25 June 2026
EMADOC-1700519818-3103120
Medicinal Products for Human Use (CHMP)

Assessment report

Jaypirca

International non-proprietary name: Pirtobrutinib

Procedure No. EMA/VR/0000316267

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	Adverse event
AEPCS	adverse events of potential clinical significance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC0−24*h,ss*	Area under the concentration vs. time curve at steady state within a dosing interval
BCL2i	B-cell lymphoma-2 inhibitors
BendaR or BR	bendamustine plus rituximab
BOR	Best overall response
BQL	Concentration below the lower limit of quantification
BTK	Bruton's Tyrosine Kinase
BTKi	Bruton's tyrosine kinase inhibitor
CAR-T	chimeric antigen receptors T-cells
C*av*	Average concentration from the start of treatment
cBTKi	covalent BTK inhibitor
CIT	chemoimmunotherapy
C*max,ss*	Maximum concentration at steady state
C*max*	Maximum concentration
C*minss*	Trough concentration at steady state
C*min*	Trough concentration within a dose interval
CI	Confidence interval
CL/F	Apparent clearance measured after extravascular dosing
CLL	Chronic lymphocytic leukemia
CR	Complete response
CR	complete remission
Cri	complete remission with incomplete hematologic recovery
CSR	clinical study report
CTCAE	Common Terminology Criteria in Adverse Events
CWRES	Conditional weighted residual
DOR	duration of response
E*max*	Maximum effect

EAIR	exposure-adjusted incidence rates
EBE	Empirical Bayes estimates
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
EFS	event-free survival
eGFR	Estimated glomerular filtration rate
ER	Exposure-response
ES	Exposure-safety
FOCE	First-order conditional estimation option in NONMEM
GOF	Goodness of fit
HR	hazard ratio
IC90	90% inhibition of BTK
IC96	96% inhibition of BTK
IIV	Inter-occasion variability
IGHV	immunoglobulin heavy chain variable region gene
IOV	Inter-occasion variability
IPRED	Individual prediction
IRC	Independent Review Committee
ITT	intent-to-treat
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive web response system
MAP	Modeling analysis plan
MedDRA	Medical Dictionary for Regulatory Activities
MTT	Mean transit time
NCI-CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
NE	Not estimable
NHL	Non-Hodgkin lymphoma
nPR	Nodular partial response
OFV	Objective function value
ORR	Overall response rate
OS	Overall survival
pcVPC	Prediction corrected visual predictive check

PD	progressive disease
PFS	Progression-free survival
PI3Ki	Phosphoinositide 3-kinase (PI3K) inhibitor
PK	Pharmacokinetic
PKPD	Pharmacokinetic-pharmacodynamic
PopPK	Population pharmacokinetic
PR	Partial response
PRED	Population prediction
PR-L	Partial Response with Lymphocytosis
PsN	Perl-speaks-NONMEM
PY	patient years
QC	Quality control
QD	once daily
R/R	relapsed or refractory
RP2D	Recommended Phase 2 dose
SAE	serious adverse event
SCM	Stepwise covariate model building tool in PsN
SLL	small lymphocytic lymphoma
SOC	system organ class
SPM	second primary malignancy
T50	Half maximal effective concentration
TE	treatment-emergent
TEC	Tyrosine Kinase Expressed in Hepatocellular Carcinoma
TEAE	Treatment-emergent adverse event
TLS	tumour lysis syndrome
TN	treatment-naïve
TTE	Time-to-Event
TTNT	Time to next treatment
TTW	Time to worsening
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
VPC	Visual predictive check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 28 November 2025 an application for a variation.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adult patients with chronic lymphocytic leukaemia (CLL) for JAYPIRCA, based on interim results from studies LOXO-BTK-20023 (BRUIN-CLL-313) and LOXO-BTK-20030 (BRUIN-CLL-314). Study 20023 is a phase 3 open-label, randomized study of pirtobrutinib (LOXO-305) versus bendamustine plus rituximab in untreated patients with CLL/SLL. Study 20030 is a phase 3 open-label, randomized study of pirtobrutinib (LOXO-305) versus ibrutinib in patients with CLL/SLL. As a consequence, sections 4.1, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0197/2021 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Information on paediatric requirements

Not applicable

Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Edward Laane

Timetable	Actual dates
Submission date	28 November 2025
Start of procedure:	27 December 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 February 2026
PRAC Rapporteur's preliminary assessment report circulated on:	26 February 2026
CHMP CoRapporteur's preliminary assessment report circulated on:	6 March 2026
PRAC RMP advice and assessment overview adopted by PRAC Joint	12 March 2026
Joint Rapporteur's updated assessment report circulated on:	19 March 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 March 2026
MAH responses submitted to the CHMP on:	24 April 2026
Joint CHMP Rapporteur's preliminary assessment report on the MAH responses circulated on:	26 May 2026
Joint Rapporteur's updated assessment report on the MAH responses circulated on:	18 June 2026
CHMP opinion:	25 June 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

CLL and SLL are incurable B-cell malignancies considered distinct clinical manifestations of the same biologic disease by the World Health Organization classification and are managed similarly; hereafter both are collectively referred to as CLL in this report (Eichhorst et al. 2015; Zelenetz et al. 2015; NCCN 2025).

Claimed therapeutic indication

The MAH is claiming a line-agnostic indication for pirtobrutinib as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL).

Epidemiology

With an estimated incidence of 4.7 new cases per 100,000 individuals, CLL is the most common form of chronic leukaemia in the US and Europe (Bosch and Dalla-Favera 2019). According to data from the cancer registries across Europe, the crude rate (per 100,000) of CLL from the years 2000 to 2002 was 4.92 (male: 5.87; female 4.01) (Sant et al. 2010). Using data from the Global Cancer Incidence and Mortality (GLOBOCAN)/European Cancer Information System (ECIS) and the Nordic database (NORDCAN), the overall complete prevalence of CLL/SLL in the EU was estimated to be approximately 5 per 10,000 (Danckert et al. 2019; Ferlay et al. 2020).

Clinical presentation and prognosis

CLL is characterised by the clonal proliferation and accumulation of mature, typically CD5-positive B cells within the blood, bone marrow, lymph nodes, and spleen (Hallek et al. 2019). The presentation and clinical course are highly variable, ranging from asymptomatic, indolent disease that may never require therapy (in approximately 30% of patients) to active disease in patients who have inflammatory or B-cell symptoms (that is, weight loss, night sweats, and fever), fatigue, recurrent infections, or autoimmune complications.

Infection is one of the most important clinical problems in patients with CLL. In a nationwide Danish cohort of all patients diagnosed with CLL between 2010 and 2016 (N = 2905), the cumulative incidence of severe infection, was 31% over 5 years. Autoimmune complications, in most cases, autoimmune thrombocytopenia or haemolytic anaemia, can also present at any time of disease without other signs of CLL progression and occur in approximately 4% to 10% of patients with CLL (Tsang and Parikh 2017; Burger 2020). Patients with CLL are at a higher risk of developing a second primary malignancy (Hisada et al. 2001; Schöllkopf et al. 2007) possibly due to reasons such as perturbed immune function and DNA damage secondary to prior treatment (Benjamini et al. 2015; Bond et al. 2020).

Although recent advances have led to improvements in patient prognosis, in the vast majority of cases, CLL remains an incurable disease. While some patients may initially follow an indolent course after diagnosis of CLL, with a 5-year relative survival of 89.3%, the trajectory can be aggressive once the disease progresses, particularly in cases where patients present with advanced disease at diagnosis or exhibit poor prognostic markers (Chiorazzi et al. 2021; SEER*Explorer 2025). CLL as an advanced disease can progress aggressively, with related complications being the primary cause of death in nearly 75% of patients (Strati et al. 2017). The outlook is further diminished for patients who fail frontline treatment, and response durations to successive treatments progressively shorten (Fischer et al. 2019; Eyre et al. 2023).

Management

The selection of one treatment strategy over another is highly influenced by patient age, comorbid illness, patient preference, prior therapy (if any), molecular prognostic factors, and treatment setting (for example, community versus academic).

According to NCCN and ESMO guidelines at the time of global study initiation and during the enrolment period for Study 20023, one of the pivotal studies in support of this application, (September 2021 to April 2023), available treatment options for TN patients with CLL and no evidence of del(17p) included the following classes: cBTKi, BCL2i, chemotherapy, and CIT. International guidelines listed targeted therapies and chemoimmunotherapy (CIT)-based regimens among recommended options, but increasing preference was given to targeted agents in many clinical settings. Real world data from several studies have reported that approximately 23% to 43% of patients with TN CLL who initiated treatment received frontline CIT (Ghosh et al. 2024; Huntington et al. 2024; Yang et al. 2024).

Covalent BTKi (ibrutinib, acalabrutinib, and zanubrutinib) have recently reshaped the treatment landscape for patients with CLL, having shown deep responses with improved PFS compared with CIT (Shanafelt et al. 2019; Sharman et al. 2019; Al-Sawaf et al. 2020; Burger et al. 2020; Sharman et al. 2020; Tam et al. 2022).

Similarly, time-limited therapy with BCL2i, namely venetoclax, in combination with anti-CD20 (obinutuzumab or rituximab) has demonstrated good efficacy in both TN and R/R CLL.

The available therapy options for the treatment of R/R CLL overlap with those used in frontline CLL and not only include cBTKi, BCL2i, and CIT, but also PI3Ki. The treatment option selected in R/R CLL is similarly influenced by patient and disease characteristics considered in frontline, but also by the choice of frontline therapy as well as the fitness of the patient (Hallek et al. 2018; Eichhorst et al. 2024; NCCN 2025). Since many patients have historically received CIT in frontline therapy, there is a large proportion of patients with R/R CLL that are cBTKi naive.

Despite these recent advances, none of these treatments can cure CLL, and CLL remains a life limiting disease. Furthermore, although they have substantially improved outcomes, existing targeted agents have limitations, including tolerability considerations, resistance mechanisms, and practical constraints that influence patient management (Tam and Thompson 2024).

2.1.2. About the product

Pirtobrutinib is an oral, reversible, small-molecule, noncovalent inhibitor of BTK. BTK is a member of the TEC family of nonreceptor tyrosine kinases and is a key component of the B-cell receptor signalling complex.

JAYPIRCA (pirtobrutinib) was initially approved as monotherapy in the EU under conditional marketing authorisation for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a BTK inhibitor (2023).

Subsequently, it was also approved as monotherapy or the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a BTK inhibitor (2025).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): pirtobrutinib			
CAS-number (if available): 2101700-15-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	pH 5 = 2.965 pH 7 = 2.850 pH 9 = 2.757	log K_{ow} <4.5 No bioaccumulation potential
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation potential - log K_{ow}	OECD 107	pH 5 = 2.965 pH 7 = 2.850 pH 9 = 2.757	not B
Persistence	OECD 308 DT_{50} at 12°C	Sediments from two different river systems: - DT_{50} water: 22.6, 148.7 d - DT_{50} whole system: 40, 393 d	vP
Toxicity	CMR	Toxicity to reproduction observed	T
PBT-statement:	Pirtobrutinib is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	0.074	µg/L	< 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Soil: K_{Foc} = 731 L·kg^{-1} (soil 1) K_{Foc} = 720 L·kg^{-1} (soil 2) K_{Foc} = 414 L·kg^{-1} (soil 3) K_{Foc} = 768 L·kg^{-1} (soil 4) Sludge: K_{oc} = 114 L·kg^{-1} (sludge 1) K_{oc} = 234 L·kg^{-1} (sludge 2) K_{oc} = 197 L·kg^{-1} (sludge 3)	Soil: average K_{Foc} used in ERA, 658 L·kg^{-1}

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 10.8 d (1), 69.7 d* (2) $DT_{50, sediment}$ = 36.7 d (1), nd (2) $DT_{50, system}$ = 18.7 d (1), 185 d (2) (1) = Tarnock (HOC) sediment, (2) = Ashpringston (LOC) sediment % shifting to sediment = 25.4 % (1), 41.6% (2) % CO_2 = 0.1% (1), 0.6% (2) % NER = 20.5% (1),13.5% (2) Transformation products >10% = YES: TP RRT 0.80: HPLC: 12.5 % (mean of two systems) TP RRT 1.02: HPLC: 51.9% (only > 10% in HOC)	at 20°C. *DFOP, k2DT50, slow phase. Sediment from two different river systems evaluated. At day 14, (%parent + %NER), Sediment risk assessment triggered At test end At test end Water, day 101 (2) Sediment, d 101 (1) TP RRT: 0.80: molecular formula: C14H13O3N4F3 TP RRT: 1.02: molecular formula: C21H19F4N5O3

Phase IIa Effect studies

Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC	504	µg/L	Growth rate and yield
Daphnia sp. Reproduction Test/*Daphnia magna*	OECD 211	NOEC	1760	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	9950	µg/L	Total length, wet weight, dry weight

Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000000	µg/L	Heterotrophic, nitrification and total respiration
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC NOEC	31 182	mg/kg mg/kg	1.7% o.c. content Emergence ratio, male and female development rate, normalised to 10% organic carbon

2.2.2. Discussion on non-clinical aspects

The CHMP agreed that no new non-clinical pharmacology/absorption, distribution, metabolism and excretion (ADME))/toxicology studies are needed to support treatment of pirtobrutinib in the targeted expanded CLL population which is being claimed with this extension of indication application. As such, there is no proposed amendments to section 5.3 of the SmPC which is also considered acceptable.

An Environmental Risk Assessment (ERA) was submitted, taking into account the Guideline on the environmental risk assessment of medicinal products for human use, (EMA/CHMP/SWP/4447/00 Rev. 1- Corr., 2O24) with this application, updating where necessary the one that was last submitted for Jaypirca (EMEA/H/C/005863/II/0002). In that application the exposure calculations were conservative using 5-year prevalence data for the overall MCL and CLL populations rather refining the prevalence based on the authorised indications of pirtobrutinib at the time.

Thus, the conclusions of the previous ERA that the use of pirtobrutinib by patients was not expected to result in a significant environmental risk, and that pirtobrutinib is neither PBT (persistent and bioaccumulative and toxic) nor vPvB (very persistent and very bioaccumulative) are still valid. The revised Guideline on the environmental risk assessment of medicinal products for human use, (EMA/CHMP/SWP/4447/00 Rev. 1- Corr., 2O24) has been taken into account for the present ERA submission

2.2.3. Conclusion on the non-clinical aspects

In accordance with the current guidelines only an update to the ERA was submitted. The risk for the environment remains unchanged with the updated ERA and thus pirtobrutinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Objectives	Study design	Dosing regimen	Enrolment	Study population	Study status
LOXO BTK 20023 (J2N-OX JZNP)	To evaluate the safety and efficacy of pirtobrutinib	Open-label, randomised, crossover optional study (crossover only applicable to Arm B)	Arm A: pirtobrutinib (200 mg QD) Arm B: bendamustine (90 mg/m2 IV Day 1 and 2, C1-C6) and rituximab (375 mg/m2 IV Day 1 C1; 500 mg/m2 IV Day 1, C2-C6)	282	Untreated CLL/SLL patients	Ongoing Primary outcome data cutoff date: 11 Jul 2025
LOXO BTK 20030 (J2N-OX JZNU)	To evaluate the safety and efficacy of pirtobrutinib	Part 1: open-label, randomised study Part 2: open-label, non-randomized	Part 1: Arm A: pirtobrutinib (200 mg QD) Arm B: ibrutinib (420 mg QD) Part 2: pirtobrutinib (200 mg QD)	Part 1: 662 randomized Part 2: 0	Part 1: BTK inhibitor naïve CLL/SLL patients (who may be treatment naïve or previously treated with other agents) Part 2: untreated CLL/SLL patients with del(17p)	Ongoing Primary outcome data (Part 1) cutoff date: 11 Jul 2025

2.3.2. Pharmacokinetics

PopPK Model

The PopPK model of pirtobrutinib developed previously (see EMEA/H/C/005863/II/0002) using data from 18001 and 20020 was used as the basis for the current updated PopPK analysis. The PopPK model was fitted to the concentration-time data from the combined dataset from Study 18001 (data

cutoff: 08 February 2023), Study 20020 (data cutoff: 29 August 2024), Study 20023 (data cutoff: 11 July 2025), and Study 20030 (data cutoff: 10 June 2025) (popPK-ER report for Studies 20023 and 20030). PK parameters were re-estimated using the nonlinear mixed effects (NONMEM).

A total of 1241 participants were included in the PK analysis population.

Demographics of the patients included in the popPK analysis are summarised in **Table 1** and **Table 2**.

