered a risk for pirtobrutinib:

- **Tumour Lysis Syndrome:** Patients with haematologic malignancies are at theoretical risk of disease-associated, as well as treatment-induced TLS. While this is a recognised rare risk of treatment with ibrutinib, it has not been an identified risk with other BTK inhibitor therapies. In Study 18001, 3 patients (0.4%) had TLS, of which 2 had a Grade 3 event and 1 had a Grade 4 event; however, none were considered related by the investigator. Even though 2 patients required dose interruption, no one had to reduce dose or discontinue from pirtobrutinib due to TLS. One case of a fatal TLS event that was assessed as being related to pirtobrutinib was reported in a separate ongoing trial

conducted in China (J2N-MC-JZNJ), not part of the OMTSAS. The event occurred in a patient with follicular lymphoma with a large retroperitoneal tumour as well as multiple lesions throughout their neck, chest, abdomen and pelvis, including lesions encasing large vessels and left kidney/ureter. Approximately 8 hours after the patient received a single dose of 200 mg pirtobrutinib, they developed acute onset of abdominal pain and distension. The patient was subsequently diagnosed with acute onset of oncolytic syndrome, abdominal blood clotting, and haemorrhage. The patient was transferred to the intensive care unit and treated aggressively for electrolyte derangement, haemorrhage, and renal failure but ultimately died. This event does not change the overall safety assessment on the risk of TLS with pirtobrutinib. While TLS is a known risk for all patients receiving anti-cancer therapy, especially in patients with haematologic malignancies and/or large tumour burden, it is not a risk unique to the nature or use of BTK inhibitor therapy specifically. Considering the overall severity of outcomes of TLS seen with pirtobrutinib and the paucity of events, TLS does not have a significant impact on the risk-benefit of pirtobrutinib and will not be considered an important risk.

- **Supraventricular tachyarrhythmias (excluding atrial fibrillation and atrial flutter) and ventricular tachyarrhythmias:**
  There were 21 patients (2.9%) with supraventricular tachyarrhythmias, mainly driven by sinus tachycardia events (2.1%, 15 patients), followed by supraventricular extrasystoles (0.4%, 3 patients) and supraventricular tachycardia (0.4%, 3 patients). All but 4 events were Grades 1/2 (3 unrelated Grade 3 events of sinus tachycardia and 1 unrelated Grade 4 event of supraventricular tachycardia) and none resulted in dose reduction or study drug discontinuation.
  Ventricular tachyarrhythmia is listed as an ADR and as an important identified risk for ibrutinib but is not listed as ADR for the second-generation BTK inhibitors acalabrutinib and zanubrutinib. In Study 18001, there were 5 patients (0.7%) with events of ventricular tachyarrhythmia (ventricular extrasystoles in 4 patients and ventricular arrhythmia in 2 patients), all classified as Grades 1/2 and none resulting in dose interruption, reduction or treatment discontinuation. Among these, only 2 events were deemed related to pirtobrutinib by the investigator: 1 non-serious event of Grade 2 non-specified ventricular arrhythmia and 1 non-serious event of Grade 1 ventricular extrasystole (premature ventricular contraction).
  No QT prolongation signal identified. No patients had a serious adverse event (SAE) of QTcF prolongation. One patient (0.1%) had a QTcF prolonged AE that led to dose interruption, and no QTcF prolongation AEs led to dose reduction or discontinuation. One event of sudden was reported in a patient with significant cardiovascular comorbidities and aggressive disease.
  At this point, there is insufficient evidence to support the classification of supraventricular tachyarrhythmias (excluding atrial fibrillation and atrial flutter) and ventricular tachyarrhythmias as important risks for pirtobrutinib.

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

Important Identified Risk 1: Serious haemorrhage

Risk-Benefit Impact:

Serious haemorrhagic events may be considered to have an impact on the risk-benefit balance of pirtobrutinib, as outcomes can be life-threatening, severely debilitating, or result in clinically relevant sequelae. Such events, defined as ≥Grade 3 haemorrhagic events (excluding bruising-related events), were observed in 2.2% of patients in Study 18001 (16 patients, with 4 [0.6%] considered as related).

Overall, 17.4% of patients reported any grade haemorrhagic events and 2.1% of patients reported any grade SAEs of haemorrhage. No patient had to undergo dose reduction due to serious haemorrhage. One Grade 5 haemorrhagic event was reported, considered not related to pirtobrutinib by the investigator. This event occurred in a patient, treated for MCL, with a prior history of bladder cancer and thrombocytopenia who had an accident and experienced a haemorrhagic event.

It is acknowledged that patients with haematologic malignancies are predisposed to bleeding-related events due to concomitant factors such as thrombocytopenia and deficient platelet aggregation.

Overall, considering the potential significant impact on the risk-benefit of the product and the fact that haemorrhage is a known class effect, serious haemorrhage is considered an important identified risk for pirtobrutinib.

Important Identified Risk 2: Serious infections

Risk-Benefit Impact:

Serious infections may be considered to have an impact on the risk-benefit profile of pirtobrutinib, due to potentially severe clinical outcomes.

Infections were commonly reported among patients treated with pirtobrutinib (47.2%), with majority of the events being Grade 1 or Grade 2 (29.4%) and only 8.7% of patients presenting infections considered related to pirtobrutinib by the investigator. Few discontinuations (2.3%) were reported, and dose was reduced for 2 (0.3%) patients due to infections.

Serious infections, characterised as Grade ≥3 events, were observed in 17.7% of patients (2.8% of patients with events deemed related to pirtobrutinib by the investigator). There were 130 patients (17.9%) with infection-related SAEs (2.5% considered related by the investigator) and 29 patients with fatal events due to infection, of which 3 were considered related to pirtobrutinib by the investigator: *Enterococcus faecium*-related septic shock, COVID-19 pneumonia and pneumonia necrotising.

It is notable that 12.7% of patients reported a TEAE of COVID-19 infection, including 6.5% of patients with SAEs and 2.1% (15 patients) with Grade 5 events, 1 of them was considered related

by the investigator. This is reflective of the COVID-19 pandemic that began during the course of Study 18001. In addition, the overall incidence of severe COVID-19 events was likely impacted by factors such as local COVID-19 case rate, access to treatments, and vaccination rates during the study.

Although the frequency of serious infections in Study 18001 is lower when compared to other BTK inhibitors and patients with B-cell malignancies are predisposed to serious infections, infection is a class label risk with a known mechanism of action and events of infectious nature are described in Section 4.8 of the pirtobrutinib SmPC. Furthermore, infections can lead to potential severe clinical outcomes; therefore, serious infection is considered an important identified risk for pirtobrutinib. This risk will be closely monitored and further characterised in the Phase 3 clinical trials.

Important Identified Risk 3: atrial fibrillation and atrial flutter

Risk-Benefit Impact:

Due to the potentially severe clinical consequences associated with atrial fibrillation and atrial flutter (e.g. shock, cardiac arrest and thromboembolic events), such events have the potential to impact the risk-benefit balance of pirtobrutinib.

Atrial fibrillation and atrial flutter were observed in 2.6% of patients (19 patients: 17 patients with atrial fibrillation and 3 patients with atrial flutter) in Study 18001. The majority of the events were Grades 1/2 (1.6%), and there was a total of 7 patients with Grade ≥ 3 events (1.0%), only 1 considered related by the investigator (0.1%). In addition, 5 patients reported SAEs of atrial fibrillation/atrial flutter (0.7%). No fatal outcomes were reported. No patient had to undergo dose reduction or treatment discontinuation due to atrial fibrillation or atrial flutter. Previous history of atrial fibrillation or atrial flutter was reported in 6 patients and, in addition, 11 patients had relevant comorbidities or other significant risk factors for the occurrence of atrial fibrillation or atrial flutter (for example, hypertension, coronary artery disease, aortic stenosis, acute myocardial infarction, cardiac failure, pacemaker insertion, asymptomatic bradycardia incidents, atrial septal defect/supraventricular tachycardia). Out of the 19 patients, 10 patients had a past medical history of atrial fibrillation (2 patients), concurrent systematic infection (4 patients), or both (4 patients).

