1. NAME OF THE MEDICINAL PRODUCT

Jaypirca 50 mg
Jaypirca 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jaypirca 50 mg film-coated tablets

Each film-coated tablet contains 50 mg of pirtobrutinib.

Excipients with known effect
Each film-coated tablet contains 38 mg of lactose (as monohydrate).

Jaypirca 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of pirtobrutinib.

Excipients with known effect
Each film-coated tablet contains 77 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Jaypirca 50 mg film-coated tablets

Blue, arc-triangle shaped tablet debossed with “Lilly 50” on one side and “6902” on the other side.

Jaypirca 100 mg film-coated tablets

Blue, round tablet debossed with “Lilly 100” on one side and “7026” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) who have been previously treated with a BTK inhibitor.

4.2 Posology and method of administration

Jaypirca therapy should be initiated and supervised by physicians experienced in the use of anticancer therapies.

Posology

The recommended dose is 200 mg pirtobrutinib once daily (QD).

Jaypirca dosing should be interrupted until recovery to Grade 1 or baseline when the patient experiences the following event:

- Grade 3 neutropenia with fever and/or infection
- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia
- Grade 3 or 4 non-haematologic toxicity

Asymptomatic lymphocytosis is not regarded as an adverse reaction, and patients experiencing this event should continue taking Jaypirca.

In the clinical studies, adverse events in a limited number of patients were managed by dose reduction (see section 5.1).

Treatment should be continued until disease progression or unacceptable toxicity.

Dosage Modifications for Concomitant Use with Strong CYP3A Inhibitors
Avoid concomitant use of strong CYP3A inhibitors with Jaypirca (see sections 4.5 and 5.2). If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the Jaypirca dose by 50 mg. If the current dosage is 50 mg once daily, interrupt Jaypirca treatment for the duration of strong CYP3A inhibitor use. After discontinuation of a strong CYP3A inhibitor for 5 half-lives, resume the Jaypirca dose that was taken prior to initiating the strong CYP3A inhibitor.

Dosage Modifications for Concomitant Use with CYP3A Inducers
Avoid concomitant use of strong or moderate CYP3A inducers with Jaypirca (see sections 4.5 and 5.2). If concomitant use with moderate CYP3A inducers is unavoidable and the current dosage of Jaypirca is 200 mg once daily, increase the dose to 300 mg. If the current dosage is 50 mg or 100 mg once daily, increase the dose by 50 mg.

Missed dose
If more than 12 hours have passed after a patient has missed a dose, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken. If vomiting occurs, the patient should not take an additional dose but continue with the next scheduled dose.

Special populations

Elderly
No dose adjustment is required based on age (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. There are no data in patients on dialysis (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Jaypirca in children and adolescents aged less than 18 years have not been established. No data are available.

Method of administration

Jaypirca is for oral use.

The tablet should be swallowed whole with a glass of water to ensure consistent performance (patients should not chew, crush, or split tablets before swallowing) and can be taken with or without food. Patients should take the dose at approximately the same time every day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Infections

Serious infections, including fatal cases, have occurred in patients treated with Jaypirca. The most frequently reported Grade 3 or higher infections were pneumonia, COVID-19 pneumonia, COVID-19, and sepsis. Prophylactic antimicrobial therapy should be considered in patients who are at increased risk for opportunistic infections. Based on the grade of infection and whether it occurs with neutropenia, dose interruption may be required (see section 4.2).

Haemorrhage

Bleeding events, including fatal cases, have occurred in patients treated with Jaypirca, with and without thrombocytopenia. Major bleeding events of Grade 3 or higher, including gastrointestinal bleeding and intracranial haemorrhage have been observed. Patients should be monitored for signs and symptoms of bleeding. Patients receiving anticoagulant or antiplatelet agents may be at increased risk of haemorrhage. The risks and benefits of anticoagulant or antiplatelet therapy should be considered when co administered with Jaypirca and consider additional monitoring for signs of bleeding. The use of Jaypirca has not been studied with warfarin or other vitamin K antagonists.
Dose interruption may be required for Grade 3 or 4 bleeding events (see section 4.2).

The benefit-risk of withholding Jaypirca for 3 to 5 days pre- and post-surgery should be considered depending upon the type of surgery and risk of bleeding.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia, anaemia and thrombocytopenia occurred in patients treated with Jaypirca. Complete blood counts should be monitored in patients during treatment as medically indicated. Based on the grade of cytopenia, dose interruption may be required (see section 4.2).