Table 1: Summary of Continuous Baseline Patient Characteristics for the PK analysis by Study

	18001 (N = 668)	20020 (N = 112)	20023 (N = 139)	20030 (N = 322)	All (N = 1241)
Age (years)					
Mean (%CV)	67.4 (15)	66.9 (13.8)	63.9 (15.5)	66.1 (14.9)	66.6 (15)
Median (range)	68 (22 - 95)	67 (42 - 85)	65 (29 - 84)	67 (39 - 90)	68 (22 - 95)
Weight (kg)					
Mean (%CV)	78.2 (22.3)	76.9 (21.3)	74.7 (24.4)	76.2 (21.3)	77.2 (22.2)
Median (range)	76.6 (35.7 - 152)	74.9 (47.4 - 128)	73 (41.9 - 138)	75 (40 - 154)	75.6 (35.7 - 154)
Not available	2 (0.3%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)
Body Mass Index (kg/m2)					
Mean (%CV)	26.7 (17.9)	26.4 (18.1)	26.2 (19.1)	26.7 (17.6)	26.6 (18)
Median (range)	26.3 (14.1 - 47.2)	25.4 (18.5 - 43)	25.8 (15.7 - 39.9)	26 (16.6 - 44.9)	26.1 (14.1 - 47.2)
Not available	35 (5.2%)	2 (1.8%)	0 (0%)	3 (0.9%)	40 (3.2%)
Albumin (g/L)					
Mean (%CV)	39.9 (13.6)	41.8 (11.7)	43.8 (9.2)	44.1 (9.5)	41.6 (12.7)
Median (range)	41 (19 - 56.5)	42 (25 - 53.3)	44 (26 - 52)	44.2 (13.7 - 55)	42 (13.7 - 56.5)
Not available	0 (0%)	2 (1.8%)	0 (0%)	2 (0.6%)	4 (0.3%)
CKD-EPI Estimated GFR (Absolute) (mL/min)					
Mean (%CV)	79.6 (29.9)	74.9 (31.5)	83.9 (23.6)	82.3 (25.6)	80.4 (28.2)
Median (range)	78.6 (26.2 - 159)	75.4 (26.6 - 134)	83 (45 - 136)	82 (30 - 149)	80.4 (26.2 - 159)
Not available	35 (5.2%)	2 (1.8%)	0 (0%)	3 (0.9%)	40 (3.2%)

CV: coefficient of variation; eGFR: estimated glomerular filtration rate (CKD-EPI); CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; N: number of patients

Table 2: Summary of Categorical Baseline Patient Characteristics for the PK analysis by Study

	18001 (N = 668)	20020 (N = 112)	20023 (N = 139)	20030 (N = 322)	All (N = 1241)
Sex					
Female	224 (33.5%)	33 (29.5%)	56 (40.3%)	112 (34.8%)	425 (34.2%)
Male	444 (66.5%)	79 (70.5%)	83 (59.7%)	210 (65.2%)	816 (65.8%)
Race					
White	563 (84.3%)	92 (82.1%)	102 (73.4%)	248 (77%)	1005 (81%)
Black or African American	22 (3.29%)	1 (0.893%)	0 (0%)	7 (2.17%)	30 (2.42%)
Asian	47 (7.04%)	14 (12.5%)	33 (23.7%)	42 (13%)	136 (11%)
Native Hawaiian or Other Pacific Islander	2 (0.299%)	0 (0%)	1 (0.719%)	1 (0.311%)	4 (0.322%)
American Indian or Alaska Native	3 (0.449%)	0 (0%)	0 (0%)	1 (0.311%)	4 (0.322%)
Other	29 (4.34%)	0 (0%)	2 (1.44%)	8 (2.48%)	39 (3.14%)
Not Reported	2 (0.299%)	5 (4.46%)	1 (0.719%)	15 (4.66%)	23 (1.85%)
Renal Function					
Normal	208 (31.1%)	29 (25.9%)	55 (39.6%)	114 (35.4%)	406 (32.7%)
Mild impairment	288 (43.1%)	54 (48.2%)	67 (48.2%)	151 (46.9%)	560 (45.1%)
Moderate impairment	132 (19.8%)	24 (21.4%)	17 (12.2%)	54 (16.8%)	227 (18.3%)
Severe impairment	5 (0.749%)	3 (2.68%)	0 (0%)	3 (0.932%)	11 (0.886%)
Not Reported	35 (5.24%)	2 (1.79%)	0 (0%)	0 (0%)	37 (2.98%)
NCI Hepatic Function Classification					
Normal	531 (79.5%)	90 (80.4%)	105 (75.5%)	259 (80.4%)	985 (79.4%)
Mild	116 (17.4%)	18 (16.1%)	10 (7.19%)	51 (15.8%)	195 (15.7%)
Moderate	18 (2.69%)	3 (2.68%)	1 (0.719%)	2 (0.621%)	24 (1.93%)
Severe	1 (0.15%)	0 (0%)	1 (0.719%)	4 (1.24%)	6 (0.483%)
Not Reported	2 (0.299%)	1 (0.893%)	22 (15.8%)	6 (1.86%)	31 (2.5%)
Cancer Type					
CLL/SLL	279 (41.8%)	112 (100%)	139 (100%)	322 (100%)	852 (68.7%)
MCL	145 (21.7%)	0 (0%)	0 (0%)	0 (0%)	145 (11.7%)
NHL	244 (36.5%)	0 (0%)	0 (0%)	0 (0%)	244 (19.7%)
Formulation					
T1	209 (31.3%)	0 (0%)	0 (0%)	0 (0%)	209 (16.8%)
T2	459 (68.7%)	112 (100%)	139 (100%)	322 (100%)	1032 (83.2%)

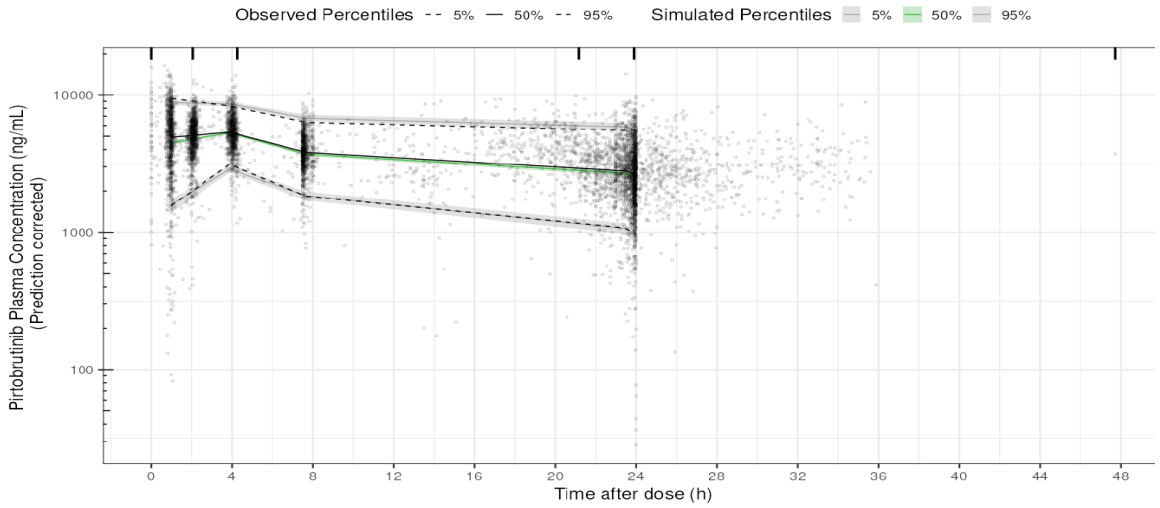
CLL: chronic lymphocytic leukaemia; CV: coefficient of variation; MCL: mantle cell lymphoma; N: number of patients; NHL: non-Hodgkin lymphoma; SLL: small lymphocytic lymphoma; T1 and T2: Tablet 1 and 2; Renal function classified by CKD-EPI: normal (eGFR ≥ 90 mL/min), mild impairment (60 mL/min ≤ eGFR <90 mL/min), moderate impairment (30 mL/minute ≤ eGFR <60 mL/min), and severe impairment (15 mL/min ≤ eGFR <30 mL/min); NCI Hepatic function classified by: National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction Patel et al. (2004). Classified as normal (TBI ≤ ULN and AST ≤ULN), mild impairment (TBI ≤ 1.5-ULN and AST >ULN) or (ULN <TBI ≤ 1.5 ULN), moderate impairment (1.5 ULN <TBI ≤ 3 ULN), or severe impairment (TBI > 3 ULN).

Graphical Assessment of Goodness-of-Fit

The prediction corrected visual predictive check (VPC) of the PopPK model is shown in **Figure 1**.

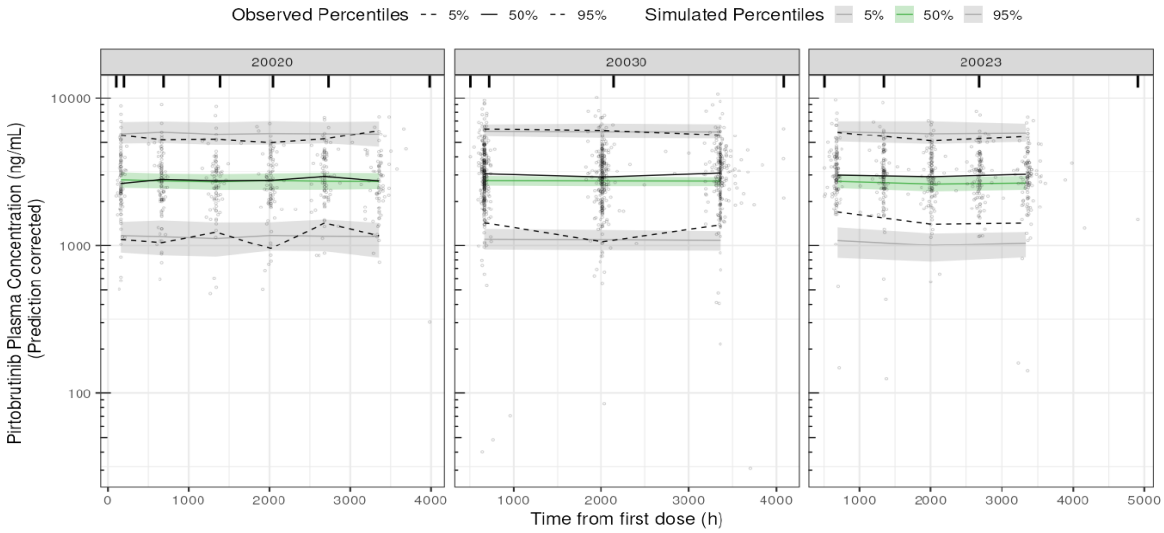
Of the phase 3 studies, study 20020 was well described, while the median as well as the 5th percentile for studies 20023 and 20030 were slightly underpredicted (**Figure 2**).

Figure 1. Prediction corrected VPC time from last dose final model, all studies



Solid Black Line: Median of the observed concentrations; Dashed lines: 5th and 95th percentiles of the observed concentrations; Shaded Areas: 95% CI around the simulated median (green area) and simulated 5th and 95th percentiles (gray areas); Black vertical stripes: Indicate bin borders.

Figure 2. Prediction corrected VPCk time from first dose final model, by Phase 3 Study

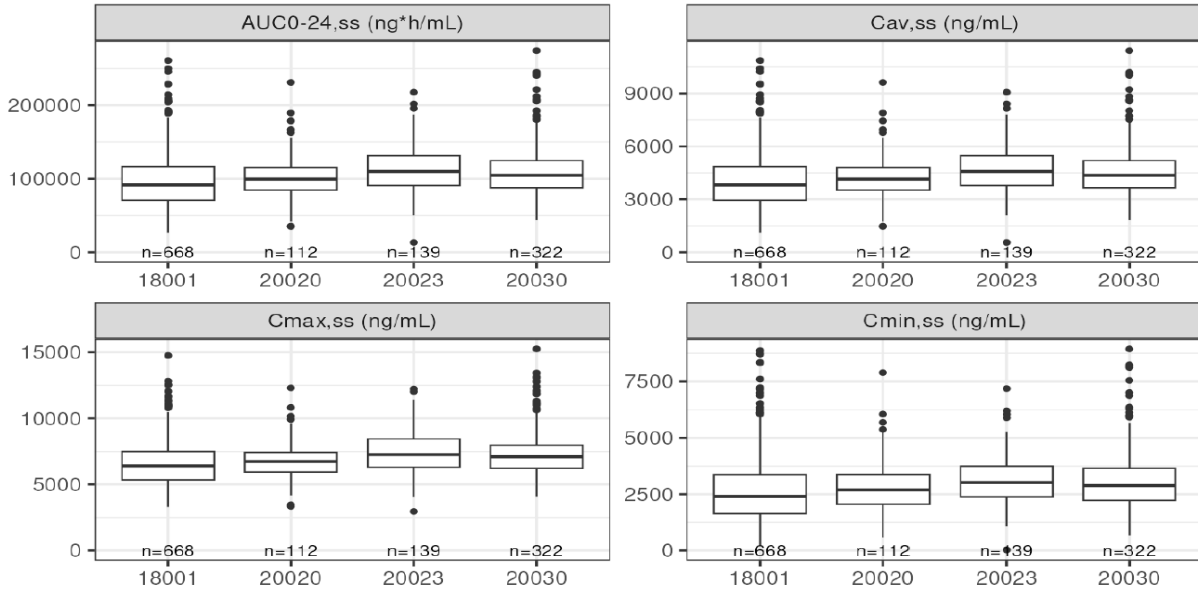


Solid Black Line: Median of the observed concentrations; Dashed lines: 5th and 95th percentiles of the observed concentrations; Shaded Areas: 95% CI around the simulated median (green area) and simulated 5th and 95th percentiles (gray areas); Black vertical stripes: Indicate bin borders

Simulation of Pirtobrutinib Pharmacokinetics

Pirtobrutinib exposures for the patients in studies 18001, 20020, 20023 and 20030 that were included in the PopPK model were simulated using their post-hoc parameter estimates with the nominal dosing regimen of 200 mg QD to steady state. The simulations are shown as boxplots in **Figure 3** and summarised in **Table 3**.

Figure 3. Simulated Exposure Metrics by Study with the Nominal Dose of 200 mg QD



Box plots depict the 25th, 50th and 75th percentiles. Whiskers represent 1.5 times the inter-quartile range. AUC0-24,ss: Area under the concentration-time profile under a dosing interval at steady state; Cmax,ss: Maximum concentration at steady-state, Cmin,ss: Trough concentration at steady-state, Cav,ss: Average concentration at steady-state

Table 3 : Simulated pirtobrutinib exposure using the population PK model with post-hoc estimates for 200 mg dose

	18001 (N = 668)	20020 (N = 112)	20023 (N = 139)	20030 (N = 322)	All (N = 1241)
AUC0-24,ss (ng*h/mL)					
Geometric mean (%CV)	91200 (37.3)	97900 (32.8)	107000 (33.8)	106000 (30.1)	97100 (35.5)
Cmin,ss (ng/mL)					
Geometric mean (%CV)	2310 (57.7)	2560 (49)	2840 (57.7)	2840 (41.5)	2520 (54.1)
Cmax,ss (ng/mL)					
Geometric mean (%CV)	6390 (24.6)	6700 (21.8)	7220 (23.1)	7110 (21.8)	6690 (24)
Cav,ss (ng/mL)					
Geometric mean (%CV)	3800 (37.3)	4080 (32.8)	4460 (33.8)	4410 (30.1)	4050 (35.5)

AUC0-24,ss: area under the concentration-time profile under a dosing interval at steady state; Cav,ss: average concentration at steady-state; Cmax,ss: maximum concentration at steady-state, Cmin,ss: trough concentration at steady-state; CV: coefficient of variation; N: number of patients; QD: once daily

The geometric mean elimination half-life of pirtobrutinib for patients in studies 18001, 20020, 20023 and 20030 is estimated to be 19.9 hours (CV 31.3%).

Parameter estimates are presented in **Table 4**.

Table 4: Parameters estimates for final population PK model

Parameter	Description	Unit	Estimate	95% CI	Shrinkage %
F1	Bioavailability	fraction	1.00 (fixed)	-	-
MTT	Mean Transit Time	h	1.05	0.989 - 1.11	-
CL	Clearance	L/h	1.98	1.94 - 2.02	-
Vc	Central volume of distribution	L	35.4	32.7 - 38	-
Q	Intercompartmental clearance	L/h	6.96	4.21 - 9.71	-
Vp	Peripheral volume of distribution	L	18.5	16.2 - 20.7	-
PRV	Proportional residual variability	-	0.233	0.23 - 0.235	-
ARV	Additive residual variability	-	0.00 (fixed)	-	-
CLWT	Allometry on CL and Q[a]	-	0.411	0.333 - 0.489	-
VWT	Allometry on Vc and Vp[b]	-	0.790	0.73 - 0.851	-
CLALB	Albumin on CLL[c]	-	-0.650	-0.725 - -0.574	-
CLGFR	GFR on CL[d]	-	0.00366	0.00316 - 0.00417	-
VcALB	Albumin on Vc[e]	-	-0.473	-0.584 - -0.361	-
IIV MTT	Interindividual variability MTT	Variance	0.0644	0.0332 - 0.0956	70.5
IIV CL	Interindividual variability CL	Variance	0.0980	0.091 - 0.105	4.79
IOV MTT	Interoccasion variability MTT	Variance	0.205	0.173 - 0.238	67.9

CI: Confidence interval; CV: Coefficient of variation; GFR: Glomerular filtration rate; Parameter uncertainty was determined by the covariance step in NONMEM; [a]CL/F = Population estimate of CL*((WT/70)**CLWT); Q/F=Population estimate of Q*(WT/70)**CLWT); [b]Vc/F = Population estimate of Vc*((WT/70)**VWT); Vp/F=Population estimate of Vp*((WT/70)**VWT; [c]CL/F = Population estimate of CL*(exp(CLGFR*(eGFR-78); [d]CL/F = Population estimate of CL*((ALB/41)**CLALB); [e]Vc/F = Population estimate of Vc*((ALB/41)**VcALB)

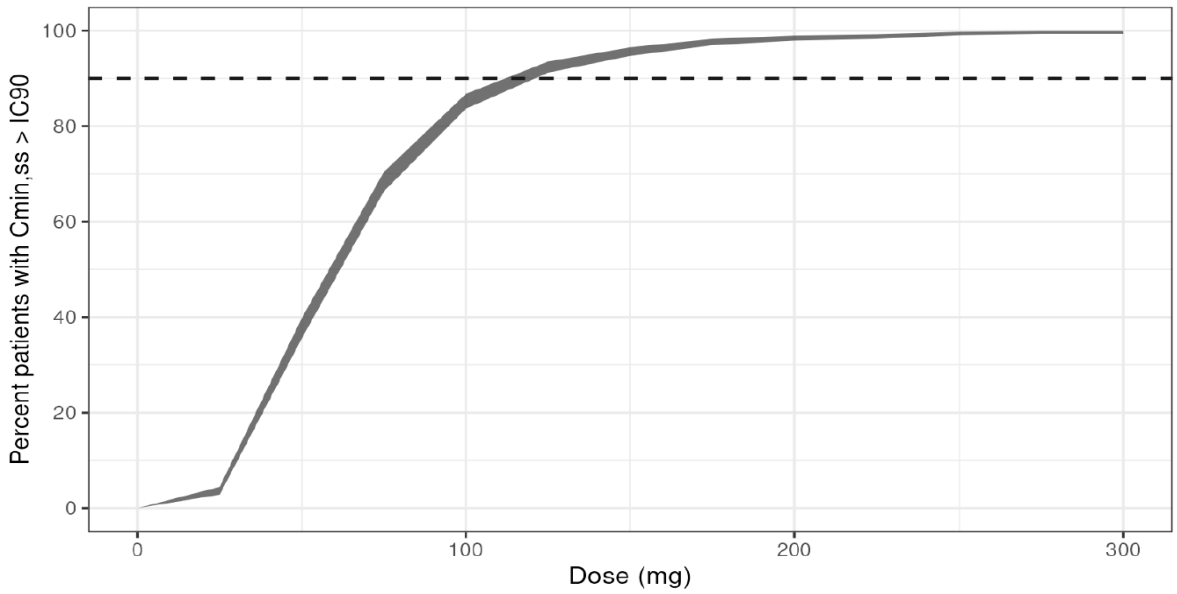
2.3.3. Pharmacodynamics

Predicted BTK inhibition

In an *in vitro* study in wild type BTK-expressing HEK293 cells, the IC50 of pirtobrutinib-mediated inhibition of BTK was determined to be 8.8 nM (data not shown). This value was used to estimate the in vivo potency of pirtobrutinib by adjusting for human plasma protein binding. This protein-binding adjusted IC50 was then used to estimate IC90 and IC96 by assuming Michaelis Menten kinetics, where Emax = 100 and Hill coefficient = 1.