Considering that atrial fibrillation and atrial flutter are known adverse reactions for both first and second generation BTKi with suggested mechanism of action and described in Section 4.8 of the pirtobrutinib SmPC, atrial fibrillation and atrial flutter are considered important identified risks and will be further characterised in the Phase 3 clinical trials.

Important Potential Risk 1: second primary non-melanoma skin cancer

Risk-Benefit Impact:

The occurrence of second primary non-melanoma skin cancer has a potential to impact the risk-benefit balance of pirtobrutinib because it can lead to increased morbidity (additional

concomitant oncologic treatment) and potentially serious outcomes depending on the subtype observed.

In Study 18001, 33 patients reported second primary non-melanoma skin cancer (68.8%). The main events were non-melanoma skin cancers in 33 patients (4.6%), with basal cell carcinoma (3.6%, 26 patients) and squamous cell carcinoma (1.4%, 10 patients) being the most common subtypes.

All except 1 were Grades 1 to 2 (4.4% of patients). Only 3 patients had events assessed as related to pirtobrutinib by the investigator (0.4%) and the occurrence of second primary non-melanoma skin cancer did not lead to dose reduction. Two patients discontinued due to second primary non-melanoma skin cancer (0.3%); neither of which was considered related to pirtobrutinib.

It is known that patients with NHL, including MCL and CLL, are at increased risk for the development of second primary malignancy, especially skin cancer, due to immune dysfunction associated with the disease, use of immunosuppressive agents, and DNA damage secondary to prior treatment (Brewer et al. 2013). Non-melanoma skin cancer including basal cell carcinoma and squamous cell carcinoma are the most common type of skin cancer in the general population, with nearly 1.2 million patients newly diagnosed each year globally (Sung et al. 2021). Non-melanoma skin cancer was also the most common second primary malignancy reported with other BTKi drugs: the incidence of second primary malignancy skin cancer (mostly non-melanoma skin cancer) ranged from 4 to 13% for ibrutinib (Imbruvica package insert, 2013), and 6% for acalabrutinib and zanubrutinib (Calquence package insert, 2022; Brukinsa package insert, 2019).

The observed frequency of second primary non-melanoma skin cancer with pirtobrutinib appears to be lower than what has been described with other BTK inhibitors. Second primary-non-melanoma skin cancer is considered an important potential risk for pirtobrutinib.

In order to characterise the risk of second primary malignancy including second primary non-melanoma skin cancer, an integrated analysis of all reports of second primary malignancy in 5 years follow up of clinical trial subjects who received pirtobrutinib 200mg QD as monotherapy supplemented with analysis of postmarketing reports will be conducted. This analysis is included as an additional PV activity for this risk. An interim analysis is planned for submission to EMA by September 2025 and a final report by June 2028 (see Part III.2 Additional Pharmacovigilance Activities).

Important Potential Risk 2: second primary malignancies other than non-melanoma skin cancer

Risk-Benefit Impact:

The occurrence of second primary malignancies other than non-melanoma skin cancer has a potential to impact the risk-benefit balance of pirtobrutinib because it can lead to increased

morbidity (additional concomitant oncologic treatment) and potentially serious outcomes depending on the organ involved, stage of disease, and subtype observed.

In Study 18001, 17 patients reported second primary malignancies other than non-melanoma skin cancer (2.3%). The most frequent events were malignant melanoma in 3 patients (0.4 %) and 2 events each of malignant melanoma in situ, second primary malignancy, and Eight events were reported with higher grade severity of ≥3 (1.1% of patients) and there was no fatal case. Only 2 patients had events assessed as related to pirtobrutinib by the investigator (0.3%), and the occurrence of SPM other than non-melanoma skin cancer did not lead to dose reduction. Two patients discontinued treatment due to SPM (0.3%); neither of which was considered related to pirtobrutinib.

Patients with MCL and CLL might be also at increased risk for the development of secondary malignancy other than non-melanoma skin cancer due to immune dysfunction and DNA damage secondary to prior treatment. In an analysis of the US SEER database, it was observed that 261 out of 3149 patients (8.29%) with MCL as primary cancer developed second primary malignancies, over a median follow-up of 31 months. A statistically significant excess risk for cancers excluding non-melanoma skin cancer, especially other haematological cancers and melanoma, was observed in patients with a primary diagnosis of MCL compared to the expected incidence of second primary malignancy in the general population (Shah and Khanal 2015). Similarly, in the analysis of the US SEER database, second solid cancers occurred in 1820 out of 16367 patients with CLL (11.1%) over the average follow-up of 5.2 years. Kaposi sarcoma, malignant melanoma, and cancers of the larynx and the lung were among the cancers associated with a statistically significant excess among patients with CLL (Hisada et al. 2001). Reported occurrence of second primary malignancies other than non-melanoma skin cancer was between 1% and 4% for ibrutinib (Imbruvica package insert, 2013), 3% for zanubrutinib (Brukinsa package insert, 2019), and 6% for acalabrutinib (Calquence package insert, 2019). The observed frequency of second primary malignancies other than non-melanoma skin cancer with pirtobrutinib appears to be lower than what has been described with other BTK inhibitors. Second primary malignancies other than non-melanoma skin cancer is considered an important potential risk for pirtobrutinib and will be further characterised in the Phase 3 studies.

Additionally, to characterize the risk of second primary malignancy, an integrated analysis of reports of all second primary malignancy in 5 years follow up of clinical trial subjects who received pirtobrutinib 200mg QD as monotherapy supplemented with analysis of postmarketing reports will be conducted. This analysis is included as an additional PV activity for this risk. An interim analysis is planned for submission to EMA by September 2025 and a final report by June 2028 (see Section III.3 Summary Table of Additional Pharmacovigilance Activities).

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

Not applicable as this is the initial RMP

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

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

Important Identified Risk 1: Serious haemorrhage

Potential mechanisms:

Increased bleeding susceptibility has been observed in association with BTK inhibitors. Ibrutinib causes GPVI and integrin αIIbβ3 platelet signalling deficiencies that result in formation of unstable thrombi and may contribute toward the bleeding events observed in patients (Bye et al. 2015). Similar to what was described previously for the atrial fibrillation and atrial flutter risk, patients with X-linked agammaglobulinemia do not present a higher risk of bleeding-related events and this increase in bleeding propensity linked to BTK inhibitors can be attributed to blockage of activation of platelets by BTK, and inhibition of the closely related tec kinase and Src-family kinases (von Hundelshausen and Siess 2021). Although major haemorrhagic events are not frequently seen in patients treated with more selective BTK inhibitors and are likely reflective of off-target inhibitory effects (Nicolson et al. 2018), haemorrhage is characterised as an important identified risk for the authorised BTK inhibitors.

Evidence sources and strength of evidence:

Serious haemorrhagic events have been reported at a low frequency in Study 18001, compatible to that expected from a highly selective BTK inhibitor, but clinically significant events have been observed, including 2.1% of patients with Grade 3 events and 1 fatal event.