Atrial fibrillation/ flutter

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

Second Primary Malignancies

Second primary malignancies have commonly occurred in patients treated with Jaypirca, with the most frequent types being non melanoma skin cancers. Patients should be monitored for the appearance of skin cancers and advise protection from sun exposure.

Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including Jaypirca.
Evaluate bilirubin and transaminases at baseline and throughout treatment with Jaypirca. For patients who develop abnormal liver tests after Jaypirca, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold Jaypirca. Upon confirmation of DILI, discontinue Jaypirca.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported rarely with Jaypirca therapy. Patients at high risk of TLS are those with high tumour burden prior to treatment. Patients should be assessed for possible risk of TLS and closely monitored as clinically indicated.

Contraception in women of childbearing potential and males

Based on findings in animals and the genotoxicity of pirtobrutinib (see section 5.3), pirtobrutinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential should use an effective method of contraception during treatment and for 5 weeks after the last dose of Jaypirca. Men are advised to use an effective method of contraception and not father a child during treatment and for 3 months after the last dose of Jaypirca (see section 4.6).

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg daily dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Pirtobrutinib is primarily metabolised by CYP3A4, UGT1A8, and UGT1A9.

Effects of other medicinal products on the pharmacokinetics of pirtobrutinib

Strong CYP3A Inhibitors
Pirtobrutinib is a CYP3A substrate. Concomitant use of Jaypirca with a strong CYP3A inhibitor increased pirtobrutinib systemic exposure (see section 5.2), which may increase the risk of Jaypirca adverse reactions. Avoid concomitant use of strong CYP3A inhibitors during treatment with Jaypirca. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the Jaypirca dosage (see section 4.2).

Strong or Moderate CYP3A Inducers
Concomitant use of Jaypirca with a strong or moderate CYP3A inducer decreased pirtobrutinib systemic exposure (see section 5.2), which may reduce Jaypirca efficacy. Avoid concomitant use of Jaypirca with strong or moderate CYP3A inducers. If concomitant use of moderate CYP3A inducers is unavoidable, increase the Jaypirca dosage (see section 4.2).

Coadministration with medicinal products that are proton pump inhibitors
No clinically significant differences in pirtobrutinib pharmacokinetics were observed when administered concomitantly with omeprazole, a proton pump inhibitor.

Effects of pirtobrutinib on the pharmacokinetics of other medicinal products (increase in plasma concentration)

CYP2C8 substrates
Pirtobrutinib is a moderate inhibitor of CYP2C8. Pirtobrutinib increased the AUC and C_{max} of repaglinide (a substrate of CYP2C8) by 130 % and 98 %, respectively. Therefore, since pirtobrutinib can increase the plasma concentrations of CYP2C8 substrates, caution is advised when co-administering with CYP2C8 substrates (e.g. repaglinide, dasabuvir, selexipag, rosiglitazone, pioglitazone, and montelukast).

BCRP substrates
Pirtobrutinib is a moderate inhibitor of BCRP. Pirtobrutinib increased the AUC and C_{max} of rosuvastatin (a BCRP substrate) by 140 % and 146 %, respectively. Therefore, since pirtobrutinib can increase the plasma concentrations of BCRP substrates, caution is advised when co-administering BCRP substrates (e.g. rosuvastatin). If co-administration with narrow therapeutic index BCRP substrates (e.g. high dose methotrexate, mitoxantrone) cannot be avoided, close clinical monitoring should be considered.

P-gp substrates
Pirtobrutinib is a weak inhibitor of P-gp. Pirtobrutinib increased the AUC and C_{max} of digoxin (a P-gp substrate) by 35 % and 55 %, respectively. Therefore, pirtobrutinib can increase the plasma concentrations of P-gp substrates. If co-administration with narrow therapeutic index P-gp substrates (e.g dabigatran etexilate and digoxin) cannot be avoided, close clinical monitoring should be considered.

CYP2C19 substrates
Pirtobrutinib is a weak inhibitor of CYP2C19. Pirtobrutinib increased the AUC and C_{max} of omeprazole (a CYP2C19 substrate) by 56 % and 49 %, respectively. Therefore, pirtobrutinib can increase the plasma concentrations of CYP2C19 substrates. If co-administration with narrow therapeutic index CYP2C19 substrates (e.g. phenobarbital and mephenytoin) cannot be avoided, close clinical monitoring should be considered.