The extent of BTK inhibition in patients was then evaluated by estimating the proportion of patients who achieve minimum steady state concentrations which exceed the protein binding-adjusted IC90 (765 ng/mL) (**Figure 4.**) and the protein binding-adjusted IC96 (2039 ng/mL) over the clinical dose range studied in Study 18001 (25 to 300 mg QD). The simulation was based on 2000 patients sampled from the combined population of studies 18001, 20020, 20023 and 20030.

Figure 4. Simulated proportion of the combined population of studies 18001, 20020, 20023 and 20030 patients achieving minimum concentrations of pirtobrutinib which exceed 90% BTK inhibition.



Cmin,ss: Trough concentration at steady state; IC90: drug concentration that produces 90% of maximum inhibitory effect (Imax). Dotted line represents 90% of patients; Shaded area corresponds to a 95% confidence interval.

2.3.4. Discussion on clinical pharmacology

The MAH used data from the two new studies to provide an updated PK population analysis using the previously developed popPK model. The updated population PK model yielded a good fit, as shown by goodness-of-fit plots and shrinkage. It can therefore be concluded that pirtobrutinib exposure in the new studies in support of this application was similar to those from previous pirtobrutinib studies in the currently approved indications.

As the model described the data adequately no further covariates relationships were investigated. The final model stays the same as the prior model but with updated parameter estimates.

The mean (CV %) steady-state AUC and C_{max} were 97 100 h*ng/mL (35.5 %) and 6 690 ng/mL (24 %), respectively, at the recommended dosage of 200 mg once daily in cancer patients.

The mean apparent central volume of distribution of pirtobrutinib is 35.4 L in cancer patients and the mean apparent clearance of pirtobrutinib is 1.98 L/h with an effective half-life of approximately 19.9 hours.

The updated parameter estimates are reflected in section 5.2 of the SmPC.

To evaluate the predicted extent of BTK inhibition at clinical exposures for patients at the proposed starting dose of 200 mg QD, simulations were performed (n=2000) sampling from the combined population of studies 18001, 20020, 20023 and 20030. PK profiles were compared to the protein binding adjusted IC50 for BTK in vitro. A pirtobrutinib dose of 200 mg QD was associated with near maximal BTK inhibition, with 98.4% of patients predicted to exceed 90% BTK inhibition, and 67.4% predicted to achieve concentrations which exceed 96% BTK inhibition for the entire dosing interval (24

hours). These simulations indicate that 200 mg QD is an appropriate dose for achieving extensive target engagement of BTK throughout the entire dosing interval.

2.3.5. Conclusions on clinical pharmacology

The available population PK data support the known PK profile of pirtobrutinib and confirm the proposed starting dose for pirtobrutinib of 200 mg for the treatment of adult patients with chronic lymphocytic leukaemia.

2.4. Clinical efficacy

2.4.1. Dose response study

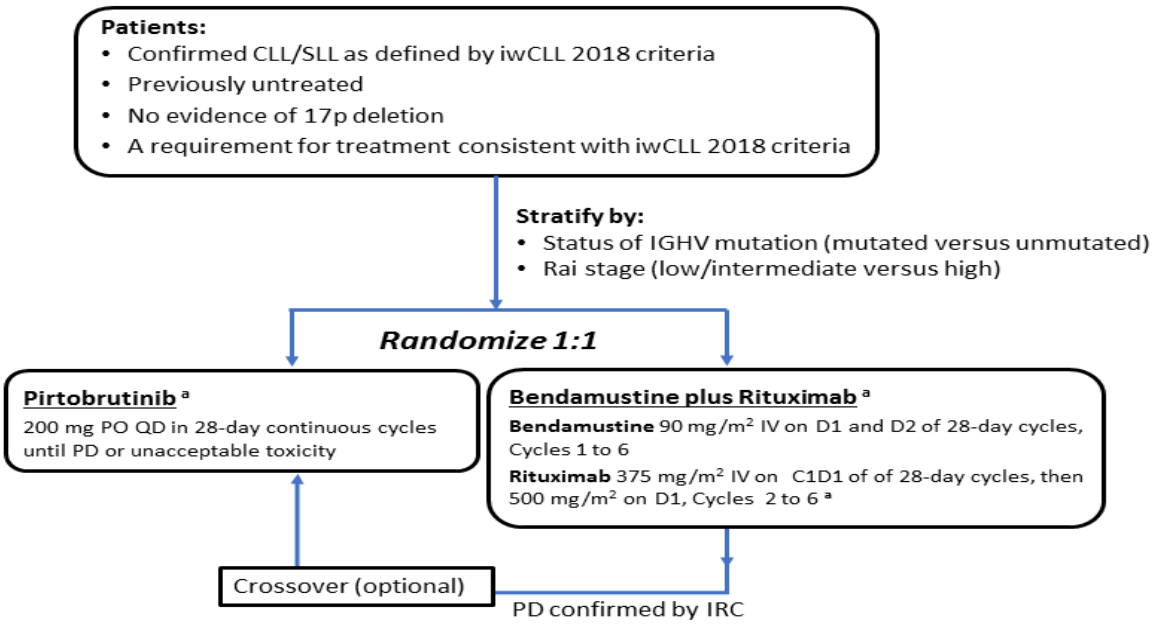
Not applicable

2.4.2. Main studies

Study 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-CLL313).

The study design is depicted in **Figure 5.**

Figure 5. Study 20023 design schema



Methods

Study participants

Investigators enrolled adult TN CLL participants with no evidence of 17p deletion, who required therapy per the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 criteria.

Key inclusion criteria

To be eligible for the study, participants had to meet the following key criteria:

- Age 18 years or older per local regulations at time of enrolment
- Confirmed diagnosis by redacted local laboratory report of CLL/SLL as defined by the iwCLL 2018 criteria
- A requirement for therapy consistent with the iwCLL 2018 criteria for initiation of therapy
- Eastern Cooperative Oncology Group performance score 0 to 2
- Adequate organ function based on results from the most recent laboratory tests prior to enrolment

Key exclusion criteria

Participants were not eligible to be included in the study if they had:

- Prior systemic therapy for CLL/SLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab, rituximab biosimilar, or steroids)
- Known or suspected Richter's transformation to diffuse large B-cell lymphoma, prolymphocytic leukaemia, or Hodgkin lymphoma at any time preceding enrolment
- Presence of 17p deletion by FISH
- Known or suspected history of central nervous system involvement by CLL/SLL
- An active second malignancy
- Active uncontrolled autoimmune cytopenia not on a stable regimen and dose for at least 4 weeks prior to study enrolment, and
- Significant cardiovascular disease.

Treatments

Table 5: Study 20023 Interventions Administered

	Arm A Pirtobrutinib	**Arm B** BendaR	
Treatment	Pirtobrutinib	Bendamustine	Rituximab
Dose	200 mg	90 mg/m^2	375 mg/m^2 on C1D1 and then 500 mg/m^2
Schedule	QD in 28-day continuous cycles	90 mg/m^2 on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6	375 mg/m^2 on C1D1 and then 500 mg/m^2 given on Day 1 of each 28-day cycle, Cycles 2 to 6
Route of administration	Oral	IV	IV
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization

Abbreviations: BendaR = bendamustine plus rituximab; C1D1 = Cycle 1 Day 1; IV = intravenous; QD = once daily.

Objectives

The primary objective was to evaluate PFS of pirtobrutinib as monotherapy (Arm A) compared to Bendamustine Rituximab (BR) (Arm B).

The secondary objectives of the study were:

To evaluate the effectiveness of Arm A compared to Arm B based on ORR and time to events outcomes.

To evaluate the safety and tolerability of each treatment arm.

To evaluate the effectiveness of Arm A compared to Arm B based on patient reported outcomes (PRO).

Outcomes/endpoints

The primary endpoint of the study was Progression free survival (PFS) defined as the time from randomisation until documented progressive diseases (PD) by independent review committee (IRC) per iwCLL 2018 criteria or death from any cause, whichever occurs first.

The secondary endpoints of the study assessed by investigator were:

- PFS per iwCLL 2018 criteria
- Overall Survival (OS), defined as the time from randomisation until death from any cause
- Time to next treatment (TTNT)

The secondary endpoints of the study assessed by IRC and investigator were:

- Overall response rate (ORR)
- Duration of response (DOR)

Secondary endpoints for PRO were:

- Time to worsening (TTW) of CLL/SLL-related symptoms
- TTW of physical functioning as measured by the physical function domain of the EORTC QLQ-C30

Sample size

The study was expected to enrol approximately 250 patients. The study was sized to achieve approximately 90% power to detect a targeted hazard ratio (HR) of 0.41 in PFS which, under the model assumptions, translates into a 144% relative improvement in median PFS comparing the pirtobrutinib arm to the comparator arm, at the 2-sided significance level of 0.05.

This sample size calculation was based on a median PFS time of 43 months in the comparator arm. The accrual period was assumed to be approximately 16 months, and a 10% of dropout was assumed by the time of the final PFS analysis.

Randomisation

Patients were to be randomised in a 1:1 ratio between pirtobrutinib (Arm A) and comparator bendamustine plus rituximab (Arm B).

Patients were stratified by Rai stage (Rai et.al, 1975) and IGHV mutation status as they are known to influence disease biology and response to treatment.

Blinding (masking)

This was an open-label study.

Statistical methods

PFS

A log-rank test, stratified by the randomisation strata, was used for the primary comparison of PFS. The HR and its 95% confidence interval were computed from a stratified Cox regression model. In addition, median PFS and its 95% CI, as well as PFS rates and associated 95% CI at selected timepoints, were provided using the Kaplan-Meier method.

The prespecified randomisation strata used for analyses included IGHV mutation status (mutated versus unmutated) and Rai stage (low/intermediate versus high) collected via the interactive voice/web-response system (IWRS).

- Intercurrent-event strategies:
    - Subsequent anticancer therapy for CLL/SLL prior to PD or death without PD is handled with hypothetical strategy.
    - Extended time without adequate disease assessment (i.e., 2 or more consecutively missed disease assessment visits) is handled with hypothetical strategy.
    - Study intervention discontinuation prior to PD or death without PD is handled with treatment policy strategy.

The final primary endpoint analysis was planned when approximately 53 IRC-assessed PFS events had occurred. Superiority of pirtobrutinib in IRC-assessed PFS was assessed at a 2-sided alpha level of 0.05. No efficacy interim analysis was planned.

The Applicant remained blinded to aggregate comparative data until the primary analyses of PFS, and any potential bias in the primary endpoint (PFS) was mitigated by an IRC evaluation. Response assessments were evaluated by both IRC (primary endpoint) and by the Investigator (secondary endpoint). The PD concordance rate between Investigator and IRC assessments was also provided.

Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, treatment effect for PFS (with a nominal 95% CI) will be estimated and plotted using forest plots within each category of the following subgroups specified below (defined based on eCRF data unless otherwise specified). If only small numbers of participants are observed in a subgroup within each treatment arm (e.g., < 10), collapsing or omission of subgroups will be considered. P-values for the interaction between the treatment arm and subgroup variables will be reported for descriptive purposes only.

- IGHV mutation (mutated, unmutated), based on central lab at C1D1
- Rai stage (low/intermediate, high)
- Age at enrollment (< 65 years vs. 65 years, < 75 years vs. ≥ 75 years, and < 85 years vs. ≥ 85 years)
- Sex (male vs. female)
- Race (White, Asian, Black or African American, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Other)
- Region (North America, South America, Europe, Asia, Australia/New Zealand, Middle East)
- Histology (CLL vs. SLL)
- ECOG performance status at baseline (0, 1, 2)
- Bulky disease (< 5 cm including no measurable lymph node vs. ≥ 5 cm,< 10 cm including no measurable lymph node vs. ≥ 10 cm)
- β2 microglobulin (mg/L) group at baseline (≤ 3.5 mg/L, > 3.5 mg/L)
- Cytogenetic features (biomarker central laboratory)

  o Presence of 11q deletion (yes, no)
- High risk features (biomarker central laboratory):

  o Complex karyotype (yes, no)

  o TP53 mutation (mutated, unmutated)

  o TP53 mutation or unmutated IGHV (yes, no)

OS

The OS analysis was similar to the main analysis for IRC-assessed PFS described above.

- Intercurrent-event strategies:
  - Study intervention discontinuation prior to death is handled with treatment policy strategy.
  - Subsequent anticancer therapy for CLL/SLL (including pirtobrutinib for crossover participants) prior to death is handled with treatment policy strategy.

At the time of the IRC-assessed PFS final analysis, and conditional on the superiority of PFS, OS was tested for superiority in an interim analysis using a 2-sided fixed alpha level of 0.000001. The final OS analysis is planned to occur at the end of the study (approximately 52 months from the first participant randomly assigned), and the remaining 2-sided alpha of 0.049999 will be spent, thereby controlling the overall 2-sided alpha at 0.05.

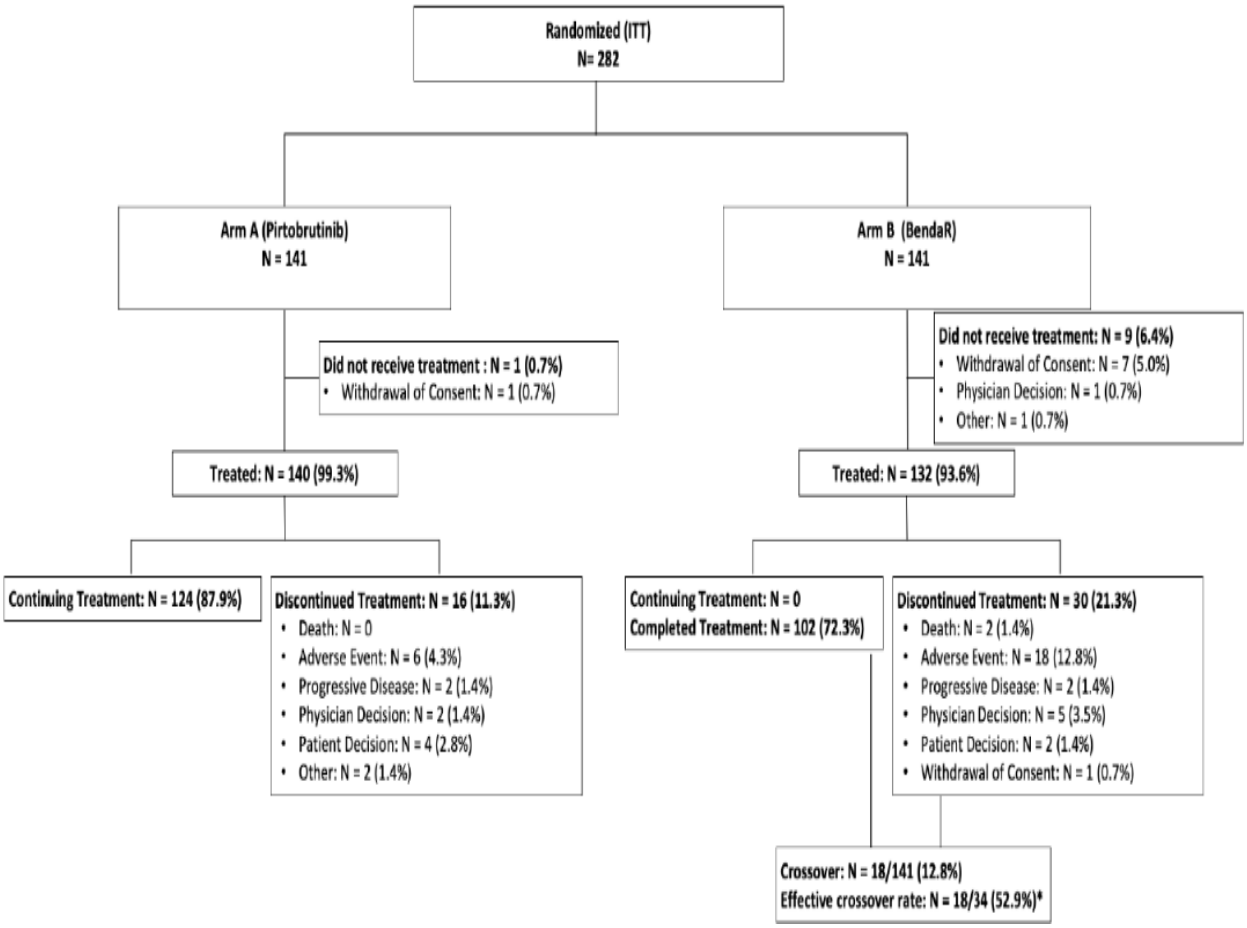
A sequential gate-keeping strategy was utilised to control the family-wise Type I error at 0.05 (2-sided). If the hypothesis test for IRC-assessed PFS is significant, the OS hypothesis will

then be tested at two-sided alpha 0.05.