Characterisation of the risk:

Bleeding events were reported in 34.3% of patients in Study 18001, which included patients with low-grade bruising events (contusion, petechiae, ecchymosis or increased tendency to bruise events in 23.2% of patients) and haemorrhagic events (17.4% of patients). The most commonly reported haemorrhage-related events were epistaxis (3.7%), haematuria (3.2%) and hematoma (2.1%), while the most common bruising-related events were contusion (19%), petechiae (4.0%) and ecchymosis (1.2%). Serious haemorrhagic events (≥Grade 3) were observed in 2.2% of patients. Overall, dose interruption occurred in 2.2% of patients due to a haemorrhagic event. No patient had to undergo dose reduction and 1 patient discontinued from treatment due to a haemorrhagic event. This event was reported in a patient with Richter's transformation as an unrelated Grade 3 GI haemorrhage. Of note, the patient passed away approximately 2 months after treatment start due to disease progression.

One Grade 5 haemorrhagic event was reported and was considered not related to pirtobrutinib by the investigator. This event occurred in a patient treated for MCL, with a prior history of bladder cancer and thrombocytopenia (baseline platelet count of $41X10^9$/L), and a chronic history of episodes of confusion and amnesia. At the start of Cycle 3, they sustained an accident and died as a result. A large amount of external bleeding was reported, which was presumed to be the

cause of patient death based upon history. No hospital records were found and no autopsy was conducted.

A total of 218 (30.1%) patients in the OMTSAS (including 43 [26.2%] in the MSAS and 97 [31.2%] in the CSAS) were reported to be on antithrombotic concomitant medications. Consistent with the approach used in other BTK inhibitor clinical studies, Study 18001 protocol prohibited the use of vitamin K-dependent anticoagulants, but allowed all other anticoagulants to minimise bleeding risk given the known benefits of direct oral anticoagulant therapies and lower bleeding risk as compared with warfarin (Eikelboom and Merli 2016). Of the 16 of 725 (2.2%) patients who reported Grade ≥3 haemorrhagic events, 11 of 725 (1.5%) had not been on antithrombotic therapy and 5 patients (Grade 3 upper GI haemorrhage in 2 patients and suprapatellar haematoma, post-operative haemorrhage, and subdural hematoma in 1 patient each) had been on antithrombotic therapy:

- 81 mg aspirin daily for cardiac prophylaxis in both patients with upper GI haemorrhage and in the patient with post-operative haemorrhage
- 325 mg aspirin daily for cardiac prophylaxis in the patient with subdural haematoma, and
- apixaban 2.5 mg twice daily for history of atrial fibrillation in the patient with suprapatellar hematoma.

Haematuria has been added as a new ADR in Section 4.8 of SmPC under group ADR term haemorrhage. Following bleeding related ADRs are already included in Section 4.8 of SmPC; haemorrhage (epistaxis and haematoma) and bruising (contusion and petechiae).

Risk factors and risk groups:

Patients presenting with severe thrombocytopenia are at increased risk of serious haemorrhagic events (Neunert et al. 2015). Per Georgantopoulos et al. 2019 and Dmitrieva et al. 2020, other reported risk factors for the occurrence of major haemorrhage in patients with MCL and CLL include

- history of major haemorrhage
- concomitant use of anticoagulants (for example, warfarin, heparin, enoxaparin) and antiplatelets (for example, acetylsalicylic acid, clopidogrel)
- renal disease
- anaemia
- thrombocytopenia, and
- alcohol abuse.

General medical conditions associated with increased propensity for haemorrhagic events include acquired coagulopathies, inherited bleeding dysfunctions, hepatopathy, renal dysfunction (leading to uraemia-induced platelet dysfunction; Boccardo et al. 2004), and connective tissue disorders leading to haematologic abnormalities.

Preventability:

Instructions on monitoring for signs and symptoms of bleeding while on treatment with pirtobrutinib will be provided in Section 4.4 of the SmPC. Patients presenting with severe thrombocytopenia and consequent increased bleeding risk will be treated according to local oncology clinical practice guidance, and treatment may include platelet transfusion and antifibrinolytic agents (Kuter 2015).

Advice on considering the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery depending upon the type of surgery and risk of bleeding is included in Section 4.4 of the SmPC.

Recommendation to consider the benefit-risk of anticoagulant or antiplatelet therapy when co-administered with pirtobrutinib is included in SmPC Section 4.4.

In Section 4.4, a statement on the fact that pirtobrutinib has not been studied with warfarin or other vitamin K antagonists is also included.

Patients presenting with Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia while on treatment with pirtobrutinib may undergo dose interruption, and this guidance is provided in Section 4.2 of the SmPC.

Impact on the risk-benefit balance of the product:

Serious haemorrhagic events can have a significant impact on individual patients, and outcomes can be life-threatening, severely debilitating or result in clinically relevant sequela.

Majority of bleeding-related events observed with pirtobrutinib were low grade, with most cases compatible with bruising (23.2% of patients) and, therefore, less clinically impactful. Section 4.4 of the SmPC provides relevant risk factors for the occurrence of bleeding and advised monitoring for signs and symptoms of bleeding to facilitate prompt diagnosis and management, thus reducing the risk of severe outcomes.

Cases of bleeding-related events of ≥Grade 3 have been observed in 2.2% of patients in Study 18001, including 1 fatal event (0.1%). Due to the occurrence of severe haemorrhagic events associated with pirtobrutinib treatment, serious haemorrhage is considered to have an impact on the risk-benefit balance of pirtobrutinib.

Public health impact:

The incidence of serious haemorrhagic events reported in Study 18001 is considered low. In addition, administration of pirtobrutinib is limited to a subset of patients with haematologic malignancies, therefore, the public health impact is estimated to be low.

Important Identified Risk 2: Serious Infections

Potential mechanisms:

BTK is an indispensable component of the B-cell receptor signalling pathway through which it mediates B-cell growth, adhesion, and survival. It utilises pathways involving innate and adaptive immunity. The clinical hallmark of congenital BTK mutations is recurrent bacterial infections in the X-linked agammaglobulinemia syndrome, and there are also reports of

opportunistic infections such as *Pneumocystis jirovecii* as index manifestation (Tillman et al 2018).

The nuclear factor of activated T cells is BTK-dependent and plays a key role in the macrophage inflammatory response to *Aspergillus fumigatus*, initiating antiviral responses and leading to activation of pro-inflammatory cytokines in response to bacterial infections (for example, *pneumococcal pneumonia*; Good et al 2021). Therefore, it is postulated that the BTK inhibition could impair the aforementioned processes and increase the susceptibility to infections.

Evidence sources and strength of evidence:

The occurrence of serious infections has the potential to impact the risk-benefit balance of pirtobrutinib. Grade ≥3 events (17.7% of patients) and fatal cases (29 patients, 4.0%) have been reported, but the causal association with pirtobrutinib is still unclear at this stage.

Infections is a known risk observed with other BTK inhibitors (Teh et al 2018; Estupiñán et al 2021). Nevertheless, sustained increases in serum immunoglobulin A levels induced by ibrutinib and acalabrutinib have also been observed, and this finding has been correlated with a lower risk of developing infections with long-term BTK inhibitor therapy (Byrd et al 2015; Pleyer et al 2020). Particular types of infections (for example, fungal infections) observed with ibrutinib are postulated to be also caused by off-target inhibition of tec protein tyrosine kinase, and this effect is diminished with pirtobrutinib due to its higher selectivity for BTK.

Although the frequency of serious infections in Study 18001 is lower when compared to other BTK inhibitors and patients with B-cell malignancies are predisposed to infections, serious infections are class label risks with a known mechanism of action, described in section 4.8 of the SmPC and have potential for severe clinical outcomes therefore, considered an important identified risk for pirtobrutinib. This risk will be closely monitored and further characterised in the Phase 3 clinical trials.