CYP3A substrates
Pirtobrutinib is a weak inhibitor of CYP3A. Pirtobrutinib increased the AUC and C_{max} of orally administered midazolam (sensitive CYP3A substrate) by 70 % and 58 %, respectively. Pirtobrutinib did not have a clinically meaningful effect on the exposure of intravenously administered midazolam. Therefore, pirtobrutinib can increase the plasma concentrations of CYP3A substrates. If co-administration with narrow therapeutic index CYP3A substrates (e.g alfentanil, midazolam, tacrolimus) cannot be avoided, close clinical monitoring should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Based on findings in animals and the genotoxicity of pirtobrutinib (see section 5.3), pirtobrutinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential should use an effective method of contraception during treatment and for 5 weeks after the last dose of Jaypirca. Men are advised to use an effective method of contraception and not father a child during treatment and for 3 months after the last dose of Jayprica (see section 4.4).

Pregnancy

There are no data from the use of Jaypirca in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Jaypirca should not be used during pregnancy.

Breast-feeding

It is unknown whether pirtobrutinib is excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Jaypirca and for one week after the last dose of Jaypirca.

Fertility

There are no data on the effect of pirtobrutinib on human fertility.

4.7 Effects on ability to drive and use machines

Jaypirca has a minor influence on the ability to drive and use machines. Fatigue, dizziness, and asthenia have been reported in some patients during treatment with Jaypirca and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions of any grade are: neutropenia (27.7 %), fatigue (26.2 %), diarrhoea (23.8 %), anaemia (20.7 %), rash (18.4 %) and contusion (17.8 %).

The most common severe (Grade ≥ 3) adverse reactions are: neutropenia (23.9 %), anaemia (11.2 %), thrombocytopenia (9.7 %), and pneumonia (9.0 %).

The frequency of treatment discontinuation due to adverse reactions is 4.2 % and the frequency of dose reductions due to adverse reactions is 4.8 %.

The most common adverse reactions (reported in more than 2 patients) leading to dose reduction are neutropenia (2.5%), rash (0.6 %), diarrhoea (0.4 %), fatigue (0.4 %) and thrombocytopenia (0.4 %). The most common adverse reactions (reported in more than 2 patients) leading to dose discontinuation are neutropenia (1.0 %), anaemia (1.0 %), pneumonia (0.9 %), thrombocytopenia (0.7 %) and rash (0.4 %).

Serious adverse reactions associated with Jaypirca have occurred in 19.4 % of patients and the most common serious adverse reactions (occurring in ≥1 % of patients) were pneumonia (8.0 %), neutropenia (3.2 %), anaemia (2.6 %), atrial fibrillation/atrial flutter (1.3 %) and urinary tract infection (1.0 %).

Clinically significant adverse reaction: Hepatotoxicity, including DILI (see section 4.4).

Fatal adverse reactions have been observed in 0.4 % of patients (3 patients) for pneumonia, in 0.3 % of patients (2 patients) for haemorrhage and in 0.1 % of patients (1 patient) for urinary tract infection.

Tabulated list of adverse reactions

Table 1 lists the adverse drug reactions (ADRs) associated with Jaypirca used as a monotherapy from clinical study data and post-marketing experience. The ADRs identified from clinical trials are based on pooled data from 690 patients treated with Jaypirca monotherapy 200 mg QD starting dose with no dose escalation in a phase 1/2 clinical study, and from patients treated with Jaypirca monotherapy 200 mg QD in a phase 3 study. Patients were treated for MCL, chronic

lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and other non-Hodgkin lymphoma (NHL). Patients were exposed to Jaypirca for a median duration of 12 months. ADRs are listed below by MedDRA body system organ class. Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000), and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 1: ADRs of patients treated with Jaypirca[a]

System organ class (MedDRA)	ADR	Frequency category (%) (All grades)	Grade ≥ 3[c] (%)
Infections and infestations	Pneumonia	Very common (13.8)	9.0
	Upper respiratory tract infection	Very common (10.1)	0.1
	Urinary tract infection	Common (9.9)	1.4
Blood and lymphatic system disorders	Neutropenia[b]	Very common (27.7)	23.9
	Anaemia[b]	Very common (20.7)	11.2
	Thrombocytopenia[b]	Very common (16.8)	9.7
	Lymphocytosis[b]	Common (6.4)	3.9
Nervous system disorders	Headache	Very common (12.6)	0.7
Cardiac disorders	Atrial fibrillation/atrial flutter	Common (3.8)	1.7
Vascular disorders	Haemorrhage[b]	Very common (20.3)	2.8
	Epistaxis	Common (5.2)	0
	Haematuria	Common (4.5)	0.1
	Haematoma	Common (1.7)	0.1
	Conjunctival haemorrhage	Common (1.7)	0.1
	Bruising[b]	Very common (19.7)	0.3
	Contusion	Very common (17.8)	0.1
	Petechiae	Common (5.7)	0
Gastrointestinal disorders	Diarrhoea	Very common (23.8)	1.0
	Nausea	Very common (16.7)	0.4
	Abdominal pain	Very common (10.4)	1.0
Hepatobiliary disorders	Hepatic enzyme increased	Not known	Not known
Skin and subcutaneous tissue disorders	Rash[b]	Very common (18.4)	1.2
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (14.6)	1.2
General disorders and administration site conditions	Fatigue	Very common (26.2)	1.9
	Oedema peripheral	Very common (11.6)	0.3

a Frequencies are derived from Jaypirca exposure in patients with B-cell malignancies

b Includes multiple adverse reaction terms

c Severity grade assignment based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