Results

Participant flow

Table 6. Disposition of patients in study 20023



Recruitment

Study initiation: 23 September 2021 ((first participant first visit)).

Data cutoff date: 11 July 2025

Conduct of the study

Protocol amendments

The protocol was amended twice, on 11 May 2021 (protocol version 2.0) and on 10 February 2023 (protocol version 3.0).

The main changes in Protocol version 2.0 were to clarify the need for highly effective contraception, both while on treatment and after was added, for men and women of childbearing potential and their partners and to removed restrictions related to cytochrome P450 3A4 for pirtobrutinib based on new data

The main changes in Protocol version 3.0 were to add a tertiary/exploratory objective allowing analysis of Health-Related Quality of Life (HRQoL) data, provide additional information on sample acquisition, update hepatic safety information to current standard language, and include updated information on safety reporting.

Protocol deviations

A total of 42 participants (14.9%) had at least 1 important protocol deviation, defined as one that could have significantly affected the completeness, accuracy, and/or reliability of data or potentially affected a participant's rights, safety, or well-being, in the ITT population including crossover period, **Table 7**.

The frequency and nature of protocol deviations were similar between Arm A and Arm B in the areas of investigational product and eligibility. Slight differences occurred in the areas of study procedures, safety, and concomitant medications.

The Sponsor reviewed protocol deviations and considered them unlikely to have substantially affected participant safety or the results and conclusions in this report.

Table 7. Summary of important protocol deviations in Study 20023 – ITT population including cross-over period

	Arm A: Pirtobrutinib (N=141) n (%)	Arm B: BendaR (N=141) n (%)	Total (N=282) n (%)
Number of Subjects with at Least One Important Protocol Deviation	18 (12.8)	24 (17.0)	42 (14.9)
Safety	8 (5.7)	14 (9.9)	22 (7.8)
Safety	8 (5.7)	14 (9.9)	22 (7.8)
Study Procedures	4 (2.8)	8 (5.7)	12 (4.3)
Efficacy	3 (2.1)	4 (2.8)	7 (2.5)
Study Procedures	1 (0.7)	2 (1.4)	3 (1.1)
Visit Schedule	0	2 (1.4)	2 (0.7)
Investigational Product	3 (2.1)	3 (2.1)	6 (2.1)
IP Administration	1 (0.7)	3 (2.1)	4 (1.4)
IP Compliance	2 (1.4)	0	2 (0.7)
Eligibility	2 (1.4)	2 (1.4)	4 (1.4)
Inclusion Criteria	2 (1.4)	2 (1.4)	4 (1.4)
Concomitant Medication	1 (0.7)	0	1 (0.4)
Concomitant Medication	1 (0.7)	0	1 (0.4)

Baseline data

Demographics and disease characteristics of subjects in study 20023 are summarised in **Table 8** and **Table 9** respectively.

Table 8. Summary of demographics in study 20023 (ITT population)

	Arm A: Pirtobrutinib (N=141)	Arm B: BendaR (N=141)	Total (N=282)
Age Group, n (%)			
<50 years	12 (8.5)	11 (7.8)	23 (8.2)
>=50 and <65 years	56 (39.7)	46 (32.6)	102 (36.2)
>=65 and <75 years	53 (37.6)	58 (41.1)	111 (39.4)
>=75 and <85 years	20 (14.2)	24 (17.0)	44 (15.6)
>=85 years	0	2 (1.4)	2 (0.7)
Age Group 1, n (%)			
<65 years	68 (48.2)	57 (40.4)	125 (44.3)
>=65 years	73 (51.8)	84 (59.6)	157 (55.7)
Age Group 2, n (%)			
<75 years	121 (85.8)	115 (81.6)	236 (83.7)
>=75 years	20 (14.2)	26 (18.4)	46 (16.3)
Age Group 3, n (%)			
<85 years	141 (100.0)	139 (98.6)	280 (99.3)
>=85 years	0	2 (1.4)	2 (0.7)
Height (cm)			
n	141	140	281
Mean (Std.Dev.)	168.0 (9.85)	168.0 (9.31)	168.0 (9.57)
Median (Q1, Q3)	168.9 (161.0, 174.0)	168.8 (161.0, 175.0)	168.9 (161.0, 175.0)
Min, Max	144.5 - 198.0	145.0 - 190.0	144.5 - 198.0
Sex, n (%)			
Male	83 (58.9)	90 (63.8)	173 (61.3)
Female	58 (41.1)	51 (36.2)	109 (38.7)
Race, n (%)			
Asian	33 (23.4)	31 (22.0)	64 (22.7)
Black or African American	0	1 (0.7)	1 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.7)	1 (0.7)	2 (0.7)
White	104 (73.8)	102 (72.3)	206 (73.0)
Not Reported	1 (0.7)	2 (1.4)	3 (1.1)
Unknown	0	1 (0.7)	1 (0.4)
Other	2 (1.4)	3 (2.1)	5 (1.8)
Ethnicity, n (%)			
Hispanic or Latino	11 (7.8)	15 (10.6)	26 (9.2)
Not Hispanic or Latino	126 (89.4)	122 (86.5)	248 (87.9)
Not Reported	4 (2.8)	3 (2.1)	7 (2.5)
Unknown	0	1 (0.7)	1 (0.4)
Age (years)			
n	141	141	282
Mean (Std.Dev.)	64.1 (9.91)	65.5 (9.66)	64.8 (9.80)
Median (Q1, Q3)	65.0 (58.0, 71.0)	66.0 (60.0, 72.0)	66.0 (59.0, 71.0)
Min, Max	29 - 84	35 - 88	29 - 88
Weight (kg)			
n	141	141	282
Mean (Std.Dev.)	74.7 (18.18)	74.2 (14.43)	74.4 (16.38)
Median (Q1, Q3)	73.0 (61.0, 85.4)	74.0 (61.8, 83.0)	73.3 (61.3, 84.0)
Min, Max	41.9 - 138.0	48.0 - 114.9	41.9 - 138.0
BMI (kg/m^2)			
n	141	140	281
Mean (Std.Dev.)	26.3 (5.01)	26.1 (3.80)	26.2 (4.44)
Median (Q1, Q3)	25.8 (22.1, 29.5)	25.8 (23.1, 28.4)	25.8 (22.8, 28.9)
Min, Max	15.7 - 39.9	17.4 - 40.0	15.7 - 40.0
BSA (m^2)			
n	141	140	281
Mean (Std.Dev.)	1.9 (0.26)	1.9 (0.22)	1.9 (0.24)
Median (Q1, Q3)	1.9 (1.7, 2.0)	1.9 (1.7, 2.0)	1.9 (1.7, 2.0)
Min, Max	1.3 - 2.7	1.4 - 2.4	1.3 - 2.7
Region, n (%)			
North America	2 (1.4)	5 (3.5)	7 (2.5)
Europe	85 (60.3)	85 (60.3)	170 (60.3)
Asia	32 (22.7)	31 (22.0)	63 (22.3)
South America	9 (6.4)	13 (9.2)	22 (7.8)
Australia/New Zealand	13 (9.2)	7 (5.0)	20 (7.1)

Table 9. Summary of disease characteristics in study 20023 (ITT population)

	Arm A: Pirtobrutinib (N=141) n (%)	Arm B: BendaR (N=141) n (%)	Total (N=282) n (%)
Duration of Disease (years)*a			
n	141	141	282
Mean (Std.Dev.)	3.7 (4.26)	3.0 (3.34)	3.3 (3.84)
Median (Q1, Q3)	2.5 (0.8, 4.9)	2.0 (0.3, 4.7)	2.3 (0.4, 4.8)
Min, Max	0.0 - 26.8	0.1 - 15.9	0.0 - 26.8
Disease Type			
CLL	131 (92.9)	129 (91.5)	260 (92.2)
SLL	10 (7.1)	12 (8.5)	22 (7.8)
ECOG PS			
0	68 (48.2)	55 (39.0)	123 (43.6)
1	66 (46.8)	77 (54.6)	143 (50.7)
2	7 (5.0)	9 (6.4)	16 (5.7)
Rai Stage*b			
Stage 0	8 (6.1)	5 (3.9)	13 (5.0)
Stage I	31 (23.7)	23 (17.8)	54 (20.8)
Stage II	43 (32.8)	53 (41.1)	96 (36.9)
Stage III	26 (19.8)	25 (19.4)	51 (19.6)
Stage IV	23 (17.6)	23 (17.8)	46 (17.7)
Bulky Disease			
Subjects with measurable target lesion (lymph node)	136 (96.5)	130 (92.2)	266 (94.3)
<5cm	97 (68.8)	95 (67.4)	192 (68.1)
>=5cm	39 (27.7)	35 (24.8)	74 (26.2)
<10cm	127 (90.1)	126 (89.4)	253 (89.7)
>=10cm	9 (6.4)	4 (2.8)	13 (4.6)
No measurable target lesion at baseline	5 (3.5)	11 (7.8)	16 (5.7)
ß2 Microglobulin (mg/L) at Baseline, n (%)			
<= 3.5	67 (47.5)	64 (45.4)	131 (46.5)
> 3.5	73 (51.8)	75 (53.2)	148 (52.5)
Missing/Unknown	1 (0.7)	2 (1.4)	3 (1.1)
Cytogenetic features (FISH panel, Biomarker Central Laboratory), n (%)			
11q Deletion Presence			
Yes	11 (7.8)	15 (10.6)	26 (9.2)
No	97 (68.8)	93 (66.0)	190 (67.4)
Missing/Unknown	33 (23.4)	33 (23.4)	66 (23.4)

High Risk Features(Biomarker Central Laboratory), n (%)			
IGHV Mutation Status			
Mutated	58 (41.1)	61 (43.3)	119 (42.2)
Unmutated	76 (53.9)	73 (51.8)	149 (52.8)
Missing/Unknown	7 (5.0)	7 (5.0)	14 (5.0)
Complex Karyotype Presence*c			
Yes	16 (11.3)	11 (7.8)	27 (9.6)
No	75 (53.2)	72 (51.1)	147 (52.1)
Missing/Unknown	50 (35.5)	58 (41.1)	108 (38.3)
TP53 Mutation Status			
Mutated	10 (7.1)	12 (8.5)	22 (7.8)
Unmutated	115 (81.6)	107 (75.9)	222 (78.7)
Missing/Unknown	16 (11.3)	22 (15.6)	38 (13.5)
TP53 mutation and/or unmutated IGHV			
Yes	81 (57.4)	76 (53.9)	157 (55.7)
No	48 (34.0)	46 (32.6)	94 (33.3)
Missing/Unknown	12 (8.5)	19 (13.5)	31 (11.0)

Numbers analysed

Table 10. Analysis populations in study 20023

Population	Description	Number of Participants		
		Arm A	Arm B	Total
ITT	All randomized participants, even if a participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed by the treatment arm they were originally assigned, regardless of the treatment they received. Unless otherwise specified, all analyses using the ITT population will include data only prior to crossover for an Arm B participant who crossed over to Arm A, except for OS-related analyses.	141	141	282
Safety	All randomized participants who take at least 1 dose (including a partial dose) of study treatment. Analysis of safety data will be based on the actual treatment a participant received on the first study treatment administration, regardless of which treatment they were randomized to receive ("as treated"). Unless otherwise specified, all analyses using the Safety Population will include data collected prior to crossover for an Arm B participant who crossed over to Arm A.	140	132	272
Crossover	A subpopulation of participants included in the ITT population who were randomized to Arm B and crossed over to receive at least 1 dose of pirtobrutinib. The Crossover Population will be used for selected safety analyses, including data collected during the crossover period starting from the date of first dose of pirtobrutinib, if deemed necessary.	N/A	N/A	18

Outcomes and estimation

Primary endpoint: PFS

Pirtobrutinib monotherapy demonstrated a statistically significant and clinically meaningful improvement in IRC-assessed PFS compared to BendaR. In the Pirtobrutinib Arm, pirtobrutinib monotherapy significantly reduced the risk of disease progression or death by 80.1% compared to BendaR (HR = 0.199; 95% CI: 0.107, 0.367; p<0.0001, **Table 11, Figure 6**).

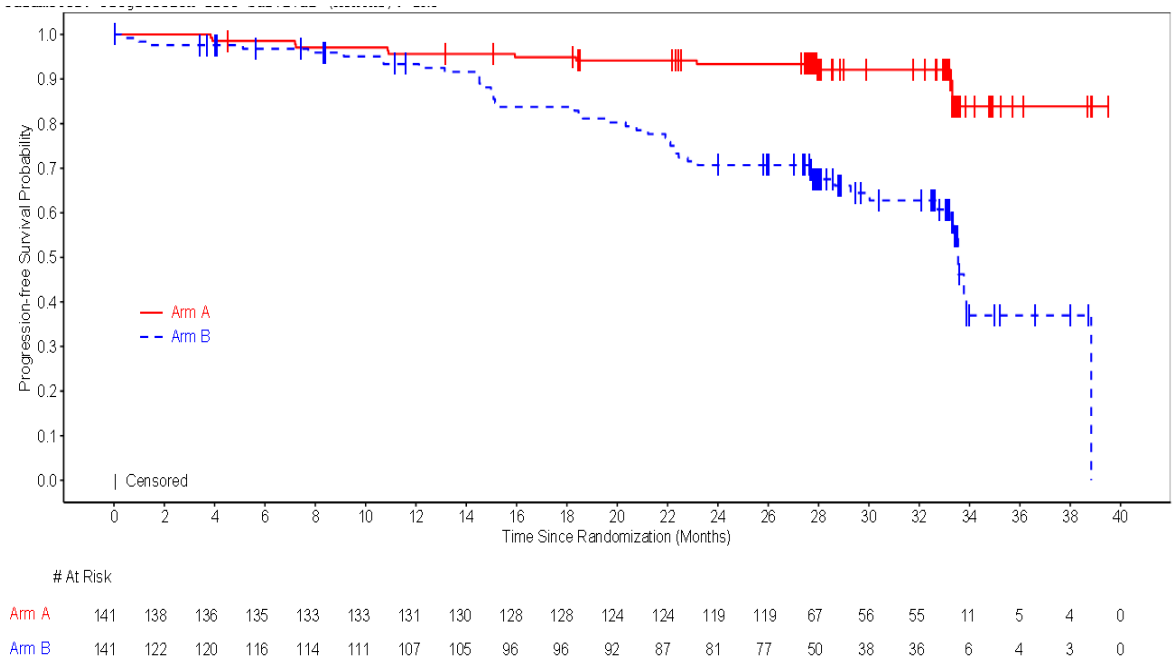
Investigator-assessed PFS results were consistent with the results of IRC-assessed PFS. Pirtobrutinib monotherapy reduced the risk of disease progression or death by 81.4% compared to BendaR (HR = 0.186; 95% CI: 0.093, 0.371, **Table 11**).

Table 11. Summary of Progression-Free Survival based on IRC and Investigator Assessments in study 20023, ITT population.