Characterisation of the risk:

Overall, infection events were commonly reported (47.2%) in patients treated with pirtobrutinib, with majority of the events being Grades 1 or 2 (29.4%) and only 8.7% of patients with infections deemed related to treatment. The most frequently reported infection events were COVID-19 (9.2%), pneumonia (8.7%), upper respiratory tract infection (8.3%), and urinary tract infection (8.0%). Excluding COVID-19-related events, infections were observed in 41.4% of patients and most frequently reported events were pneumonia (8.7%), upper respiratory tract infection (8.3%) and urinary tract infection (8.0%).

Serious infections, characterised as Grade ≥ 3 events, were observed in 17.7% of patients (2.8% with events deemed related to pirtobrutinib by the investigator). The most frequent Grade ≥ 3 events were pneumonia (4.8%), COVID-19 pneumonia (3.7%), COVID-19 (2.3%), sepsis (2.2%) and urinary tract infection (1.4%). Excluding COVID-19-related events, the incidence of serious infections (Grade ≥ 3 events) was 13.1%, with main reported events of pneumonia (4.8%), sepsis (2.2%) and urinary tract infection (1.4%).

Infections were primarily managed through concomitant medications with antivirals and antibacterial agents, the 2 most commonly used concomitant medication classes in Study 18001, and dose interruption in 113 (15.6%) patients. Overall, there were few discontinuations (2.3% of patients) and dose reduction in only 2 patients (0.3%) due to infections. There were 130 patients (17.9%) with infection-related SAEs (2.5% considered related by the investigator), and 29 patients with fatal events due to infection. Among the Grade 5 events, over half of these patients (15/29, 51.7%) had fatal COVID-19-related events.

Three fatal infection events were considered related to pirtobrutinib by the investigator: *Enterococcus faecium*-related septic shock, COVID-19 pneumonia and pneumonia necrotising.

The event of Grade 5 *Enterococcus faecium*-related septic shock occurred in a patient with CLL, within 8 days of the last dose of study drug (on Study Day 23). The patient previously had an AE of Grade 3 Escherichia sepsis that began on Study Day 3, the study treatment was interrupted, the event resolved on Study Day 16 and was not considered to be related to study treatment. The patient had multiple underlying concomitant risk factors; including underlying disease, recent splenectomy prior to enrolment and 11 prior lines of therapy. While the investigator did not deem pirtobrutinib directly causative, the study treatment was believed to be contributory to the event severity.

The other 2 related Grade 5 infection events occurred in the context of COVID-19 infections. The event of bacterial necrotising/cavitary pneumonia occurred concomitantly to a COVID-19 infection, in a patient with Waldenstrom's macroglobulinemia and medical history of hypogammaglobulinemia. The Grade 5 event of COVID-19 lung infection was reported in a patient with CLL, who had been treated with multiple lines of therapy and had not received COVID-19 vaccination. After an internal committee assessment, it was felt that pirtobrutinib could not be ruled out as a potential contributing factor to the COVID-19 lung infection, thus the event was deemed related by investigator.

There were 12.7% of patients who reported a TEAE of COVID-19 infection, including 6.5% of patients with SAEs (47 patients) and 2.1% (15 patients) with Grade 5 events, only 1 was considered related. It is noteworthy to mention that 7 patients who presented with COVID-related Grade 5 events were from 2 sites in the same country and the COVID-19 pandemic status at that time might have had an impact in the occurrence of severe COVID-19 events. Therefore, the risk of a severe COVID-19 infection in the studied population might have been further enhanced by local case rates, access to treatment and the lack of availability of vaccines during the time in which most patients were enrolled in the study. Nevertheless, the proportion of patients with COVID-19 events who died due to those events in the OMTSAS (15 of 92 [16.3%] patients) is lower than those (30% to 34%) reported elsewhere (Roeker et al. 2020). Patients with MCL presented with fewer infection events when compared to patients with CLL (36% versus 61.1%, respectively) and lower rates of Grade 5 infection events (2.4% versus 6.8%). This could in part be explained by the known humoral and cellular immune dysfunction in CLL patients, illustrated in part by a higher prevalence of prior hypogammaglobulinemia (13.8% of patients with CLL, 1.8% of patients with MCL) and secondary immunodeficiency (1.6% of patients with CLL, no patients with MCL) among patients with CLL in Study 18001. The most frequently

reported infection events (excluding COVID-19-related events) of pneumonia, upper respiratory tract infection and urinary tract infection are considered ADRs for pirtobrutinib and will be further included in Section 4.8 of the SmPC.

Risk factors and risk groups:

Identified risk factors for the occurrence of serious infections include neutropenia (with longer duration and severity of neutropenia increasing the risk; Crawford et al 2004), delayed antimicrobial therapy initiation and patient-related factors (for example, age, previous comorbidities, nutritional status, performance status, prior chemotherapy; Nucci and Anaissie 2017; Xiao et al 2020). It has been described that ≥ 3 prior treatments, diabetes and liver disease have been associated with the development of opportunistic infections in patients treated with ibrutinib (Rogers et al 2019).

Preventability:

Antimicrobial prophylaxis can be considered in patients who are at increased risk of opportunistic infections and this is indicated in Section 4.4 of the SmPC (Taplitz et al 2018).

Prompt initiation of antimicrobial therapy in the event of an infection is also advised in order to minimise the risk of serious events (Ramphal 2005; Tang et al 2020). Monitoring neutrophil counts and promptly managing neutropenia reduces the risk of developing serious infections. Dose interruption instructions in the event of Grade 3 neutropenia with fever and/or infection, Grade 4 neutropenia lasting ≥ 7 days or Grade 3 or Grade 4 non-haematologic toxicity is included in Section 4.2 of the SmPC.

Impact on the risk-benefit balance of the product:

Serious infections can have a significant impact on individual patients, as they can be associated with potentially life-threatening outcomes. Fatal infections have been observed in Study 18001, but considering the severity of the treated disease, paucity of alternative treatment options, and known predisposition to infections in patients with haematologic malignancies, the risk is considered to have a low impact on the risk-benefit balance of pirtobrutinib. In addition, considering a significant number of the fatal infection events were driven by COVID-19 infection, it is expected the incidence of such events will go down as vaccination rates rise worldwide, therapeutic interventions become broadly available, and the severity of cases reduces accordingly.

Public health impact:

Considering that serious infections during the treatment with pirtobrutinib have been observed at a lower frequency when compared to other BTK inhibitors, and also the limited patient population exposed to pirtobrutinib, the public health impact is estimated to be low.

Important Identified Risk 3: Atrial Fibrillation/Atrial Flutter

Potential mechanisms:

The exact mechanisms linking atrial fibrillation and atrial flutter to BTK inhibitors is unknown. Patients with X-linked agammaglobulinemia, a primary immunodeficiency disease, characterised by BTK deficiency, secondary to BTK gene mutations, do not have a higher risk of developing atrial fibrillation and atrial flutter, implying that other kinases may be involved in the pathophysiology of such events (Tang et al 2018). This is corroborated by the fact that more selective BTK inhibitors, with reduced off-target activity, present a lower rate of atrial fibrillation and atrial flutter compared to less selective BTK inhibitors, such as ibrutinib (Brukinsa package insert, 2019; Calquence package insert, 2019; Imbruvica package insert, 2020; Brukinsa summary of product characteristics 2019; Calquence summary of product characteristics, 2019; Imbruvica summary of product characteristics, 2020). McMullen et al. 2014 hypothesised that the first generation BTK inhibitor ibrutinib causes atrial fibrillation by inhibition of BTK and related kinases such as tec protein tyrosine kinase, ultimately impacting the protective PI3K–Akt pathway in the heart.