No maximum tolerated dose was reached in the phase 1 study in which patients received repeated doses up to 300 mg once daily. In healthy volunteer studies, no dose related toxicity was observed when a maximum single dose of 900 mg was administered. Signs and symptoms of pirtobrutinib overdose have not been established and there is no specific treatment for pirtobrutinib overdose.
For patients who experience overdose, closely monitor and provide appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EL05

Mechanism of action

Pirtobrutinib is a reversible, noncovalent inhibitor of BTK. BTK is a signalling protein of the B-cell antigen receptor (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 harboring C481 mutations leading to inhibition of BTK kinase activity.

Pharmacodynamic effects

Cardiac electrophysiology
The effect of a single 900 mg dose of pirtobrutinib on the corrected QT (QTc) interval was evaluated in a study with placebo and positive controls in 30 healthy subjects. The selected dose is equivalent to approximately 2 times higher than the concentrations achieved at steady state at the recommended dosage of 200 mg once daily. Pirtobrutinib had no clinically meaningful effect on the change in QT corrected for heart rate using Fridericia's formula (QTcF) interval (i.e., > 10 ms) and there was no relationship between pirtobrutinib exposure and change in QTc interval.

Clinical efficacy and safety

Mantle Cell Lymphoma
The efficacy of Jaypirca was evaluated in adult patients with MCL in a phase 1/2 multicenter, open label, single arm clinical study: Study 18001 (BRUIN). The study included two parts: a phase 1 dose escalation, in which the dose range of monotherapy pirtobrutinib of 25 mg to 300 mg once daily was investigated, and a phase 2 dose expansion. The primary objective of the phase 1 portion was to determine the recommended phase 2 dose of pirtobrutinib, which was found to be 200 mg once daily, with a maximum tolerated dose not being established. The primary objective of the phase 2 part was to assess the anti-tumor activity of pirtobrutinib based on overall response rate as assessed by an independent review committee. Patients received Jaypirca orally daily until disease progression or unacceptable toxicity.

Study 18001 enrolled and treated a total of 164 patients with a diagnosis of MCL and the primary analysis set (PAS) for the assessment of efficacy was based on the first 90 patients with MCL enrolled who had no known central nervous system (CNS) involvement, were treated with a prior BTK inhibitor, had received one or more doses of Jaypirca and had at least 1 site of radiographically assessable disease. The median age was 70 years (range: 46 to 87 years), 80 % were male, 84.4 % were White, 67.8 % had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 31.1 % had ECOG performance status of 1. Patients had a median number of 3 prior lines of therapy (range: 1 to 8), with the reason for discontinuation from the most recent prior BTK inhibitor therapy being progression in 81.1 % of

patients and intolerance in 13.3 % of patients. 95.6 % of patients received prior anti-CD20 therapy, 87.8 % chemotherapy, 18.9 % autologous stem cell transplantation, 4.4 % allogenic stem cell transplantation, 15.6 % prior BCL2 inhibitor and 4.4 % received prior chimeric antigen receptor-modified T cells (CAR-T) therapy. 38.9 % patients had extranodal involvement and 26.7 % had tumour bulk greater than or equal to 5 cm. The simplified MCL International Prognostic Index (sMIPI) score was low in 22.2 %, intermediate in 55.6 % and high in 22.2 % of patients.

Of the 164 patients with MCL enrolled in Study 18001, 9 patients had a dose reduction, including 6 responders that were able to remain on therapy and maintain a durable response following dose reductions to 150 mg QD (3), 100 mg QD (2), and 50 mg QD (1).

The efficacy of Jaypirca was based on a response as assessed using 2014 Lugano criteria for malignant lymphoma. Efficacy results for patients that received at least one prior BTK inhibitor and included in the PAS are summarised in Table 2. For the 90 patients in the PAS, 79 received at least 1 dose of 200 mg QD. Of these 79 patients, 77 started at 200 mg QD, 1 dose escalated from a lower dose and 1 dose reduced from a higher dose. The median time on treatment was 5.24 months (range: 0.2 to 39.6 months). Among the 51 responders, the median time to response was 1.84 months (range: 1.0 to 7.5 months).