Parameter	ITT Population N = 282	
	Pirtobrutinib N = 141	**BendaR N = 141**
IRC-Assessed PFS		
Number of Events, n (%)	13 (9.2)	48 (34.0)
PD	13 (9.2)	40 (28.4)
Death	0	8 (5.7)
Number of Participants Censored, n (%)	128 (90.8)	93 (66.0)
Event after 2 or more consecutively missed disease assessment visits	0	1 (0.7)
Event after subsequent anticancer therapy	1 (0.7)	1 (0.7)
No adequate disease assessment at post-baseline	2 (1.4)	12 (8.5)
No documented disease progression or death on or before data cutoff	117 (83.0)	66 (46.8)
Study exit	5 (3.5)	6 (4.3)
Subsequent anticancer therapy without event	1 (0.7)	1 (0.7)
Two or more consecutively missed disease assessment visits without event	2 (1.4)	6 (4.3)
Progression-free Survival, (months)		
Median (95% CI)	NR (NE , NE)	33.54 (32.72, NE)
Min, Max[a]	0.03+, 39.52+	0.03+, 38.83
Stratified Analysis (versus Arm B)[b]		
Hazard Ratio (95% CI)	0.199 (0.107, 0.367)	
p-value[c]	<0.0001	
PFS Follow-up Time (months)		
Median (95% CI)	28.06 (27.89, 32.23)	28.32 (27.83, 32.07)
Min, Max[a]	0.03+, 39.52+	0.03+, 38.83
PFS Rate, % (95% CI)		
At 12 months	95.6 (90.5, 98.0)	93.4 (87.2, 96.6)
At 18 months	94.9 (89.6, 97.5)	83.8 (75.7, 89.3)
At 24 months	93.4 (87.6, 96.5)	70.7 (61.5, 78.1)
INV-Assessed PFS		
Number of Events, n (%)	11 (7.8)	42 (29.8)
Progression-free Survival, (months)		
Median (95% CI)	NR (35.19, NE)	NR (33.38, NE)

Parameter	ITT Population N = 282	
	Pirtobrutinib N = 141	**BendaR N = 141**
Stratified Analysis (versus Arm B)[b]		
Hazard Ratio (95% CI)	0.186 (0.093, 0.371)	
PFS Follow-up Time (months)		
Median (95% CI)	27.96 (27.83, 31.77)	28.78 (27.86, 32.56)
PFS Rate, % (95% CI)		
At 24 months	92.7 (86.8, 96.0)	72.6 (63.7, 79.7)

Figure 6. Kaplan-Meier plot of progression-free survival based on IRC assessments in study 20023 (ITT population)



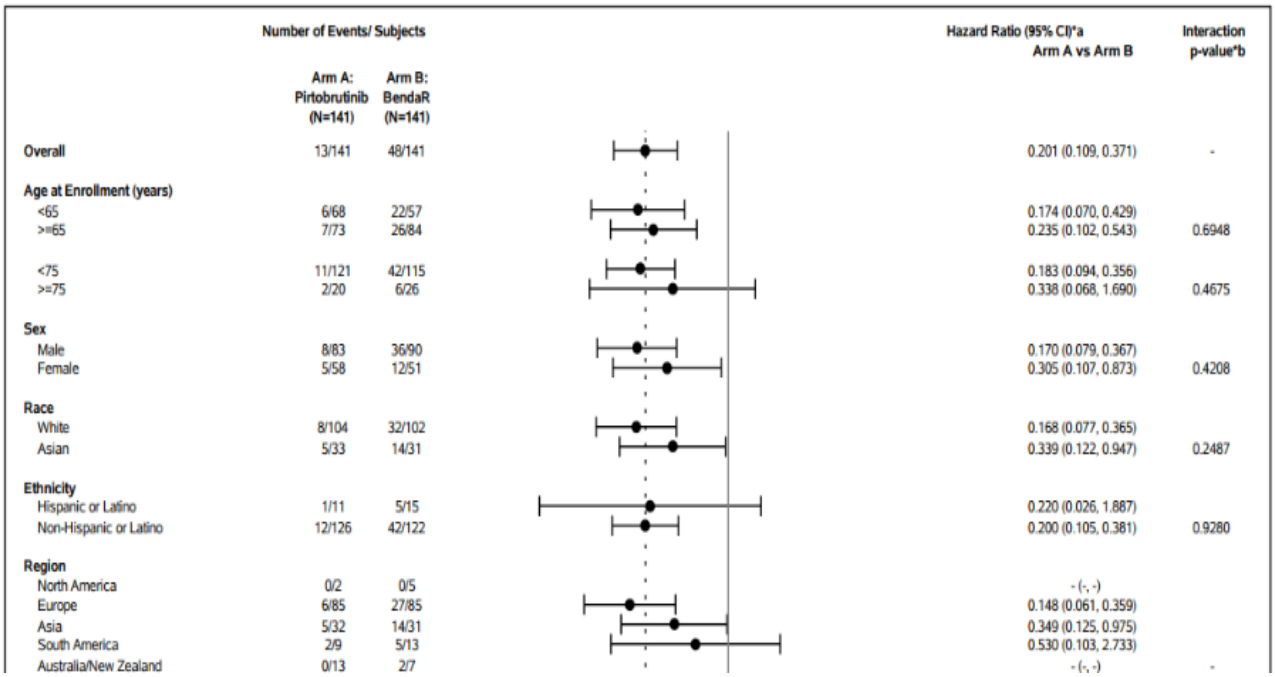
The concordance rate between IRC- and Investigator-assessed PD for Arm A was 89.4% (95% CI: 83.1, 93.9) and for Arm B was 89.4% (95% CI: 83.1, 93.9, **Table 12**).

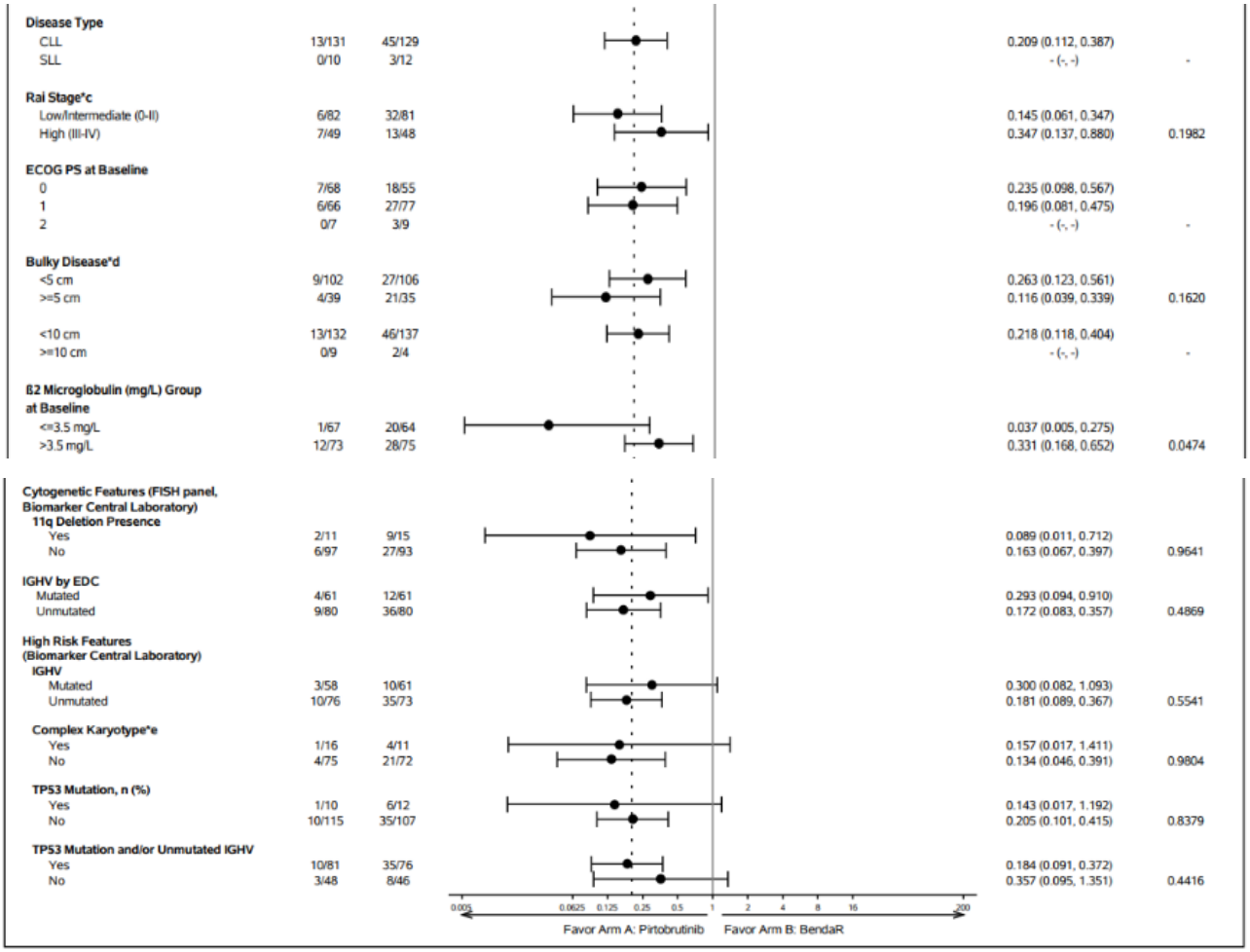
Table 12. Concordance between IRC and investigator-assessed PD in study 20023– ITT population

	Arm A: Pirtobrutinib (N = 141)		Arm B: BendaR (N = 141)	
	Investigator Assessment		Investigator Assessment	
Independent Review Committee	Progression: Yes	Progression: No	Progression: Yes	Progression: No
Progression: Yes	4	9	30	11
Progression: No	6	122	4	96
Concordance Rate				
n (%)		126 (89.4)		126 (89.4)
95% Confidence Interval		83.1, 93.9		83.1, 93.9

Subgroup analyses showed pirtobrutinib provided PFS benefit consistent across all subgroups (**Figure 7).**

Figure 7. Forest plot of PFS based on IRC assessment by subgroup in study 20023 (ITT population)





Secondary endpoint: OS

The key secondary endpoint of OS was analysed in the ITT population and included the crossover period. At the OS interim analysis, there were 3 deaths (2.1%) in the pirtobrutinib Arm and 10 deaths (7.1%) in the BendaR Arm, and OS trended in favour of pirtobrutinib with no OS detriment observed. The HR comparing OS between pirtobrutinib and BendaR was 0.257 (95% CI: 0.070, 0.934; 2-sided p-value = 0.0261) but given a small 2-sided alpha of 0.000001 allocated at this interim analysis, the criteria for superiority was not yet met.

The 24-month OS estimates were 97.8% (95% CI: 93.3, 99.3) with pirtobrutinib and 93.0% (95% CI: 87.0, 96.3) with BendaR. The median OS was not reached in either arm at a median OS follow-up time of 32.72 months in the Pirtobrutinib Arm and 31.74 months in the BendaR Arm.

Secondary endpoint: ORR

The secondary endpoint of ORR by IRC was higher in the Pirtobrutinib Arm (94.3%; 95% CI: 89.13, 97.52) compared with BendaR (80.9%; 95% CI: 73.38, 86.99). In each arm, most responses were PR.

When assessed by Investigators, the ORR was 94.3% (95% CI: 89.13, 97.52) in the Pirtobrutinib Arm and was 82.3% (95% CI: 74.95, 88.18) in the BendaR Arm.

ORR, including Partial Response with Lymphocytosis(PR-L) as assessed by IRC and Investigator, were also evaluated, and results were consistent with ORR results in both arms.

IRC and Investigator response assessments of PR or better (yes versus no) were highly concordant at 97.2% (95% CI: 92.9, 99.2) in the Pirtobrutinib Arm and 95.7% (95% CI: 91.0, 98.4) in the BendaR Arm.

Secondary endpoint: Duration of response

Pirtobrutinib showed a favourable trend in IRC-assessed DOR compared with BendaR (HR = 0.178, 95% CI: 0.089, 0.356). The 24-month DOR estimates were 94.5% (95% CI: 88.7, 97.3) with pirtobrutinib and 71.6% (95% CI: 61.8, 79.3) with BendaR. The median DOR was not reached in the Pirtobrutinib Arm and was 29.86 months (28.32, NE) in the BendaR Arm at the median DOR follow-up time of 24.08 months (95% CI: 23.95, 24.87) in the Pirtobrutinib Arm and 27.17 months (95% CI: 24.11, 28.06) in the BendaR Arm.

The Investigator-assessed DOR was consistent with the IRC-assessed DOR. The HR comparing investigator-assessed DOR between the Pirtobrutinib Arm and the BendaR Arm was 0.193 (95% CI: 0.089, 0.418). The median DOR was not reached in either arm at the median DOR follow-up of 23.95 months (95% CI: 23.95, 24.25) in the Pirtobrutinib Arm and 25.07 months (95% CI: 24.08, 27.86) in the BendaR Arm.

Results from these endpoints by IRC are summarised in **Table 13**.

Table 13. Summary of overall survival, overall response rate and duration of response based on IRC Assessments in study 20023, ITT population

		Study 20023 ITT Population N = 282	
	Parameter	**Pirtobrutinib N = 141**	**BendaR N = 141**
OS	Median OS, % (95% CI)	NR (NE, NE)	NR (NE, NE)
	HR (95% CI) stratified	0.257 (0.070, 0.934)	
	18-month OS rates, % (95% CI)	99.3 (95.0, 99.9)	93.8 (88.1, 96.9)
	24-month OS rates, % (95% CI)	97.8 (93.3, 99.3)	93.0 (87.0, 96.3)
	Median FU time, months (95% CI)	32.72 (31.90, 33.28)	31.74 (30.46, 32.99)
ORR IRC	ORR, % (95% CI)	94.3 (89.13, 97.52)	80.9 (73.38, 86.99)
DOR IRC	Median DOR, months (95% CI)	NR (NE, NE)	29.86 (28.32, NE)
	12-month DOR rates, % (95% CI)	97.7 (93.1, 99.3)	88.1 (80.4, 92.9)
	HR (95% CI) stratified	0.178 (0.089, 0.356)	

Time to Next Treatment

The TTNT results showed improvement for pirtobrutinib monotherapy compared to ibrutinib (HR = 0.136; 95% CI: 0.056, 0.332). The 24-month TTNT estimates were 96.4% (95% CI: 91.5, 98.5) with pirtobrutinib and 80.6% (95% CI: 72.5, 86.6) with BendaR. Median TTNT was not reached for either the Pirtobrutinib Arm or the BendaR Arm.

Patient-reported outcomes

Both secondary and exploratory PROs were assessed in Study 20023. Analysis of all PRO endpoints in this study were not controlled for type I error and any p-value reported is nominal.

The overall PRO completion rate at baseline was 79% and ranged between 48% to 91% during postbaseline assessment timepoints in the Pirtobrutinib Arm while it was 72% at baseline and ranged between 36% and 83% at postbaseline assessment timepoints in the BendaR Arm.

Time-to-worsening in PROs: In the ITT population, pirtobrutinib reduced the risk of worsening of CLL/SLL-related symptoms (HR: 0.501; 95% CI: 0.291, 0.863) and fatigue (HR: 0.560; 95% CI: 0.323, 0.971) compared to BendaR. The HR comparing TTW in physical functioning between pirtobrutinib and BendaR was 0.578 (95% CI: 0.304, 1.099) and was 0.561 (95% CI: 0.281, 1.122) comparing overall QoL between pirtobrutinib and BendaR.

Within-arm change from baseline in PROs: In the ITT population, participants treated with pirtobrutinib demonstrated consistent, clinically meaningful within-arm reductions in CLL/SLL-related symptoms and fatigue at nearly all post-baseline timepoints, while those treated with BendaR achieved similar reductions starting from Week 29 (CLL/SLL-related symptoms) or Week 33 (fatigue) onwards. Additionally, participants treated with pirtobrutinib showed early and sustained clinically meaningful within-arm improvements in physical functioning through Week 133, while those treated with BendaR demonstrated such improvements only at select later timepoints. Lastly, those treated with pirtobrutinib showed within-arm improvements in overall QoL from Week 33 onwards, while those treated with BendaR showed such improvements from Week 25 onwards.

Between-arm differences in change from baseline in PROs: In the ITT population, greater and clinically meaningful reductions in CLL/SLL-related symptoms and fatigue were demonstrated by participants treated with pirtobrutinib compared to those who received BendaR at the following assessment timepoints:

(a) CLL/SLL-related symptoms: Week 5 (LSM difference = -4.99; 95% CI: -8.25, -1.72) and Week 9 (LSM difference = -5.27; 95% CI: -9.36, -1.18);

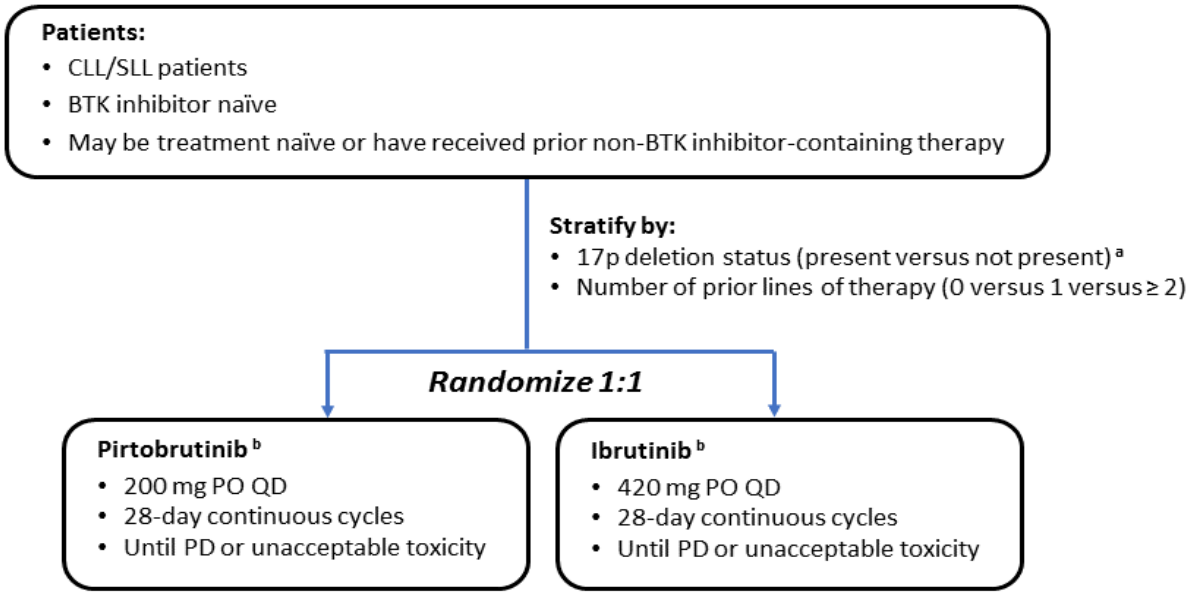
(b) fatigue: Week 5 (LSM difference = -5.15; 95% CI: -9.37, -0.92) and Week 25 (LSM difference = -5.19; 95% CI: -9.82, -0.55).