Evidence source(s) and strength of evidence:

Atrial fibrillation and atrial flutter are considered class effects based on the safety profile of other BTK inhibitors, although they are less frequently reported with the second-generation (and more selective) covalent agents (that is, acalabrutinib and zanubrutinib).

Considering atrial fibrillation and atrial flutter are known adverse reactions for both first and second generation BTKi with suggested mechanisms of actions and described in section 4.8 of the pirtobrutinib SmPC, atrial fibrillation and atrial flutter are considered important identified risks and will be further characterised in the Phase 3 clinical trials.

Characterisation of the risk:

The overall incidence of atrial fibrillation and atrial flutter TEAEs was 2.6% (19 patients out of which 17 with atrial fibrillation and 3 with atrial flutter). Most of the events were Grades 1 or2 (12 patients, 1.65%), and there was a total of 7 patients with Grades ≥3 events (1.0%), Overall, 5 events (0.7% of patients) were considered related by the investigator, and only 1 of those was a Grade ≥3 event. No Grade 5 events were reported. While 4 patients (0.6%) had to undergo dose interruption, no patient underwent dose reduction or treatment discontinuation due to atrial fibrillation or atrial flutter.

It is noteworthy to mention that 11.3% (n = 82) and 0.6% (n = 4) of patients in study 18001 had a medical history of atrial fibrillation or atrial flutter, respectively. This includes 6 out of the 19 patients with TEAEs of atrial fibrillation or atrial flutter events described here. Additionally, among the patients with TEAE of atrial fibrillation or atrial flutter, 11 had other relevant comorbidities or significant risk factors for the occurrence of atrial fibrillation/atrial flutter (for example, hypertension, coronary artery disease, aortic stenosis, acute myocardial infarction, cardiac failure, pacemaker insertion, asymptomatic bradycardia incidents, atrial septal defect/supraventricular tachycardia).

Out of the 19 patients, 10 patients had a past medical history of atrial fibrillation (2 patients), concurrent systematic infection (4 patients), or both (4 patients). Additionally, 2 of the 19

patients had atrial fibrillation events with temporal fever events, 1 had an atrial fibrillation event during worsening heart failure, and another patient's atrial fibrillation event developed during an endoscopy procedure and was cardioverted.

Risk factors and risk groups:

Patients at risk for the occurrence of atrial fibrillation and atrial flutter include those with a history of coronary artery disease (especially if complicated with acute myocardial infarction or heart failure; Crenshaw et al 1997), congestive heart failure (Santhanakrishnan et al 2016), hypertension (Krahn et al 1995), valvular heart disease (Grigioni et al 2002). Other conditions that predispose the occurrence of atrial fibrillation and atrial flutter include infectious events (Musher et al 2007), hyperthyroidism (Woeber 1992), obesity (Nalliah et al 2016) and alcohol consumption (Ettinger et al 1978).

Preventability:

Section 4.4 of the SmPC advises to monitor for signs and symptoms of atrial fibrillation and atrial flutter and to obtain an ECG as medically indicated. ECG patterns associated with atrial fibrillation and atrial flutter are distinctive of such conditions and lead to prompt recognition and treatment, which ultimately minimises the risk of serious outcomes.

In addition, dose interruption instructions in the event of a Grade 3 or 4 non-haematologic toxicity are included in Section 4.2 of the SmPC.

Impact on the risk-benefit balance of the product:

Atrial fibrillation and atrial flutter, if not promptly recognised and treated, can lead to significant morbidity and in some cases to serious outcomes, such as cardiac arrest, cardiogenic shock, myocardial ischaemia and thromboembolic events (Chen et al 2014; Lip and Apostolakis 2014). Since the observed incidences of atrial fibrillation and atrial flutter in Study 18001 are low, and considering that such events are rapidly recognised, manageable and potentially reversible, the impact of atrial fibrillation and atrial flutter on the risk-benefit balance of pirtobrutinib is considered limited.

Public health impact:

Considering the incidence of atrial fibrillation and atrial flutter reported in Study 18001, which is within what is expected for the treated population, and limited population exposed to pirtobrutinib, the public health impact is estimated to be low.

Important Potential Risk 1: Second primary non-melanoma skin cancer

Potential mechanisms:

NHL, including MCL, and CLL, are associated with an increased risk of second primary non-melanoma skin cancer, due to reasons such as perturbed immune function and DNA damage secondary to prior treatment (Benjamini et al 2015; Bond et al 2020; Kyasa et al 2004).

Evidence source(s) and strength of evidence:

Second primary non-melanoma skin cancer has been described in the labels of other BTK inhibitors as an important identified risk ("second primary malignancy") for acalabrutinib; important potential risk (Second primary non-melanoma skin cancer) for zanubrutinib. Non-melanoma skin cancer was also the most common second primary malignancy reported with other BTKi drugs: the incidence of second primary malignancy skin cancer (mostly non-melanoma skin cancer) ranged from 4 to 13% for ibrutinib (Imbruvica package insert, 2013), and 6% for acalabrutinib and zanubrutinib (Calquence package insert, 2022; Brukinsa package insert, 2019).

There have been cases of SPM observed in Study 18001 (6.6% of patients) and most of those were non melanoma skin cancers (4.6%). Given there is a high predisposition of skin cancers among the patients with the types of haematologic malignancies evaluated in Study 18001 and considering that such events are not uncommon in the elderly population, second primary non-melanoma skin cancer is considered to be an important potential risk for pirtobrutinib since the association with the drug is still unclear.

In order to characterize both risks of second primary malignancies other than non-melanoma skin cancer and second primary non-melanoma skin cancer an integrated analysis of reports of all second primary malignancy in 5 years follow up of clinical trials supplemented with analysis of post marketing reports will be conducted. This analysis is included as an additional PV activity for this risk (refer to part III.2 Additional Pharmacovigilance Activities).

Characterisation of the risk:

In Study 18001, 33 patients reported second primary non-melanoma skin cancer (4.6%). The main events were basal cell carcinoma (3.6%, 26 patients) and squamous cell carcinoma (1.4%, 10 patients)

All except one were Grades 1 to 2 (4.4% of patients). Only 3 patients had events assessed as related to pirtobrutinib by the investigator (0.4%) and the occurrence of second primary non-melanoma skin cancer did not lead to dose reduction. Two patients discontinued due to event (0.3%); neither of which was considered related to pirtobrutinib.

The median time to onset of second primary non-melanoma skin cancer diagnosis was 39 weeks. Three (0.4%) patients developed second primary non-melanoma skin cancer within the first 4 weeks of treatment, 3 (0.4%) patients had onset between 5 and 8 weeks, 3 (0.4%) patients had onset between 9 and 12 weeks, and 22 (3.0%) patients had onset after more than 12 weeks on treatment. While some of the late onset events may have been compounded by the on-target effects of pirtobrutinib treatment and its resultant immunosuppression, those with earlier onset events are less likely to have been impacted by pirtobrutinib and more likely reflect the impact of underlying disease and prior treatment history.

Of note, past medical history of neoplasms (benign and malign conditions) was observed in 25% of the study population (181 patients). In addition, among patients with non-melanoma skin cancer (n = 33), 15 had a medical history of skin cancer (basal cell carcinoma, squamous cell

carcinoma or melanoma) or pre-cancerous lesions (actinic keratosis), which might suggest an increased propensity for the development of non-melanoma skin cancer in these patients.