While subgroup analyses represent a limited number of patients, clinically meaningful efficacy results were observed across important subgroups, including patients that discontinued prior BTK inhibitor therapy due to intolerance or progression and irrespective of number and type of prior therapies.

Table 2: Summary of efficacy data in Study 18001 for MCL patients who received at least one prior BTK inhibitor

	Pirtobrutinib N=90
Objective response rate (Complete response + partial response)	
Rate – percent (95 % CI)	56.7 (45.8, 67.1)
CR – percent	18.9
PR – percent	37.8
Duration of response	
Median - months (95 % CI)	17.61 (7.29, 27.24)

Abbreviations: CI = confidence interval, NE= not estimable, CR = complete response, PR = partial response.
Data cut-off date: 29 July 2022. The median follow-up time for duration of response was 12.68 months.

Chronic Lymphocytic Leukaemia
The efficacy of Jaypirca in patients with BTK-inhibitor pretreated CLL was evaluated in a randomised, multicentre, international, open-label, actively-controlled trial (BRUIN CLL-321, Study 20020). The trial enrolled 238 patients with CLL/SLL who were previously treated with a BTK inhibitor. Patients were randomised in a 1:1 ratio to receive either Jaypirca given orally once daily at a dose of 200 mg until disease progression or unacceptable toxicity, or Investigator's choice:

- Idelalisib plus a rituximab product (IR): Idelalisib 150 mg orally twice daily until disease progression or unacceptable toxicity, in combination with 8 infusions of a rituximab product (375 mg/m2 intravenously on Day 1 of Cycle 1, followed by 500 mg/m2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses), with a 28-day cycle length.
- Bendamustine plus a rituximab product (BR): Bendamustine 70 mg/m2 intravenously (Day 1 and 2 of each 28-day cycle), in combination with a rituximab product (375 mg/m2 intravenously on Day 1 of Cycle 1, then 500 mg/m2 on Day 1 of subsequent cycles), for up to 6 cycles.

Randomisation was stratified by 17p deletion status (yes/no) and receipt of prior venetoclax treatment (yes/no). Of the 238 patients total, 119 were assigned to Jaypirca monotherapy, 82 to IR and 37 to BR. After confirmed disease progression, patients randomised to IR or BR had the option to cross over to Jaypirca monotherapy. Baseline characteristics were similar between treatment arms. Overall, the median age was 67 years (range: 42 to 90 years), 70 % were male and 81 % were White. Baseline ECOG performance status was 0 or 1 in 93% of patients and 44% of patients

had Rai stage III or IV disease. Among those patients with central testing available, 57 % (101 of 176 patients) had 17p deletion and/or TP53 mutation, 86 % (164 of 190 patients) had unmutated IGHV, and 65 % (97 of 149) had complex karyotype.

Patients received a median number of 3 prior lines of therapy (range: 1 to 13) with 57 % having at least 3 prior therapies and 51 % having had prior BCL2-inhibitor therapy. The most common prior BTK inhibitors received were ibrutinib (87 %), acalabrutinib (16 %), and zanubrutinib (7 %). 70 % of patients discontinued the most recent BTK inhibitor for refractory or progressive disease, 15 % discontinued for toxicity, and 15 % discontinued for other reasons.