Between-arm differences in PF and overall QoL were not clinically meaningful.

Study 20030: A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Ibrutinib in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-314)

The study design is depicted in **Figure 8.**

Figure 8. Study 20030 design schema



Methods

Study participants

Key inclusion criteria

Participants were eligible to be included in Part 1 of the study only if all of the following key criteria applied:

- Confirmed diagnosis of CLL/SLL, as defined by iwCLL 2018 criteria.
- A requirement for therapy consistent with iwCLL 2018 criteria for initiation of therapy.
- Known del(17p) status (wildtype for 17p or positive for 17p deletion) assessed by FISH.
- Adequate organ function.
- ECOG 0 to 2.

Key exclusion criteria

Participants were excluded from Part 1 of the study if any of the following key criteria applied:

- Previous exposure to BTK inhibitor (covalent or noncovalent).
- Concurrent use of investigational agent or anticancer therapy except hormonal therapy.
- Known or suspected Richter's transformation to diffuse large B-cell lymphoma, prolymphocytic leukaemia, or Hodgkin's lymphoma at any time preceding enrolment
- Known or suspected history of CNS involvement by CLL/SLL.
- Significant cardiovascular disease (including atrial fibrillation or flutter ongoing at the time of screening).
- Patients requiring therapeutic anticoagulation with warfarin or another Vitamin K antagonist.

Treatments

Table 14: Study 20030 interventions administered

	Pirtobrutinib	Ibrutinib
Treatment	Pirtobrutinib	Ibrutinib
Dose	200 mg	420 mg
Schedule	QD in 28-day continuous cycles	QD in 28-day continuous cycles
Route of Administration	Oral	Oral
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization	Authorized and used according to EU authorization

Objectives

The primary objective of the study was to evaluate ORR of pirtobrutinib (Arm A) compared to ibrutinib (Arm B).

The secondary objective of the study was to evaluate the effectiveness of Arm A compared to Arm based on PFS, EFS, ORR, DOR, OS, and TTNT.

Outcomes/endpoints

Primary endpoints: ORR as assessed by IRC per iwCLL 2018 criteria in

- pretreated population or
- ITT population

ORR is defined as the proportion of participants who achieve a BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anti-cancer therapy.

Key secondary endpoints:

- PFS by IRC in the pretreated population
- PFS by IRC in the ITT population

PFS by IRC is defined as the time from the date of randomisation until PD (per iwCLL 2018 criteria) or death from any cause, whichever occurs first.

Additional secondary endpoints:

Endpoints assessed in the pretreated and the ITT population:

- DOR (assessed by IRC and Investigator): DOR is defined as the time from the date of the first documented response of CR, CRi, nPR, or PR to the earlier of the documentation of definitive PD (per iwCLL 2018 criteria) or death from any cause
- DOR (assessed by IRC and Investigator) as defined above plus PR-L
- ORR (assessed by IRC and Investigator) as defined for the primary endpoint plus PR-L

- ORR (assessed by Investigator) evaluated per iwCLL 2018
- EFS (assessed by IRC and Investigator) (per iwCLL 2018 criteria) is defined as the time from the date of randomization to the first occurrence of:

  o Treatment discontinuation due to AE/toxicity

  o Treatment-emergent atrial fibrillation or atrial flutter of any grade (assessed by Investigator)

  o PD (per iwCLL 2018 criteria) or death
- PFS (assessed by Investigator) evaluated per iwCLL 2018
- OS (assessed by Investigator): OS is defined as the time from randomisation until death from any cause
- TTNT (assessed by Investigator): TTNT is defined as time from the date of randomisation to the date of the initiation of the next systemic anticancer therapy for CLL/SLL or death due to any cause, whichever occurs first

Sample size

The published data from REASONATE-2 study demonstrated superiority of ibrutinib (reference/comparator product in this study) comparing ORR to that with treatment of chlorambucil (rate ratio=2.32, 95% CI: 1.82, 2.95) (Byrd et al. 2015). Following a fixed margin approach (FDA Non-Inferiority Guidance Document) and also the method in Wangge et al (Wangge et al. 2013), the Non-Inferiority (NI) margin of 0.880 for the response rate ratio is calculated using the lower bound of the 95% CI (1.82) from REASONATE-2, which corresponds to a 79% preservation of ibrutinib's total treatment effect.

Study 20030 was expected to enrol approximately 650 patients. Patients were randomised in a 1:1 ratio between pirtobrutinib (Arm A) and ibrutinib (Arm B). Assuming a 75% ORR in ibrutinib, the sample size of this study was determined to have approximately 80% power to show NI of pirtobrutinib to ibrutinib in ORR at a one-sided significance level of 2.5% based on standard Wald Test (Wald et al. 1940): the lower bound of a 2-sided 95% CI of ORR ratio > 0.880 (NI bound). The final analysis of ORR will be performed when all patients are followed for at least 12 months or discontinue the study, which is projected to be at approximately 34 months from randomization of the first patient. Patients will continue to be followed for the assessment of EFS and PFS.

For PFS, assuming two interim efficacy analyses and a subsequent final analysis, 193 PFS events in the pretreated population are required to provide approximately 80% power to detect a HR of 0.665 using the log-rank test and a one-sided significance level of 2.5%. Assuming a 2-year progression free rate of 70% for Arm B, and a HR of 0.665 which corresponds to a median PFS of approximately 46.6 and 70.1 months in Arms B and A respectively. . Assuming a 22-month accrual period, with a 10% dropout rate. The final analysis of PFS is projected to be at approximately 65 months from the randomization of the first patient.

Randomisation

Participants were randomly assigned 1:1 to Arm A:Arm B and were stratified by del(17p) status (present versus not present), and number of prior lines of therapy (0 versus 1 versus≥2), to ensure balance across treatment arms in these CLL prognostic factors. (Ghia et al. 2020; Seymour et al. 2018; Munir et al. 2019; Byrd et al. 2014; Byrd et al. 2013; O'Brien et al. 2014; Byrd et al. 2015; O'Brien et al. 2016).

Blinding (masking)

This was an open-label study.

The Applicant remained blinded to aggregate comparative data until the primary analysis of ORR and any potential bias in the primary endpoint (ORR) was mitigated by evaluation of response by an IRC. Following the primary analysis of ORR, the study team was re-blinded to accumulating and evolving aggregate data to minimize bias and maintain the integrity of the planned testing of the key secondary endpoint.

Statistical methods

ORR

IRC-assessed ORR was the alpha-controlled primary endpoint to be tested for non-inferiority based on the ORR ratio (ORR for pirtobrutinib relative to ORR for ibrutinib) in the pretreated and ITT populations. The NI hypotheses were tested by Wald tests based on the stratified Mantel-Haenszel Estimator (Mantel and Haenszel 1959) adjusted for randomization strata. The NI margins of the ORR ratios in the pretreated and ITT populations were 0.86 and 0.88, respectively. Descriptive analyses of differences in ORR between arms were evaluated using the Cochran-Mantel-Haenszel test (Mantel and Haenszel 1959), adjusted for randomization strata, and were not alpha-controlled.

No interim analysis was planned for the primary endpoint of IRC-assessed ORR. The final ORR analysis was planned when all randomly assigned participants had the opportunity to be followed up for at least 12 months from the time of randomization or study discontinuation, whichever occurred first.

At the time of the ORR final analysis, a 2-sided alpha of 0.05 was allocated to the testing of ORR NI in the pretreated and ITT populations, with initial allocations of 0.045 and 0.005, respectively.

Response assessments were evaluated by both IRC (primary endpoint) and by the Investigator (secondary endpoint). The BOR concordance rate (PR or better) between Investigator and IRC assessments was also provided.

- Intercurrent-event strategies:
    - Subsequent anticancer therapy for CLL/SLL, PD or death is handled with while on-treatment strategy.
    - A patient's BOR is the best response recorded from Cycle 1 Day 1 until data cutoff data, PD, or start of new anticancer treatment whichever is first
    - Responses recorded after initiation of new anticancer therapy will be considered as non-responders
    - Study intervention discontinuation is handled with treatment policy strategy.

PFS

PFS, as assessed by IRC, was the alpha-controlled key secondary endpoint to be tested for superiority in the pretreated and ITT populations using a log-rank test, stratified by the randomization strata. The treatment effect was summarized by HR and its corresponding 95% CI from a stratified Cox regression model (Cox 1972). In addition, median PFS and its 95% CI, as well as PFS rates and associated 95% CI at selected timepoints, were provided using the Kaplan-Meier method (Kaplan and Meier 1958).

Two interims and one final analysis were planned for the key secondary endpoint of PFS. The first interim analysis of PFS occurred at the time of the ORR final analysis and was meant to be descriptive, with a small technical 2-sided alpha of 0.000002 applied to account for the interim look at the data. The second interim PFS analysis is planned to occur when approximately 145 PFS events have occurred in the Pretreated population, and the final PFS analysis is planned to occur when approximately 193 PFS events have occurred in the Pretreated population. Testing for the superiority of PFS is planned at both the second interim and final PFS analyses. The 2-sided alpha for testing PFS in the Pretreated and ITT populations will be allocated based on the graphical testing scheme.

The graphical approach (Bretz et al. 2009; Mauer and Bretz 2013) was used for testing the 2 ORR primary hypotheses and the 2 PFS key secondary hypotheses, to adjust for multiplicity and control the overall family-wise type I error rate at 0.05 (2-sided). Initially, the overall 2-sided alpha level of 0.05 was split between testing ORR NI in the Pretreated population (at 0.045) and ITT population (at 0.005). No alpha was initially assigned to the PFS hypotheses.

- Intercurrent-event strategies:
    - Subsequent anticancer therapy for CLL/SLL prior to PD or death without PD is handled with hypothetical strategy.
    - Extended time without adequate disease assessment (i.e., 2 or more consecutively missed disease assessment visits) is handled with hypothetical strategy.
    - Study intervention discontinuation prior to PD or death without PD is handled with treatment policy strategy.

Sensitivity analysis

To determine whether the treatment effect is consistent across various subgroups, treatment effect for ORR in terms of ORR difference, DoR in terms of HR and PFS in terms of HR (with a nominal 95% CI) will be estimated and plotted using forest plots within each category of the following subgroups:

- Number of prior lines of therapy (0, 1, ≥2)
- Presence of 17p deletion (yes, no)
- Prior treatment status (treatment-naïve, pretreated) for the ITT population only
- Rai stage (low/intermediate, high)
- Age at enrollment (< 65 years vs. 65 years, < 75 years vs. ≥ 75 years, and < 85 years vs. ≥ 85 years)
- Sex (male vs. female)
- Race (White, Asian, Black or African American, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Other)
- Region (North America, South America, Europe, Asia, Australia/New Zealand, Middle East)

- Bulky disease (< 5 cm including no measurable lymph node vs. ≥ 5 cm,< 10 cm including no measurable lymph node vs. ≥ 10 cm)
- Receipt of prior B-cell lymphoma-2 treatment in pretreated patients (yes, no)
- Histology (CLL vs. SLL)
- ECOG performance status at baseline (0, 1, 2)
- β2 microglobulin (mg/L) group at baseline (≤ 3.5 mg/L, > 3.5 mg/L)
- Cytogenetic features (biomarker central laboratory)
  - o Presence of 17p deletion (yes, no)
  - o Presence of 11q deletion (yes, no)
- High risk features (biomarker central laboratory):
  - o IGHV (mutated, unmutated)
  - o Complex karyotype (yes, no)
  - o TP53 mutation (yes, no)
  - o TP53 mutation and/or deletion of 17p (yes, no)
  - o TP53 mutation and deletion of 17p (yes, no)
  - o TP53 mutation without deletion of 17p (yes, no)
  - o TP53 mutation, deletion of 17p, or unmutated IGHV (yes, no)

Results

Participant flow

The ITT population included 662 total participants randomly assigned to either the Pirtobrutinib Arm or the Ibrutinib Arm.

Pirtobrutinib Arm:

- Of 331 participants randomly assigned, 330 (99.7%) received treatment.
- Median time on study was 21.85 months (range: 0 to 33.8 months).

Ibrutinib Arm:

- Of the 331 participants randomly assigned, 325 (98.2%) received treatment
- Median time on study was 20.93 months (range: 0.1 to 32.2 months).

The most common reason for treatment discontinuation in the Pirtobrutinib Arm was due to AE and occurred in 26 participants (7.9%), similar to the frequency of 24 participants (7.3%) in the Ibrutinib Arm. In the Ibrutinib Arm, the most common reason for treatment discontinuation was due to PD (36 participants [10.9%]), versus 15 participants (4.5%) in the Pirtobrutinib Arm. Additionally, 6 participants (1.8%) in the Pirtobrutinib Arm and 11 participants (3.3%) in the Ibrutinib Arm discontinued treatment due to death.

The Pretreated population included 437 randomly assigned participants.

Pirtobrutinib Arm:

- Of 219 participants randomly assigned, 218 (99.5%) received treatment.
- Median time on study was 18.83 months (range: 0 to 32.5 months).

Ibrutinib Arm:

- Of the 218 participants randomly assigned, 216 (99.1%) received treatment
- Median time on study was 17.74 months (range: 0.1 to 31.7 months).

The most common reason for treatment discontinuation in the Pirtobrutinib Arm was due to AE and occurred in 20 participants (9.1%) versus 13 participants (6.0%) in the Ibrutinib Arm. In the Ibrutinib Arm, the most common reason for treatment discontinuation was due to PD and occurred in 21 participants (9.6%) versus 13 participants (5.9%) in the Pirtobrutinib Arm. Additionally, 6 participants (2.7%) in the Pirtobrutinib Arm and 10 participants (4.6%) in the Ibrutinib Arm discontinued treatment due to death.

Recruitment

Study initiation: 22 July 2022 (first participant first visit).

Data cutoff date: 10 June 2025

Conduct of the study

Protocol amendments

The protocol was amended 7 times.

Version 2.0. (02 December 2021) and Version 3.0. (31 January 2023) updated the inclusion and exclusion criteria of the study.

Version 6.0. (27 November 2024) added ORR NI in the pretreated population as a primary endpoint and PFS superiority in the pretreated population as a key secondary endpoint. In addition, separate analyses in the pretreated population for the secondary objectives of the trial were added, and the ORR IA at 455 participants with 9 months follow-up was removed and the final ORR analysis timing was postponed to 12 months follow-up from randomization of the last participant. The event-driven PFS interim analysis timing was shifted later with approximately 75% information fraction.

Version 7.0. (21 March 2025) added a Part 2 to study consisting of a new cohort of treatment-naïve participants that have del(17p).

There were no substantial changes in the conduct of the study in protocol amendment version 4.0 (29 November 2023), 5.0 (05 April 2024), and 8.0 (09 May 2025).

Protocol deviations

Table 15. Summary of important protocol deviations in Study 20030 – ITT

Derivation Type	Arm A: Pirtobrutinib (N=331) n (%)	Arm B: Ibrutinib (N=331) n (%)	Total (N=662) n (%)
Number of Subjects With at Least One Important Protocol Deviation	33 (10.0)	18 (5.4)	51 (7.7)
Eligibility	7 (2.1)	4 (1.2)	11 (1.7)
Exclusion Criteria	4 (1.2)	2 (0.6)	6 (0.9)
Inclusion Criteria	3 (0.9)	2 (0.6)	5 (0.8)
Informed Consent	0	1 (0.3)	1 (0.2)
Informed Consent and Process	0	1 (0.3)	1 (0.2)
Investigational Product	10 (3.0)	4 (1.2)	14 (2.1)
IP Administration	4 (1.2)	0	4 (0.6)
Subject IP Compliance	6 (1.8)	4 (1.2)	10 (1.5)
Study Procedures	7 (2.1)	4 (1.2)	11 (1.7)
Randomization	5 (1.5)	2 (0.6)	7 (1.1)
Efficacy	1 (0.3)	0	1 (0.2)
Laboratory Assessment	1 (0.3)	2 (0.6)	3 (0.5)
Safety	10 (3.0)	5 (1.5)	15 (2.3)
Safety	10 (3.0)	5 (1.5)	15 (2.3)

Baseline data

Summary of demographics, baseline disease characteristics and prior cancer therapy are presented in the overall and pretreated populations in study 20030 in the following tables.