Risk factors and risk groups:

Significant and unprotected sun exposure, fair skin color, smoking, advanced age, male gender, specific comorbidities (for example, chronic obstructive pulmonary disease, cirrhosis), and previous treatment (radiotherapy, fludarabine-combination chemotherapy, BTK inhibitors) are considered risk factors for the occurrence of second primary malignancy in patients with CLL or MCL (Morrison et al 2002; Lam et al 2005; Chien et al 2015; Bond et al 2020).

Preventability:

Most of the SPM cases observed are skin cancers, therefore advice on protection from sun exposure and on monitoring patients for the appearance of suspicious skin lesions is provided in Section 4.4 of the SmPC. In Study18001, active second malignancy unless in remission and with life expectancy > 2 years are excluded from enrolment and similar guidance is provided in other phase 3 studies in order to prevent development of cancer in high risk population.

Impact on the risk-benefit balance of the product:

Non-melanoma skin cancer was the main type of SPM observed, with most non-melanoma skin cancer events being low grade. Considering that skin cancers are potentially preventable and curable if diagnosed early, SPM is considered to not have a significant impact on the risk-benefit balance of pirtobrutinib.

Public health impact:

Second primary non-melanoma skin cancers have been observed in a small subset of patients in Study 18001, the majority of events were composed of low-grade non-melanoma skin cancer, and the indication of pirtobrutinib is limited to a subset of haematologic malignancies, therefore, the public health impact is estimated to be low.

Important Potential Risk 2: Second primary malignancies other than non-melanoma skin cancer

Potential mechanisms:

NHL, including MCL, and CLL, are associated with an increased risk of second primary malignancy, due to reasons such as perturbed immune function and DNA damage secondary to prior treatment (Benjamini et al 2015; Bond et al 2020;Kyasa et al 2004).

Evidence source(s) and strength of evidence:

Second primary malignancy has been described in with the labels of other BTK inhibitors and as an important identified risk for acalabrutinib (second primary malignancy); important potential risk for ibrutinib (other malignancies (excluding non-melanoma skin cancer) and zanubrutinib [Second primary malignancies (other than non-melanoma skin cancer)]

In Study18001 study 2.3% of patients reported second primary malignancies other than non-melanoma skin cancer. Although the causal association with pirtobrutinib is still unclear, considering an increased risk of second primary malignancy associated with haematologic malignancies, especially in the older age group similar to our study population and the immunomodulatory effect of BTKi class of drugs SPM other than non-melanoma skin cancer is considered to be an important potential risk for pirtobrutinib.

In order to characterize both risks of second primary malignancies other than non-melanoma skin cancer and second primary non-melanoma skin cancer an integrated analysis of reports of all second primary malignancy in 5 years follow up of clinical trials supplemented with analysis of post marketing reports will be conducted. This analysis is included as an additional PV activity for this risk (refer to part III.2 Additional Pharmacovigilance Activities).

Characterisation of the risk:

In Study 18001, 17 patients reported second primary malignancies other than non-melanoma skin cancer (2.3%). The main events were malignant melanoma in 3 patients (0.4 %) and 2 events each of malignant melanoma in situ, second primary malignancy and squamous cell carcinoma of head and neck.

Eight events were reported with higher grade severity of ≥3 (1.1% of patients) and there was no fatal case. Only 2 patients had events assessed as related to pirtobrutinib by the investigator (0.3%) and the occurrence of SPM did not lead to dose reduction. Two patients discontinued treatment due to SPM (0.3%); these 2 events were considered related to pirtobrutinib.

The median time to onset of second primary malignancies other than non-melanoma skin cancer diagnosis was 36 weeks. One (0.1%) patient developed the event within the first 4 weeks of treatment, 2 (0.3%) patients had onset between 5 and 8 weeks, and 13 (1.8%) patients had onset after more than 12 weeks on treatment. While some of the late onset events may have been compounded by the on-target effects of pirtobrutinib treatment and its resultant immunosuppression, those with earlier onset events are less likely to have been impacted by pirtobrutinib and more likely reflect the impact of underlying disease and prior treatment history.

Of note, past medical history of neoplasms (benign and malign conditions) was observed in 25% of the study population (181 patients).

Risk factors and risk groups:

Smoking, advanced age, male gender, specific comorbidities (for example, chronic obstructive pulmonary disease, cirrhosis), previous treatment (radiotherapy, fludarabine-combination chemotherapy, BTK inhibitors), significant and unprotected sun exposure are considered risk factors for the occurrence of second primary malignancy in patients with CLL or MCL (Morrison et al. 2002; Lam et al. 2005; Chien et al. 2015; Bond et al. 2020).

Preventability:

In Study 18001 active second malignancy unless in remission and with life expectancy >2 years are excluded from enrolment and similar guidance is provided in other Phase 3 studies in order to prevent development of cancer in high risk population. Additionally, risk of second primary malignancy has been communicated through label for the awareness of the prescribers.

Impact on the risk-benefit balance of the product:

Second primary malignancies other than non-melanoma skin cancer has been reported with a very low frequency, with most SPM events are judged as not related to pirtobrutinib by the investigator. Therefore, the risk is considered to not have a significant impact on the risk-benefit balance of pirtobrutinib.

Public health impact:

Second primary malignancies other than non-melanoma skin cancer have been observed in a small subset of patients in Study 18001 and the indication of pirtobrutinib is limited to a subset of haematologic malignancies; therefore, the public health impact is estimated to be low.

SVII.3.2 Presentation of the Missing Information

None

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Serious haemorrhage Serious infections Atrial fibrillation and atrial flutter
Important potential risks	Second primary malignancies other than non-melanoma skin cancer Second primary non-melanoma skin cancer
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires: None

Other forms of routine pharmacovigilance activities:

The safety concerns identified for pirtobrutinib will be included in routine and regular safety signal detection and management activities.

III.2 Additional Pharmacovigilance Activities

No other specific additional pharmacovigilance activities are planned. However, further safety information to confirm the positive benefit-risk of the conditional marketing authorisation for pirtobrutinib for the treatment of MCL will be established in the confirmatory Phase 3 Study LOXO-BTK-20019 for MCL. This study is included as a post-authorisation efficacy study (see Part IV in this RMP).

In order to characterise the risk of second primary malignancies other than non-melanoma skin cancer and second primary non-melanoma skin cancer, an integrated analysis of SPM in 5 years follow up of clinical trials supplemented with analysis of post marketing reports of SPM will be conducted. The Applicant has a post marketing commitment with the US FDA to provide an integrated safety analysis of approximately 1400 patients treated with pirtobrutinib 200mg monotherapy) with haematologic malignancies treated with pirtobrutinib monotherapy at the 200 mg daily dose in clinical trials. The clinical trials contributing to this analysis are Phase 1/2 Study 18001 and four ongoing randomised Phase 3 studies, including the Study LOXO-BTK-20019 in the MCL population. The integrated safety analysis will focus on the SPM incidence rates, types, severity, time to onset, potential predisposing factors, and outcomes. Patients from the Phase 1/2 Study 18001 will have a minimum follow-up of 5 years and patients from the four ongoing randomized Phase 3 studies will have up to 5 years of follow-up to assess SPM. See the Section III.3 Summary Table of Additional Pharmacovigilance Activities for details on timelines for fulfilment of this commitment.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
LOXO-305 A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL) **Status:** ongoing	To integrate the analysis for SPM for a 5 year follow up	- Second primary malignancies other than non-melanoma skin cancer - Second primary non-melanoma skin cancer	An interim analysis is planned for submission to EMA by September 2025	final report by June 2028
LOXO-BTK-20019 A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN MCL-321 **Status:** ongoing				
LOXO-BTK-20020 A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321) **Status:** ongoing				
LOXO-BTK-20023 A Phase 3 Open Label, Randomized. Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-313) **Status:** ongoing				
LOXO-BTK-20030 A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Ibrutinib in High-Risk Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL 314) **Status:** ongoing				