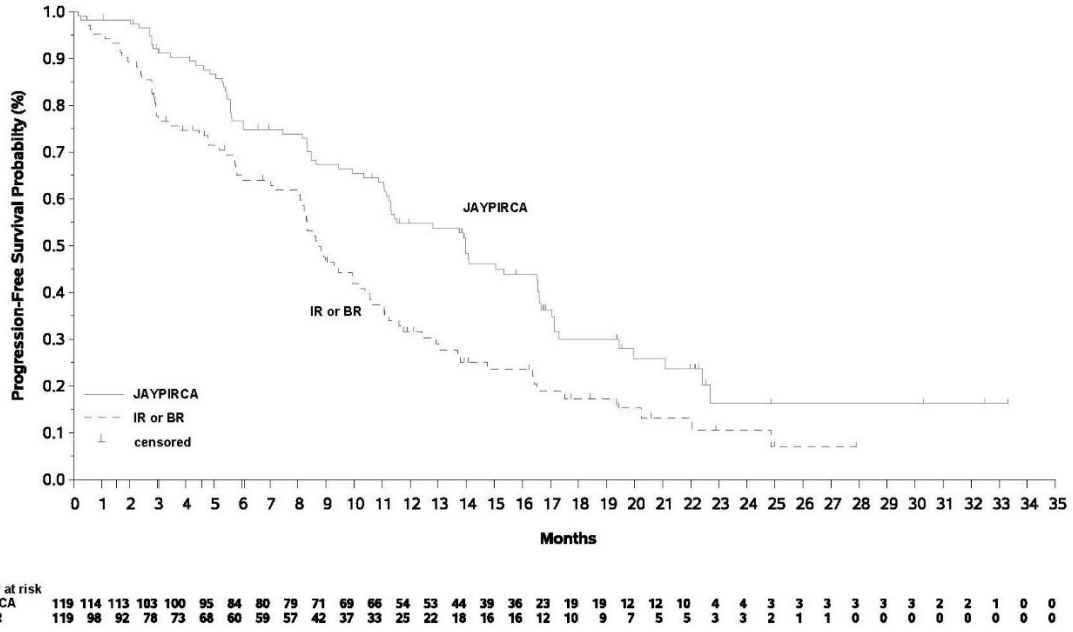
Efficacy was based on progression-free survival (PFS) of pirtobrutinib monotherapy versus investigator's choice arm as assessed by an Independent Review Committee (IRC). The study met its primary endpoint at the prespecified time of final analysis for IRC-assessed PFS (29 Aug 2023 cut-off). At an updated analysis (29 Aug 2024 cut-off) with a median follow-up of 19.4 months (range 0.03 to 33.3 months) for pirtobrutinib and 17.7 months (range 0.03 to 27.9 months) for the investigator's choice arm, improved IRC-assessed PFS was observed with pirtobrutinib compared to the investigator's choice arm, consistent with the primary analysis. Clinically meaningful efficacy results in favour of pirtobrutinib were observed across important subgroups, including patients who discontinued prior BTK inhibitor therapy due to intolerance or progression and irrespective of number and type of prior therapies. Efficacy results are presented in Table 3. The Kaplan-Meier curve for PFS is shown in Figure 1.

Table 3: Efficacy Results per IRC in Patients with CLL Previously Treated with a BTK Inhibitor – ITT Population (Study 20020)

	Pirtobrutinib 200 mg once daily (N = 119)	**Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab (N = 119)**
Progression-free Survival[a]		
Number of Events, n	74 (62 %)	79 (66 %)
Disease Progression	60 (50 %)	66 (55 %)
Death	14 (12 %)	13 (11 %)
Median PFS (95 % CI), months [b]	14.0 (11.2, 16.6)	8.7 (8.1, 10.4)
HR (95 % CI) [c]	0.54 (0.39, 0.75)	
P-value [d]	0.0002	

CI, confidence interval; HR, hazard ratio.
Data cut-off date 29 Aug 2024
[a] Efficacy was assessed using the 2018 International Workshop for Chronic Lymphocytic Leukemia (iwCLL) guidelines.
[b] Based on Kaplan-Meier estimation.
[c] Based on stratified Cox proportional hazards model.
[d] 2-sided nominal p-value based on stratified log-rank test.

Figure 1: Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL Previously Treated with a BTK Inhibitor in Study 20020



With a median overall survival (OS) follow-up time of 20.4 months for pirtobrutinib and 19.2 months in investigator's choice arm, 38 patients (32.0 %) in the pirtobrutinib arm and 32 patients (27.0 %) in the investigator's choice arm died. Median OS was 29.7 months (95 % CI: 27.1, NE) in the pirtobrutinib arm and not reached in the investigator's choice arm. The HR was 1.090 (95% CI: 0.679, 1.749; p = 0.7202). OS analysis may be confounded by the 50 out of 119 patients who crossed over from the investigator's choice arm to pirtobrutinib.

5.2 Pharmacokinetic properties

The pharmacokinetics of pirtobrutinib were characterized in healthy subjects and in patients with cancer. Doses ranged from 25 mg to 300 mg once daily (0.125 to 1.5 times the recommended dosage of 200 mg once daily), up to single doses of 900 mg. Increases in plasma exposure were approximately dose proportional. Steady state was achieved within 5 days of once daily dosing, and in cancer patients the mean [coefficient of variation (CV %)] accumulation ratio after administration of 200 mg once daily was 1.63 (26.7 %) based on AUC. Three patient factors were attributed to changes in pirtobrutinib PK: body weight, serum albumin, and absolute eGFR. An increase in body weight from 70 kg to 120 kg is predicted to increase pirtobrutinib clearance by 24 %; a decrease in absolute eGFR from 90 mL/min to 30 mL/min is predicted to reduce pirtobrutinib clearance by 16 %; and a decrease in serum albumin from 40 g/L to 30 g/L is predicted to increase pirtobrutinib clearance by 21 %. These factors alone are unlikely to result in meaningful changes to pirtobrutinib PK and no dose adjustments are recommended.