Table 16. Summary of demographics study 20030, ITT population

	Arm A: Pirtobrutinib (N=331)	Arm B: Ibrutinib (N=331)	Total (N=662)
Sex, n (%)			
Male	213 (64.4)	215 (65.0)	428 (64.7)
Female	118 (35.6)	116 (35.0)	234 (35.3)
Race, n (%)			
American Indian or Alaska Native	1 (0.3)	0	1 (0.2)
Asian	43 (13.0)	51 (15.4)	94 (14.2)
Black or African American	8 (2.4)	10 (3.0)	18 (2.7)
Native Hawaiian or Other Pacific Islander	1 (0.3)	1 (0.3)	2 (0.3)
White	254 (76.7)	250 (75.5)	504 (76.1)
Not Reported	14 (4.2)	12 (3.6)	26 (3.9)
Unknown	2 (0.6)	2 (0.6)	4 (0.6)
Other	8 (2.4)	5 (1.5)	13 (2.0)
Ethnicity, n (%)			
Hispanic or Latino	50 (15.1)	58 (17.5)	108 (16.3)
Not Hispanic or Latino	269 (81.3)	260 (78.5)	529 (79.9)
Not Reported	11 (3.3)	9 (2.7)	20 (3.0)
Unknown	1 (0.3)	4 (1.2)	5 (0.8)
Age (years)			
n	331	331	662
Mean (Std.Dev)	66.2 (9.80)	65.6 (10.37)	65.9 (10.09)
Median	67.0	67.0	67.0
Q1, Q3	60.0, 73.0	59.0, 74.0	59.0, 73.0
Min, Max	39, 90	34, 86	34, 90

Age Group, n (%)			
<50 years	20 (6.0)	27 (8.2)	47 (7.1)
>=50 and <65 years	117 (35.3)	105 (31.7)	222 (33.5)
>=65 and <75 years	128 (38.7)	127 (38.4)	255 (38.5)
>=75 and <85 years	59 (17.8)	70 (21.1)	129 (19.5)
>=85 years	7 (2.1)	2 (0.6)	9 (1.4)
Age Group 1, n (%)			
<65 years	137 (41.4)	132 (39.9)	269 (40.6)
>=65 years	194 (58.6)	199 (60.1)	393 (59.4)
Age Group 2, n (%)			
<75 years	265 (80.1)	259 (78.2)	524 (79.2)
>=75 years	66 (19.9)	72 (21.8)	138 (20.8)
Age Group 3, n (%)			
<85 years	324 (97.9)	329 (99.4)	653 (98.6)
>=85 years	7 (2.1)	2 (0.6)	9 (1.4)
Height (cm)			
n	328	329	657
Mean (Std.Dev)	168.27 (9.419)	168.06 (9.970)	168.17 (9.692)
Median	169.75	170.00	170.00
Q1, Q3	161.50, 175.13	160.00, 175.00	161.00, 175.00
Min, Max	139.30, 189.00	145.00, 191.00	139.30, 191.00
Missing	3	2	5
Weight (kg)			
n	331	331	662
Mean (Std.Dev)	76.04 (16.050)	75.95 (16.544)	75.99 (16.287)
Median	74.80	75.10	75.00
Q1, Q3	65.60, 85.00	63.90, 86.00	65.00, 85.50
Min, Max	40.00, 154.22	40.90, 129.82	40.00, 154.22
BMI (kg/m^2)			
n	328	329	657
Mean (Std.Dev)	26.70 (4.661)	26.74 (4.790)	26.72 (4.723)
Median	25.88	26.30	26.16
Q1, Q3	23.62, 29.15	23.38, 29.44	23.49, 29.30
Min, Max	16.59, 44.86	17.30, 45.73	16.59, 45.73
Missing	3	2	5
Region, n (%)			
North America	26 (7.9)	21 (6.3)	47 (7.1)
Europe	174 (52.6)	171 (51.7)	345 (52.1)
Asia	42 (12.7)	51 (15.4)	93 (14.0)
South America	61 (18.4)	64 (19.3)	125 (18.9)
Australia/New Zealand	14 (4.2)	11 (3.3)	25 (3.8)
Middle East	14 (4.2)	13 (3.9)	27 (4.1)

Table 17. Summary of demographics study 20030, pretreated population

	Arm A: Pirtobrutinib (N=219)	Arm B: Ibrutinib (N=218)	Total (N=437)
Sex, n (%)			
Male	145 (66.2)	144 (66.1)	289 (66.1)
Female	74 (33.8)	74 (33.9)	148 (33.9)
Race, n (%)			
American Indian or Alaska Native	1 (0.5)	0	1 (0.2)
Asian	28 (12.8)	32 (14.7)	60 (13.7)
Black or African American	4 (1.8)	8 (3.7)	12 (2.7)
Native Hawaiian or Other Pacific Islander	1 (0.5)	1 (0.5)	2 (0.5)
White	168 (76.7)	162 (74.3)	330 (75.5)
Not Reported	8 (3.7)	9 (4.1)	17 (3.9)
Unknown	2 (0.9)	1 (0.5)	3 (0.7)
Other	7 (3.2)	5 (2.3)	12 (2.7)
Ethnicity, n (%)			
Hispanic or Latino	42 (19.2)	46 (21.1)	88 (20.1)
Not Hispanic or Latino	170 (77.6)	163 (74.8)	333 (76.2)
Not Reported	6 (2.7)	6 (2.8)	12 (2.7)
Unknown	1 (0.5)	3 (1.4)	4 (0.9)
Age (years)			
n	219	218	437
Mean (Std.Dev)	66.0 (9.51)	65.9 (10.44)	65.9 (9.97)
Median	67.0	67.0	67.0
Q1, Q3	59.0, 73.0	59.0, 74.0	59.0, 73.0
Min, Max	42, 87	38, 86	38, 87

Age Group, n (%)			
<50 years	13 (5.9)	18 (8.3)	31 (7.1)
>=50 and <65 years	80 (36.5)	67 (30.7)	147 (33.6)
>=65 and <75 years	82 (37.4)	84 (38.5)	166 (38.0)
>=75 and <85 years	42 (19.2)	47 (21.6)	89 (20.4)
>=85 years	2 (0.9)	2 (0.9)	4 (0.9)
Age Group 1, n (%)			
<65 years	93 (42.5)	85 (39.0)	178 (40.7)
>=65 years	126 (57.5)	133 (61.0)	259 (59.3)
Age Group 2, n (%)			
<75 years	175 (79.9)	169 (77.5)	344 (78.7)
>=75 years	44 (20.1)	49 (22.5)	93 (21.3)
Age Group 3, n (%)			
<85 years	217 (99.1)	216 (99.1)	433 (99.1)
>=85 years	2 (0.9)	2 (0.9)	4 (0.9)
Height (cm)			
n	217	216	433
Mean (Std.Dev)	168.45 (9.478)	167.92 (10.487)	168.19 (9.986)
Median	170.00	170.00	170.00
Q1, Q3	163.00, 175.00	159.30, 176.00	160.00, 176.00
Min, Max	139.30, 189.00	145.00, 191.00	139.30, 191.00
Missing	2	2	4
=Weight (kg)			=
n	219	218	437
Mean (Std.Dev)	76.54 (16.379)	76.30 (17.075)	76.42 (16.711)
Median	75.50	75.20	75.40
Q1, Q3	65.90, 85.00	63.00, 86.36	64.70, 85.80
Min, Max	43.00, 154.22	40.90, 129.82	40.90, 154.22
BMI (kg/m^2)			
n	217	216	433
Mean (Std.Dev)	26.78 (4.620)	26.83 (4.553)	26.81 (4.581)
Median	26.12	26.75	26.30
Q1, Q3	23.95, 29.04	23.23, 29.46	23.53, 29.27
Min, Max	16.59, 44.86	17.30, 40.96	16.59, 44.86
Missing	2	2	4
Region, n (%)			
North America	12 (5.5)	13 (6.0)	25 (5.7)
Europe	107 (48.9)	108 (49.5)	215 (49.2)
Asia	27 (12.3)	32 (14.7)	59 (13.5)
South America	58 (26.5)	57 (26.1)	115 (26.3)
Australia/New Zealand	5 (2.3)	3 (1.4)	8 (1.8)
Middle East	10 (4.6)	5 (2.3)	15 (3.4)

Table 18. Summary of baseline disease characteristics, ITT population

	Arm A: Pirtobrutinib (N=331)	Arm B: Ibrutinib (N=331)	Total (N=662)
Duration of Disease (years) *a			
n	331	331	662
Mean (Std.Dev)	6.40 (5.248)	6.33 (5.271)	6.36 (5.256)
Median	5.62	5.26	5.46
Q1, Q3	2.20, 8.91	1.88, 9.73	2.02, 9.39
Min, Max	0.02, 30.87	0.01, 26.29	0.01, 30.87
Disease Type, n (%)			
CLL	306 (92.4)	294 (88.8)	600 (90.6)
SLL	25 (7.6)	37 (11.2)	62 (9.4)
ECOG PS, n (%)			
0	176 (53.2)	170 (51.4)	346 (52.3)
1	143 (43.2)	151 (45.6)	294 (44.4)
2	12 (3.6)	10 (3.0)	22 (3.3)
Rai Stage, n (%) *b			
Stage 0	5 (1.6)	12 (4.1)	17 (2.8)
Stage I	73 (23.9)	72 (24.5)	145 (24.2)
Stage II	90 (29.4)	87 (29.6)	177 (29.5)
Stage III	63 (20.6)	36 (12.2)	99 (16.5)
Stage IV	72 (23.5)	83 (28.2)	155 (25.8)
Missing	3 (1.0)	4 (1.4)	7 (1.2)

Bulky Disease, n (%)			
Subjects with measurable target lesion (lymph node)	317 (95.8)	311 (94.0)	628 (94.9)
<5cm	210 (63.4)	195 (58.9)	405 (61.2)
>=5cm	107 (32.3)	116 (35.0)	223 (33.7)
<10cm	294 (88.8)	286 (86.4)	580 (87.6)
>=10cm	23 (6.9)	25 (7.6)	48 (7.3)
No measurable target lesion at baseline	14 (4.2)	20 (6.0)	34 (5.1)
ß2 Microglobulin (mg/L) at Baseline, n (%)			
<= 3.5	107 (32.3)	118 (35.6)	225 (34.0)
> 3.5	213 (64.4)	207 (62.5)	420 (63.4)
Missing/Unknown	11 (3.3)	6 (1.8)	17 (2.6)
Cytogenetic features (FISH panel, Biomarker Central Laboratory), n (%)			
17p Deletion Presence			
Yes	37 (11.2)	36 (10.9)	73 (11.0)
No	243 (73.4)	222 (67.1)	465 (70.2)
Missing/Unknown	51 (15.4)	73 (22.1)	124 (18.7)
11q Deletion Presence			
Yes	57 (17.2)	48 (14.5)	105 (15.9)
No	198 (59.8)	178 (53.8)	376 (56.8)
Missing/Unknown	76 (23.0)	105 (31.7)	181 (27.3)
High Risk Features(Biomarker Central Laboratory), n (%)			
IGHV Mutation Status			
Mutated	94 (28.4)	94 (28.4)	188 (28.4)
Unmutated	199 (60.1)	183 (55.3)	382 (57.7)
Missing/Unknown	38 (11.5)	54 (16.3)	92 (13.9)
Complex Karyotype Presence *c			
Yes	104 (31.4)	78 (23.6)	182 (27.5)
No	155 (46.8)	149 (45.0)	304 (45.9)
Missing/Unknown	72 (21.8)	104 (31.4)	176 (26.6)
TP53 Mutation Presence			
Yes	92 (27.8)	78 (23.6)	170 (25.7)
No	192 (58.0)	195 (58.9)	387 (58.5)
Missing/Unknown	47 (14.2)	58 (17.5)	105 (15.9)
TP53 mutation and/or 17p Deletion			
Yes	102 (30.8)	90 (27.2)	192 (29.0)
No	159 (48.0)	145 (43.8)	304 (45.9)
Missing/Unknown	70 (21.1)	96 (29.0)	166 (25.1)

	Arm A: Pirtobrutinib (N=331)	Arm B: Ibrutinib (N=331)	Total (N=662)
TP53 mutation with 17p Deletion			
Yes	27 (8.2)	24 (7.3)	51 (7.7)
No	276 (83.4)	272 (82.2)	548 (82.8)
Missing/Unknown	28 (8.5)	35 (10.6)	63 (9.5)
TP53 mutation without 17p Deletion			
Yes	47 (14.2)	34 (10.3)	81 (12.2)
No	226 (68.3)	226 (68.3)	452 (68.3)
Missing/Unknown	58 (17.5)	71 (21.5)	129 (19.5)
TP53 mutation and/or 17p Deletion and/or unmutated IGHV			
Yes	230 (69.5)	217 (65.6)	447 (67.5)
No	55 (16.6)	48 (14.5)	103 (15.6)
Missing/Unknown	46 (13.9)	66 (19.9)	112 (16.9)
Cytopenia at Baseline, n (%)			
Neutropenia - Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L	51 (15.4)	31 (9.4)	82 (12.4)
Anemia - Hgb <11 g/dL	135 (40.8)	109 (32.9)	244 (36.9)
Thrombocytopenia - Platelet Counts < 100 x 10^9/L	96 (29.0)	97 (29.3)	193 (29.2)
Any of the Above	193 (58.3)	178 (53.8)	371 (56.0)
No Cytopenia at Baseline	138 (41.7)	153 (46.2)	291 (44.0)

Disease Related Symptoms, n (%)			
Weight loss	44 (13.3)	38 (11.5)	82 (12.4)
Fever	7 (2.1)	7 (2.1)	14 (2.1)
Night sweats	126 (38.1)	114 (34.4)	240 (36.3)
Fatigue	41 (12.4)	56 (16.9)	97 (14.7)
Any of the Above	159 (48.0)	146 (44.1)	305 (46.1)
Del17p Status			
n	331	331	662
Present	52(15.7)	51(15.4)	103(15.6)
Not Present	279(84.3)	280(84.6)	559(84.4)
Number of prior lines of therapy			
n	331	331	662
0	112(33.8)	113(34.1)	225(34.0)
1	150(45.3)	149(45.0)	299(45.2)
>=2	69(20.8)	69(20.8)	138(20.8)

Table 19. Summary of baseline disease characteristics in study 20030, pretreated population

	Arm A: Pirtobrutinib (N=219)	Arm B: Ibrutinib (N=218)	Total (N=437)
Duration of Disease (years) *a			
n	219	218	437
Mean (Std.Dev)	8.16 (5.240)	7.90 (5.240)	8.03 (5.236)
Median	7.29	7.45	7.32
Q1, Q3	4.55, 10.75	3.84, 10.97	4.16, 10.91
Min, Max	0.14, 30.87	0.19, 26.29	0.14, 30.87
Disease Type, n (%)			
CLL	208 (95.0)	189 (86.7)	397 (90.8)
SLL	11 (5.0)	29 (13.3)	40 (9.2)
ECOG PS, n (%)			
0	118 (53.9)	107 (49.1)	225 (51.5)
1	94 (42.9)	104 (47.7)	198 (45.3)
2	7 (3.2)	7 (3.2)	14 (3.2)
Rai Stage, n (%) *b			
Stage 0	4 (1.9)	8 (4.2)	12 (3.0)
Stage I	45 (21.6)	44 (23.3)	89 (22.4)
Stage II	63 (30.3)	52 (27.5)	115 (29.0)
Stage III	37 (17.8)	21 (11.1)	58 (14.6)
Stage IV	57 (27.4)	61 (32.3)	118 (29.7)
Missing	2 (1.0)	3 (1.6)	5 (1.3)
Bulky Disease, n (%)			
Subjects with measurable target lesion (lymph node)	208 (95.0)	203 (93.1)	411 (94.1)
<5cm	139 (63.5)	120 (55.0)	259 (59.3)
>=5cm	69 (31.5)	83 (38.1)	152 (34.8)
<10cm	194 (88.6)	182 (83.5)	376 (86.0)
>=10cm	14 (6.4)	21 (9.6)	35 (8.0)
No measurable target lesion at baseline	11 (5.0)	15 (6.9)	26 (5.9)
ß2 Microglobulin (mg/L) at Baseline, n (%)			
<= 3.5	66 (30.1)	76 (34.9)	142 (32.5)
> 3.5	145 (66.2)	136 (62.4)	281 (64.3)
Missing/Unknown	8 (3.7)	6 (2.8)	14 (3.2)
Cytogenetic features (FISH panel, Biomarker Central Laboratory), n (%)			
17p Deletion Presence			
Yes	26 (11.9)	25 (11.5)	51 (11.7)
No	160 (73.1)	152 (69.7)	312 (71.4)
Missing/Unknown	33 (15.1)	41 (18.8)	74 (16.9)

11q Deletion Presence			
Yes	47 (21.5)	42 (19.3)	89 (20.4)
No	122 (55.7)	113 (51.8)	235 (53.8)
Missing/Unknown	50 (22.8)	63 (28.9)	113 (25.9)
High Risk Features(Biomarker Central Laboratory), n (%)			
IGHV Mutation Status			
Mutated	53 (24.2)	55 (25.2)	108 (24.7)
Unmutated	141 (64.4)	129 (59.2)	270 (61.8)
Missing/Unknown	25 (11.4)	34 (15.6)	59 (13.5)
Complex Karyotype Presence *c			
Yes	76 (34.7)	60 (27.5)	136 (31.1)
No	92 (42.0)	90 (41.3)	182 (41.6)
Missing/Unknown	51 (23.3)	68 (31.2)	119 (27.2)
TP53 Mutation Presence			
Yes	81 (37.0)	59 (27.1)	140 (32.0)
No	108 (49.3)	120 (55.0)	228 (52.2)
Missing/Unknown	30 (13.7)	39 (17.9)	69 (15.8)
TP53 mutation and/or 17p Deletion			
Yes	85 (38.8)	67 (30.7)	152 (34.8)
No	88 (40.2)	92 (42.2)	180 (41.2)
Missing/Unknown	46 (21.0)	59 (27.1)	105 (24.0)
TP53 mutation with 17p Deletion			
Yes	22 (10.0)	17 (7.8)	39 (8.9)
No	180 (82.2)	180 (82.6)	360 (82.4)
Missing/Unknown	17 (7.8)	21 (9.6)	38 (8.7)
TP53 mutation without 17p Deletion			
Yes	45 (20.5)	29 (13.3)	74 (16.9)
No	133 (60.7)	141 (64.7)	274 (62.7)
Missing/Unknown	41 (18.7)	48 (22.0)	89 (20.4)
TP53 mutation and/or 17p Deletion and/or unmutated IGHV			
Yes	166 (75.8)	151 (69.3)	317 (72.5)
No	26 (11.9)	26 (11.9)	52 (11.9)
Missing/Unknown	27 (12.3)	41 (18.8)	68 (15.6)
Cytopenia at Baseline, n (%)			
Neutropenia - Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L	39 (17.8)	27 (12.4)	66 (15.1)
Anemia - Hgb <11 g/dL	84 (38.4)	75 (34.4)	159 (36.4)
Thrombocytopenia - Platelet Counts < 100 x 10^9/L	74 (33.8)	73 (33.5)	147 (33.6)
Any of the Above	133 (60.7)	130 (59.6)	263 (60.2)
No Cytopenia at Baseline	86 (39.3)	88 (40.4)	174 (39.8)
Disease Related Symptoms, n (%)			
Weight loss	31 (14.2)	30 (13.8)	61 (14.0)
Fever	5 (2.3)	5 (2.3)	10 (2.3)
Night sweats	86 (39.3)	84 (38.5)	170 (38.9)
Fatigue	30 (13.7)	40 (18.3)	70 (16.0)
Any of the Above	111 (50.7)	102 (46.8)	213 (48.7)