Part IV: Plans for Post-Authorisation Efficacy Studies

Table Part IV.1. Planned and Ongoing Post- Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
None				
Efficacy studies that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
LOXO-BTK-20019 A Phase 3 Open-Label, Randomised Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN-MCL-321) **Status:** Ongoing	- To compare PFS of pirtobrutinib as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) in patients with previously treated MCL - To evaluate the safety and tolerability of each treatment arm	Long-term efficacy; confirmatory study for initial marketing authorization application for MCL	First patient visit	08 April 2021
			Final study report	31 December 2026

Abbreviations: BTK = Bruton Tyrosine Kinase; MAA = Marketing Authorisation Application; MCL = mantle cell lymphoma; PFS = progression-free survival.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

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

Safety Concern	Routine Risk Minimisation Activities
Serious haemorrhage	Routine risk communication: SmPC Section 4.2, 4.4, 4.8 and the corresponding sections of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to monitor patients for signs and symptoms of bleeding is included in SmPC Section 4.4. • Recommendation to consider the benefit-risk of anticoagulant or antiplatelet therapy when co-administered with pirtobrutinib is included in SmPC Section 4.4. A statement is included in the same section that the use of pirtobrutinib has not been studied with warfarin or other vitamin K antagonists. • Recommendation to consider the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery depending on the type of surgery and risk of bleeding is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of the bleeding event and whether it occurs with thrombocytopenia is provided in SmPC Section 4.2. • Communication to the prescribers of various bleeding events considered ADRs for pirtobrutinib through labelling under the SmPC section 4.8.
Serious infections	Routine risk communication: SmPC Sections 4.2, 4.4, 4.8 and the corresponding sections of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to consider prophylactic antimicrobial therapy in patients who are at increased risk for opportunistic infections is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of infection and whether it occurs with neutropenia is included in SmPC Section 4.2 • Communication to the prescribers of various infection events considered ADRs for pirtobrutinib through labelling under the SmPC Section 4.8.

Atrial fibrillation and atrial flutter	Routine risk communication: SmPC Sections 4.2, 4.4, 4.8 and the corresponding section of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of atrial fibrillation/atrial flutter is included in SmPC Section 4.2. • Communication to the prescribers of ADRs atrial fibrillation and atrial flutter through labelling under the SmPC section 4.8.
Second primary malignancies other than non-melanoma skin cancer	Routine risk communication: SmPC Section 4.4 and the corresponding section of the PL. Routine risk minimisation activities: communicating the risk of second primary malignancy included in SmPC Section 4.4. and recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4.:
Second primary non-melanoma skin cancer	Routine risk communication: SmPC Section 4.4 and the corresponding section of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4.

Abbreviations: ADR: adverse drug reaction; PL = patient leaflets; ECG = electrocardiogram; SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of Risk Minimisation Measures

Table Part V.2. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious haemorrhage	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 • Recommendation to monitor patients for signs and symptoms of bleeding is included in SmPC Section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Recommendation to consider the benefit-risk of anticoagulant or antiplatelet therapy when co-administered with pirtobrutinib is included in SmPC Section 4.4. A statement is included in the same section that the use of pirtobrutinib has not been studied with warfarin or other vitamin K antagonists. • Recommendation to consider the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery depending on the type of surgery and risk of bleeding is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of the bleeding event and whether it occurs with thrombocytopenia is provided in SmPC Section 4.2. Additional risk minimisation measures: Not applicable	
Serious infections	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 • Recommendation to consider prophylaxis in patients who are at increased risk for opportunistic infections is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of infection and whether it occurs with neutropenia is included in SmPC Section 4.2. Additional risk minimisation measures: Not applicable	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Atrial fibrillation and Atrial flutter	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 • Recommendation to monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated is included in SmPC Section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Guidance on dose interruption based on the grade of atrial fibrillation/atrial flutter is included in SmPC Section 4.2 Additional risk minimisation measures: Not applicable	
Second primary malignancies other than non-melanoma skin cancer	Routine risk minimisation measures: SmPC Sections 4.2 4.4, • Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4. Additional risk minimisation measures: Not applicable	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Integrated analysis of reports of SPM in 5 -years follow up of clinical trials supplemented with analysis of postmarketing reports of SPM.
Second primary non-melanoma skin cancer	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4, • Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4. Additional risk minimisation measures: Not applicable	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Integrated analysis of reports of SPM in 5 years follow up of clinical trials supplemented with analysis of postmarketing reports of SPM.

Abbreviations: ECG = electrocardiogram; SmPC = Summary of Product Characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for pirtobrutinib

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

Pirtobrutinib's SmPC and package leaflet give essential information to healthcare professionals and patients on how pirtobrutinib should be used.

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

I - The Medicine and What It is Used for

Pirtobrutinib is proposed as a single agent for the treatment of adult patients with MCL who have been previously treated with a BTK inhibitor (see SmPC for the full indication). It contains pirtobrutinib as the active substance and it is given by oral dosing in the form of a film-coated tablets in dose strengths of 50 mg or 100 mg.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

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

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

Together, these measures constitute *routine risk minimisation* measures.

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

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

II.A List of Important Risks and Missing Information

Important risks of pirtobrutinib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important

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

List of Important Risks and Missing Information	
Important identified risks	Serious haemorrhage Serious infections Atrial fibrillation and atrial flutter
Important potential risks	Second primary malignancies other than non-melanoma skin cancer Second primary non-melanoma skin cancer
Missing information	None

II.B Summary of Important Risks

Important Identified Risk 1: Serious haemorrhage	
Evidence for linking the risk to the medicine	Serious haemorrhagic events have been reported at a low frequency in Study 18001, compared with that expected from a highly selective BTK inhibitor. However, clinically significant events have been observed which included higher grade and fatal events. Since haemorrhage is considered a class effect and characterised as an important identified risk for the authorised BTK inhibitors, the risk of serious haemorrhage will be classified as an important identified risk.
Risk factors and risk groups	Patients presenting with severe thrombocytopenia are at increased risk of serious haemorrhagic events (Neunert et al 2015). Other reported risk factors for the occurrence of major haemorrhage in patients with MCL and other haematologic malignancies include history of major haemorrhage, concomitant use of anticoagulants (for example, warfarin, heparin, enoxaparin) and antiplatelets (for example, acetylsalicylic acid, clopidogrel), renal disease, anaemia, thrombocytopenia, and alcohol abuse (Georgantopoulos et al. 2019, Dmitrieva et al. 2020). General medical conditions associated with increased propensity for haemorrhagic events include acquired coagulopathies, inherited bleeding dysfunctions, hepatopathy, renal dysfunction (leading to uraemia-induced platelet dysfunction; Boccardo et al. 2004), and connective tissue disorders leading to haematologic abnormalities.
Risk minimisation measures	Routine risk minimisation measures*:* • Recommendation to monitor patients for signs and symptoms of bleeding is included in SmPC Section 4.4. • Recommendation to consider the benefit-risk of anticoagulant or antiplatelet therapy when co-administered with pirtobrutinib is included in SmPC Section 4.4. A statement is included in the same section that the use of pirtobrutinib has not been studied with warfarin or other vitamin K antagonists.