The mean (CV %) steady-state AUC and C_{max} were 92600 h*ng/mL (39 %) and 6500 ng/mL (25 %), respectively, at the recommended dosage of 200 mg once daily in cancer patients.

At the recommended dosage, pirtobrutinib achieves pharmacokinetic exposures that can exceed the BTK IC_{96} at trough and thus deliver tonic BTK target inhibition throughout the once daily dosing period, regardless of the intrinsic rate of BTK turnover.

Absorption

The absolute bioavailability of pirtobrutinib after a single oral 200 mg dose is 85.5 % in healthy subjects. The median time to reach peak plasma concentration (t_{max}) is approximately 2 hours in both cancer patients and healthy subjects. There is no pH dependency for absorption.

Effect of food
A high-fat, high-calorie meal administered to healthy subjects decreased the C_{max} of pirtobrutinib by 23 % and delayed t_{max} by 1 hour. There was no effect on pirtobrutinib AUC. Pirtobrutinib can be taken with or without food.

Distribution

The mean apparent central volume of distribution of pirtobrutinib is 34.2 L in cancer patients. The plasma protein binding is 96 % and was independent of concentration between 0.5 and 50 µM. In plasma from healthy subjects and subjects with severe renal impairment the protein binding was 96 %. Mean blood-to-plasma ratio is 0.79.

Biotransformation

Hepatic metabolism is the main route of clearance for pirtobrutinib. Pirtobrutinib is metabolised to several inactive metabolites by CYP3A4, UGT1A8 and UGT1A9.

Strong CYP3A Inhibitors: Co-administration of a single 200 mg dose of pirtobrutinib with itraconazole (strong CYP3A inhibitor) increased AUC of pirtobrutinib by 49%.

Moderate CYP3A Inhibitors: Verapamil and diltiazem (moderate CYP3A inhibitors) are predicted to increase the AUC of pirtobrutinib by 30% and 20%, respectively.

Strong CYP3A inducers: Coadministration of a single 200 mg dose of pirtobrutinib with rifampin (strong CYP3A inducer) decreased the AUC of pirtobrutinib by 71%.

Moderate CYP3A Inducers: Efavirenz and bosentan (moderate CYP3A inducers) are predicted to decrease the AUC of pirtobrutinib by 49% and 27%, respectively.

Pirtobrutinib inhibits CYP2C8, CYP2C9 and CYP3A4 *in vitro* and minimally inhibits CYP1A2, CYP2B6, CYP2C19 or CYP2D6 at 60 µM. *In vitro* pirtobrutinib induces CYP3A4, CYP3A5, CYP2C19, and CYP2B6.

Pirtobrutinib minimally inhibits UGT1A1 *in vitro* with an IC50 = 18 µM.

Co-administration with transport substrates/inhibitors
In vitro studies indicated that pirtobrutinib is a substrate of P-gp and BCRP.

Pirtobrutinib is an *in vitro* inhibitor of P-gp and BCRP. Pirtobrutinib affected the PK of digoxin, a P-gp substrate, and rosuvastatin, a BCRP substrate, in clinical studies (see section 4.5).

Elimination

The mean apparent clearance of pirtobrutinib is 2.05 L/h with an effective half-life of approximately 19.9 hours. Following a single radiolabeled dose of pirtobrutinib 200 mg to healthy subjects, 37 % of the dose was recovered in faeces (18 % unchanged) and 57 % in urine (10 % unchanged).

Special populations

Age, gender, race and body weight
Based on a population pharmacokinetic analysis in patients with cancer, age (range 22-95 years), race, gender, and body weight (range 35.7-152 kg) had no clinically meaningful effect on the exposure of pirtobrutinib.

Renal impairment
In a population PK analysis of cancer patients, patients with mild (eGFR 60 to < 90 ml/min) or moderate renal impairment (eGFR 30 to < 60 ml/min), pirtobrutinib clearance was 16 % to 27 % lower compared to clearance in patients with normal renal function, resulting in expected exposure of AUC = 94100 ng*h/mL and C_{max} = 6680 ng/mL in patients with mild renal impairment (16-19 % higher compared to patients with normal renal function) and AUC = 108000 ng*h/mL and C_{max} = 7360 ng/mL in patients with moderate renal impairment (28 to 36 % higher compared to patients with normal renal function).

In a clinical pharmacology study of otherwise healthy volunteers, apparent clearance was 35 % lower in four participants with severe renal impairment (eGFR 15 to < 30 ml/min) compared to eight participants with normal renal function (eGFR ≥ 90 ml/min), resulting in exposures of $AUC_{0\text{-}inf}$ = 115000 ng*h/mL and C_{max} = 2980 ng/mL (62 % higher and 7 % lower, respectively, compared to normal renal function).

Patients with end-stage renal disease receiving dialysis were not studied (see section 4.2).

Hepatic impairment
There were no clinically significant differences in the PK of pirtobrutinib for any degree of hepatic impairment (by Child-Pugh A, B, and C or any total bilirubin and any AST). In a dedicated hepatic impairment study mean AUC and C_{max} of pirtobrutinib were similar between subjects with mild hepatic impairment (Child-Pugh A) and subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh B) the AUC was 15 % lower compared to normal hepatic function and the C_{max} was similar. In subjects with severe hepatic impairment (Child-Pugh C) the AUC of pirtobrutinib was 21 % lower and mean C_{max} was 24 % lower compared to subjects with normal hepatic function. The fraction unbound (fu) for pirtobrutinib in subjects generally increased as the severity of hepatic impairment increased. Therefore, after correcting pirtobrutinib PK exposure parameters with fu, there was no clinically significant difference observed in the unbound pirtobrutinib PK exposure parameters (AUCu and C_{max},u) between subjects with any degree of hepatic impairment and normal hepatic function.

Paediatric population
No pharmacokinetic studies were performed with pirtobrutinib in patients under 18 years of age.

5.3 Preclinical safety data

In the repeat-dose studies decreased T-cell dependent antibody response in rats (at 0.69-fold human exposure at the recommended dose of 200 mg based on AUC) and minimal to mild corneal lesions in dogs (at 0.42-fold human exposure) were observed. Mild to moderate vascular necrosis and vascular/perivascular inflammation in large pulmonary blood vessels were observed only in rats. These effects occurred at clinically relevant exposure levels.

Genotoxicity / Carcinogenicity

Pirtobrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay. Pirtobrutinib was aneugenic in two *in vitro* micronucleus assays using human peripheral blood lymphocytes. Pirtobrutinib had no effect in an *in vivo* rat bone marrow

micronucleus assay at doses up to 2000 mg/kg (single dose), which is approximately 11-fold higher exposure (considering unbound C_{max} value in female animals) than human exposure at 200 mg.

Carcinogenicity studies have not been conducted with pirtobrutinib.

Embryotoxicity/ Teratogenicity

In animal reproduction studies, administration of pirtobrutinib to pregnant rats during organogenesis resulted in decreased foetal weight, embryo-foetal mortality, and foetal malformations at maternal exposures 3.0-fold human exposure at the recommended dose of 200 mg based on AUC.

Reproduction toxicity

No fertility studies have been conducted with pirtobrutinib. In repeat-dose toxicity studies of up to 3 months duration, pirtobrutinib had no effect on male reproductive organs at 0.69-fold and 0.42-fold human exposure in rats and dogs, respectively, at the recommended dose of 200 mg based on AUC. Pirtobrutinib had no effect on female reproductive organs at 4.0-fold and 0.42-fold human exposure in rats and dogs, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pirtobrutinib Spray Dray Dispersion:
Hypromellose Acetate Succinate

Other Core Tablet Ingredients:
Microcrystalline Cellulose
Lactose monohydrate
Croscarmellose sodium
Silicon Dioxide
Magnesium stearate

Film-coating:
Color Mixture Blue 03K105008

Color Mixture Blue 03K105008:
Hypromellose
Titanium dioxide
Triacetin
FD&C Blue #2- Aluminum Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Jaypirca 50 mg film-coated tablets

White 75 ml HDPE (High Density Polyethylene) bottle with child-resistant closure (CRC) containg an aluminium foil induction heat seal (HIS) liner.
Pack size: bottle of 30 tablets.

Jaypirca 100 mg film-coated tablets

White 75 ml HDPE (High Density Polyethylene) bottle with child-resistant closure (CRC) containg an aluminium foil induction heat seal (HIS) liner.
Pack sizes: bottle of 30 tablets (a physician sample only) and bottle of 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

8. LICENSE HOLDER

Eli Lilly Israel Ltd., 4 HaSheizaf St., P.O.Box 4246, Ra'anana 4366411

9. LICENSE NUMBER

Jaypirca 50 mg**:** 175-13-37717-99
Jaypirca 100 mg: 175-14-37718-99

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