Important Identified Risk 1: Serious haemorrhage	
	• Recommendation to consider the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery depending on the type of surgery and risk of bleeding is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of the bleeding event and whether it occurs with thrombocytopenia is provided in SmPC Section 4.2. • Communication to the prescribers of various bleeding events considered ADRs for pirtobrutinib through labelling under the SmPC section 4.8 Additional risk minimisation measures*:* Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Not applicable

Important Identified Risk 2: Serious infections	
Evidence for linking the risk to the medicine	The occurrence of serious infections has the potential to impact the risk-benefit balance of pirtobrutinib. Grades ≥3 events observed in 17.7% of patients (2.8% of patients with events deemed related to pirtobrutinib by the investigator) and 29 (4.0%) patients with fatal events due to infection, of which 3 were considered related to pirtobrutinib by the investigator. Serious infections have been commonly reported in patients taking other BTK inhibitors (Teh et al 2018, Estupiñán et al 2021), nevertheless, sustained increases in serum IgA levels induced by ibrutinib and acalabrutinib have been observed, and this finding has been correlated with a lower risk of developing infections with long-term BTK inhibitor therapy (Byrd et al 2015; Pleyer et al 2020). Although the frequency of serious infections in Study 18001 is lower when compared to other BTK inhibitors and patients with B-cell malignancies are predisposed to infections, serious infections are a class label risk with a known mechanism of action, described in Section 4.8 of the SmPC and have potential for severe clinical outcomes; therefore, considered an important identified risk for pirtobrutinib. This risk will be closely monitored and further characterised in the Phase 3 clinical trials.
Risk factors and risk groups	Identified risk factors for the occurrence of serious infections include neutropenia (with longer duration and severity of neutropenia increasing the risk; Crawford et al 2004), delayed antimicrobial therapy initiation and patient-related factors (e.g., age, previous comorbidities, nutritional status, performance status, prior chemotherapy; Nucci and Anaissie 2017; Xiao et al 2020). It has been described that ≥ 3 prior treatments, diabetes and liver disease have been associated with the development of opportunistic infections in patients treated with ibrutinib (Rogers et al 2019).
Risk minimisation measures	Routine risk minimisation measures: • Recommendation to consider prophylaxis in patients who are at increased risk for opportunistic infections is included in SmPC Section 4.4.

	• Guidance on dose interruption based on the grade of infection and whether it occurs with neutropenia is included in SmPC Section 4.2. • Communication to the prescribers of various infection events considered ADRs for pirtobrutinib through labelling under the SmPC Section 4.8. Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Not applicable.

Important Identified Risk 3: atrial fibrillation and atrial flutter	
Evidence for linking the risk to the medicine	Atrial fibrillation and atrial flutter are considered class effects based on the safety profile of other BTK inhibitors, although they are less frequently reported with the second-generation (and more selective) covalent agents (*i.e*., acalabrutinib and zanubrutinib). Considering atrial fibrillation and atrial flutter are known adverse reaction for both first and second generation BTK inhibitors with suggested mechanisms of actions and described in Section 4.8 of the SmPC, atrial fibrillation and atrial flutter are considered important identified risks and will be further characterised in the Phase 3 clinical trials.
Risk factors and risk groups	Patients at risk for the occurrence of atrial fibrillation and atrial flutter include those with a history of coronary artery disease (especially if complicated with acute myocardial infarction or heart failure; Crenshaw et al 1997), congestive heart failure (Santhanakrishnan et al 2016), hypertension (Krahn et al 1995) and valvular heart disease (Grigioni et al 2002). Other conditions that predispose the occurrence of atrial fibrillation and atrial flutter include infectious events (Musher et al 2007), hyperthyroidism (Woeber 1992), obesity (Nalliah et al 2016) and alcohol consumption (Ettinger et al 1978).
Risk minimisation measures	Routine risk minimisation measures: • Recommendation to monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of atrial fibrillation/atrial flutter is included in Section 4.2 • Communication to the prescribers of ADRs atrial fibrillation and atrial flutter through labelling under the SmPC Section 4.8. Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Not applicable

Important Potential Risk 1: second primary malignancies other than non-melanoma skin cancer	
Evidence for linking the risk to the medicine	Second primary malignancy has been described in association with other BTK inhibitors and is included as an important potential risk for ibrutinib ("other malignancies [excluding non-melanoma skin cancer]") and

	identified risk ("non-melanoma skin cancer") for ibrutinib and as an important identified risk ("second primary malignancy") for acalabrutinib (Ghia et al 2020; Sharman et al 2020). In Study 18001 study 2.3% of patients reported second primary malignancies other than non-melanoma skin cancer. Although, the association with the drug is still unclear, considerinng an increased risk of second primary malignancy associated with haematologic malignancies, especially in the older age group similar to our study population and the immunomodulatory effect of BTKi class of drugs SPM other than non-melanoma skin cancer is considered to be an important potential risk for pirtobrutinib
Risk factors and risk groups	Smoking, advanced age, male gender, specific comorbidities (e.g., chronic obstructive pulmonary disease, cirrhosis), previous treatment (radiotherapy, fludarabine-combination chemotherapy, BTK inhibitors), excessive and unprotected sun exposure are considered risk factors for the occurrence of second primary malignancy in patients with MCL and other haematologic malignancies (Bond et al 2020; Chien et al 2015; Lam et al 2005; Morrison et al 2002).
Risk minimisation measures	Routine risk minimisation measures: - Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4. Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities*:* Integrated analysis of reports of SPM in 5 years follow up of clinical trials supplemented with analysis of postmarketing reports of SPM.
Important Potential Risk 2: second primary non-melanoma skin cancer	
Evidence for linking the risk to the medicine	Second primary non-melanoma skin cancer has been described in the labels of other BTK inhibitors and as an important identified risk ("second primary malignancy") for acalabrutinib; important potential risk (Second primary non-melanoma skin cancer) for zanubrutinib.There have been cases of SPM observed in Study 18001 (6.6% of patients) and most of those were non-melanoma skin cancers (4.6%) with basal cell carcinoma (3.6%, 26 patients) and squamous cell carcinoma (1.4%, 10 patients) being the most common subtypes; 2.3% of patients reported second primary malignancies other than non-melanoma skin cancer.. Given there is a high predisposition of skin cancers among patients with the types of haematologic malignancies evaluated in Study 18001 and considering that such events are not uncommon in the elderly population, SPM will be considered an important potential risk for pirtobrutinib since the association with the drug is still unclear.
Risk factors and risk groups	Smoking, advanced age, male gender, specific comorbidities (e.g., chronic obstructive pulmonary disease, cirrhosis), previous treatment (radiotherapy, fludarabine-combination chemotherapy, BTK inhibitors), excessive and unprotected sun exposure are considered risk factors for the occurrence of second primary malignancy in patients with MCL and other haematologic malignancies (Bond et al. 2020; Chien et al. 2015; Lam et al. 2005; Morrison et al. 2002).
Risk minimisation measures	Routine risk minimisation measures:

	- Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4. Additional risk minimisation measures: Not applicable
Additional pharmacovigilance activities	Integrated analysis of reports of SPM in 5 years follow up of clinical trials supplemented with analysis of postmarketing reports of SPM.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

The following study is a condition of the marketing authorisation:

Study short name: **LOXO-BTK-20019 (BRUIN MCL-321; Study 20019)**

Purpose of the study: The study will compare pirtobrutinib, a non-covalent BTK inhibitor versus investigator's choice of covalent BTK inhibitor therapy, evaluating the differences in efficacy, safety and tolerability in this patient population and confirming the activity and safety of pirtobrutinib in patients with relapsed MCL.

The primary objective is to compare PFS of pirtobrutinib as monotherapy to investigator choice of covalent BTK inhibitor monotherapy in patients with previously treated MCL.

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

None

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

None

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not Applicable