Table 20. Summary of prior cancer therapy in study 20030– pretreated population

	Arm A: Pirtobrutinib (N=219)	Arm B: Ibrutinib (N=218)	Total (N=437)
Summary of Lines of Prior Systemic Therapy			
n	219	218	437
Mean (Std.Dev)	1.5 (1.03)	1.5 (1.02)	1.5 (1.02)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	1, 9	1, 8	1, 9
Number of Lines of Prior Systemic Therapy, n (%)			
1	148 (67.6)	150 (68.8)	298 (68.2)
2	43 (19.6)	39 (17.9)	82 (18.8)
3	15 (6.8)	18 (8.3)	33 (7.6)
>=4	13 (5.9)	11 (5.0)	24 (5.5)
Prior Systemic Therapies, n (%)			
Prior BCL2 inhibitor	22 (10.0)	17 (7.8)	39 (8.9)
Prior Venetoclax	21 (9.6)	17 (7.8)	38 (8.7)
Prior Chemotherapy	201 (91.8)	208 (95.4)	409 (93.6)
Prior Steroid	37 (16.9)	45 (20.6)	82 (18.8)
Prior Anti-CD20 Antibody	158 (72.1)	166 (76.1)	324 (74.1)
Prior PI3K Agent	6 (2.7)	6 (2.8)	12 (2.7)
Prior IMID/Immunomodulator	1 (0.5)	1 (0.5)	2 (0.5)
Prior CART	0	0	0
Prior Stem Cell Transplant Therapy	2 (0.9)	2 (0.9)	4 (0.9)
Auto-SCT	1 (0.5)	2 (0.9)	3 (0.7)
Allo-SCT	1 (0.5)	1 (0.5)	2 (0.5)
Prior Other Systemic Therapy	0	3 (1.4)	3 (0.7)
Prior Other Molecular Pathways/small molecule inhibitors	0	0	0
Prior Other Immuno-therapies excluding antiCD20	0	3 (1.4)	3 (0.7)
Reason for Discontinuation from Last Prior Therapy, n (%)			
Disease Progression	31 (9.4)	35 (10.6)	66 (10.0)
Toxicity	23 (6.9)	25 (7.6)	48 (7.3)
Patient Choice	7 (2.1)	9 (2.7)	16 (2.4)
Finished Course Of Therapy	148 (44.7)	141 (42.6)	289 (43.7)
Other	9 (2.7)	7 (2.1)	16 (2.4)
Missing	1 (0.3)	1 (0.3)	2 (0.3)
Not Applicable	112 (33.8)	113 (34.1)	225 (34.0)
Prior Radiotherapy, n (%)			
Yes	2 (0.6)	4 (1.2)	6 (0.9)
No	329 (99.4)	327 (98.8)	656 (99.1)

Numbers analysed

Table 21. Analysis populations in study 20030

Population	Description	Number of Participants		
		Arm A	Arm B	Total
ITT	All randomized participants, even if a participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed according to the treatment group they were assigned to regardless of what actual treatment they receive.	331	331	662
Pretreated ITT (Pretreated)	Participants in the ITT population who were previously treated.	219	218	437
Treatment-naïve ITT (Treatment-naïve)	Participants in the ITT population who were not previously treated.	112	113	225
Safety	All randomized participants who take at least 1 dose (including a partial dose) of study drug. Analysis of safety data will be based on the actual treatment a participant received on the first study drug administration, regardless of which treatment they were randomized to receive ("as treated").	330	325	655
Pretreated Safety	Participants in the Safety population who were previously treated.	218	216	434
Treatment-naïve Safety	Participants in the Safety population who were not previously treated.	112	109	221
Per-Protocol	All randomized participants who take at least 1 dose (including a partial dose) of study drug and who do not have important protocol deviations that impact efficacy analysis. These protocol deviations will be decided and defined prior to any interim or final analysis using per-protocol population.	326	322	648
Pretreated Per-Protocol	Participants in the Per-Protocol population who were previously treated.	214	214	428
Treatment-naïve Per-Protocol	Participants in the Per-Protocol population who were not previously treated.	112	108	220

2.4.2.1. Results

Outcomes and estimation

ORR

Pirtobrutinib monotherapy demonstrated statistically significant non-inferiority in IRC-assessed ORR of PR or better compared to ibrutinib in the ITT population (stratified ORR ratio: 1.1080 [95% CI: 1.034, 1.187]; 2-sided p-value against NI margin of 0.88 was <0.0001) (2-sided significance level = 0.005) and in the Pretreated population (stratified ORR ratio: 1.1233 [95% CI: 1.020, 1.237]; 2-sided p-value against NI margin of 0.86 was <0.0001) (2-sided significance level = 0.045) (**Table 22**).

Table 22. Summary of best overall response and overall response rate, ITT and pretreated populations

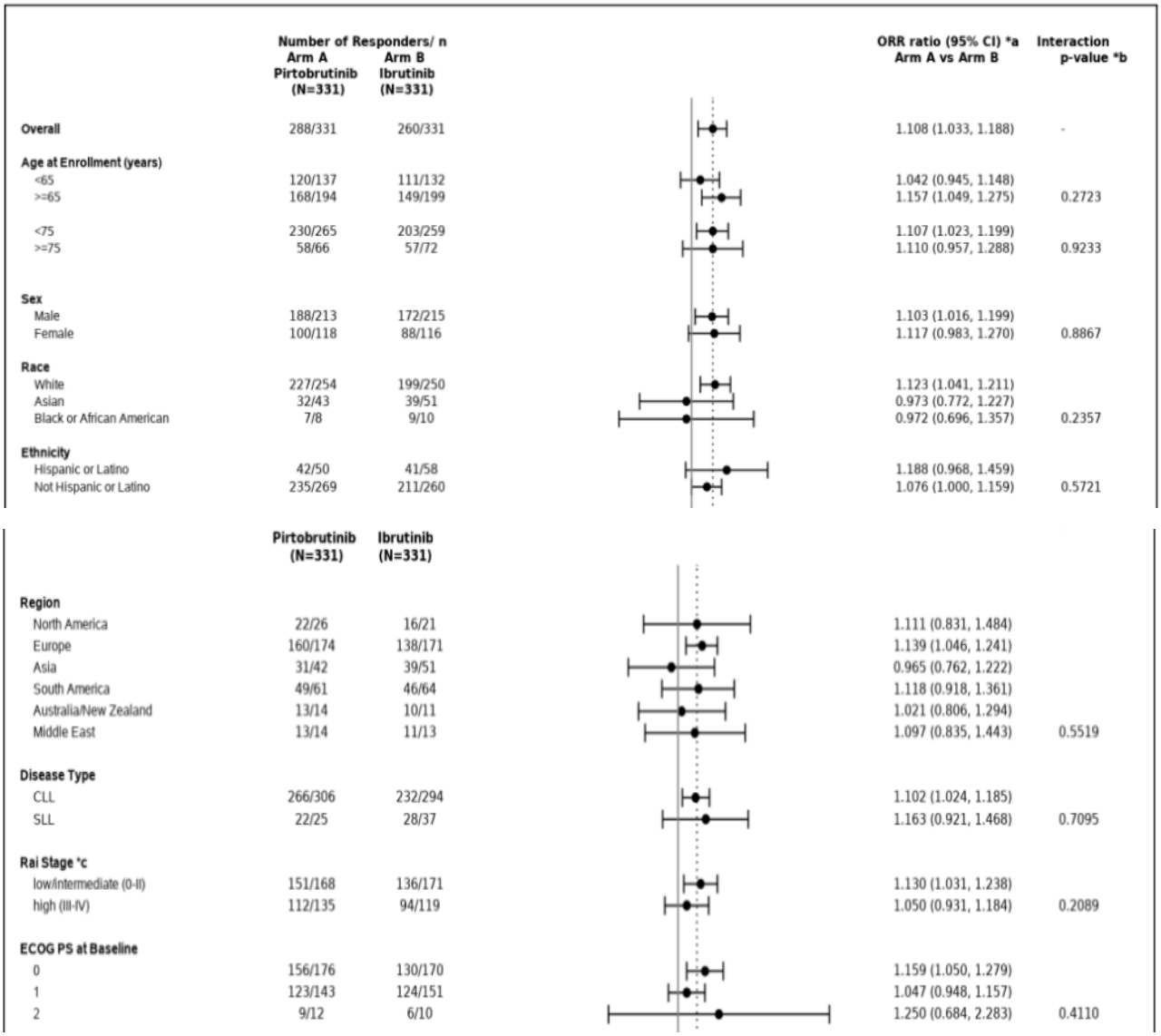
	ITT Population N = 662		Pretreated Population N = 437	
	Pirtobrutinib N = 331	**Ibrutinib N = 331**	**Pirtobrutinib N = 219**	**Ibrutinib N = 218**
Parameter	**IRC-Assessed Response[a]**			
Best overall response[a], n (%)				
Complete remission	15 (4.5)	8 (2.4)	8 (3.7)	4 (1.8)
Complete remission with incomplete bone marrow recovery	1 (0.3)	0	0	0
Nodular partial remission	0	0	0	0
Partial remission	272 (82.2)	252 (76.1)	176 (80.4)	159 (72.9)
Partial remission with lymphocytosis	8 (2.4)	13 (3.9)	7 (3.2)	10 (4.6)
Stable disease	18 (5.4)	36 (10.9)	15 (6.8)	31 (14.2)
Non-progressive disease	1 (0.3)	0	1 (0.5)	0
No evidence of disease	0	0	0	0
Progressive disease	5 (1.5)	4 (1.2)	5 (2.3)	4 (1.8)
Unknown	5 (1.5)	6 (1.8)	3 (1.4)	5 (2.3)
NA[b]	6 (1.8)	12 (3.6)	4 (1.8)	5 (2.3)
Overall response rate (partial remission or better)				
n (%)	288 (87.0)	260 (78.5)	184 (84.0)	163 (74.8)
95% CI[c]	82.90, 90.44	73.73, 82.85	78.48, 88.61	68.46, 80.39
Nominal p-value[d]	0.0035		0.0175	
Overall response rate (partial remission or better) Ratio Stratified Analysis				
ORR ratio	1.1080		1.1233	
95% CI	1.034, 1.187		1.020, 1.237	
p-value for NI[e]	<0.0001		<0.0001	
Overall response rate including partial remission with lymphocytosis				
n (%)	296 (89.4)	273 (82.5)	191 (87.2)	173 (79.4)
95% CI[c]	85.60, 92.52	77.95, 86.42	82.05, 91.33	73.37, 84.53
Nominal p-value[d]	0.0093		0.0286	
	INV-Assessed Response[a]			
Overall response rate (partial remission or better)				
n (%)	295 (89.1)	261 (78.9)	192 (87.7)	164 (75.2)
95% CI[c]	85.26, 92.27	74.05, 83.13	82.57, 91.72	68.95, 80.81
Overall response rate (partial remission or better) Ratio Stratified Analysis				
ORR ratio	1.1304		1.1646	
95% CI	1.057, 1.208		1.063, 1.275	
Overall response rate including partial remission with lymphocytosis				
n (%)	304 (91.8)	273 (82.5)	198 (90.4)	173 (79.4)
95% CI[c]	88.35, 94.56	77.95, 86.42	85.72, 93.97	73.37, 84.53

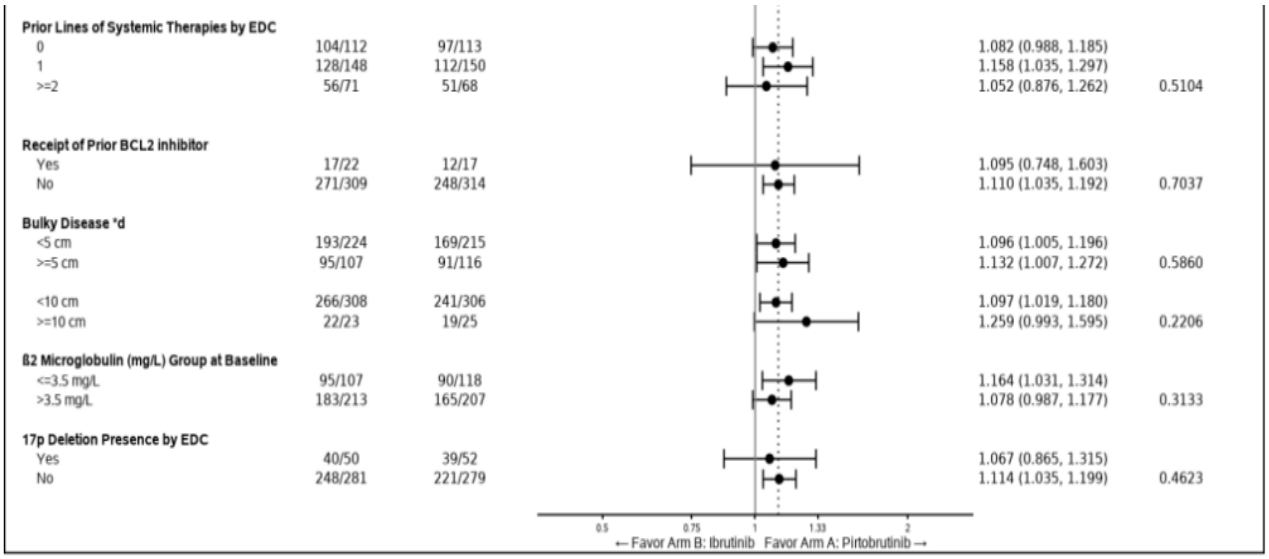
Investigator-assessed ORR was a secondary endpoint, and results were supportive of IRC-assessed ORR results. The investigator-assessed ORR in the ITT population was

- 89.1% (95% CI: 85.26, 92.27) for Arm A and
- 78.9% (95% CI: 74.05, 83.13) for Arm B

The subgroup analyses of IRC-assessed ORR in the ITT (**Figure 9**) and pretreated populations (**Figure 10**) demonstrated a generally consistent treatment effect across most subgroups, favouring pirtobrutinib.

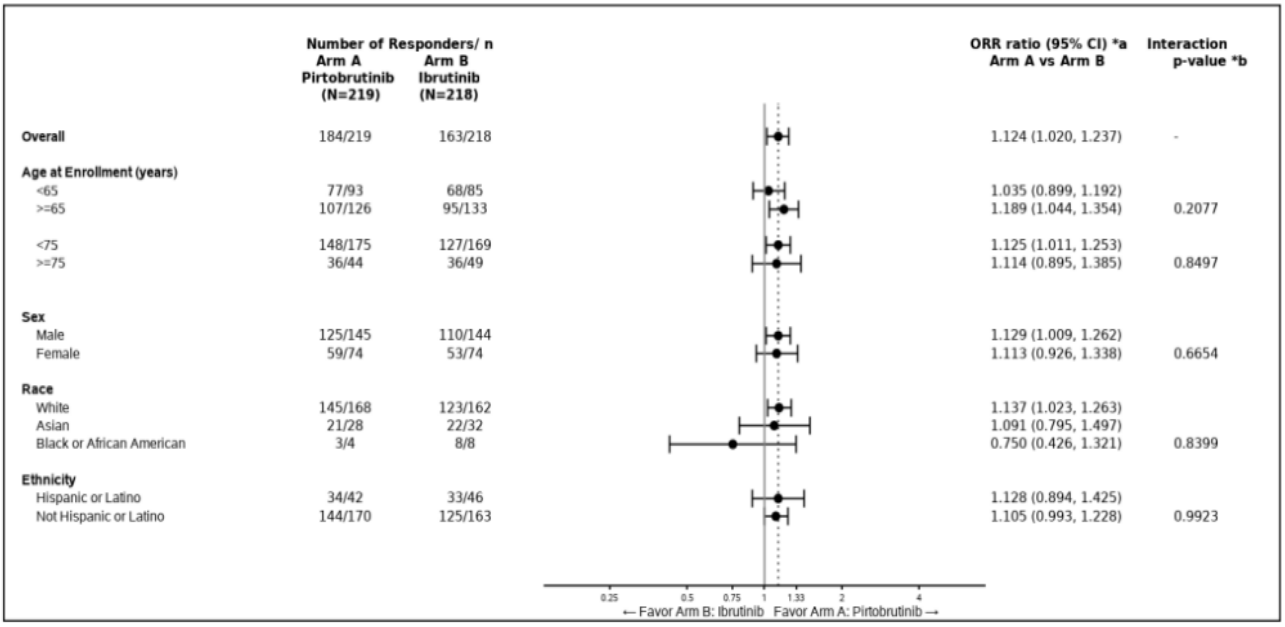
Figure 9. Subgroup analysis of ORR based on IRC assessments in study 20030, ITT population



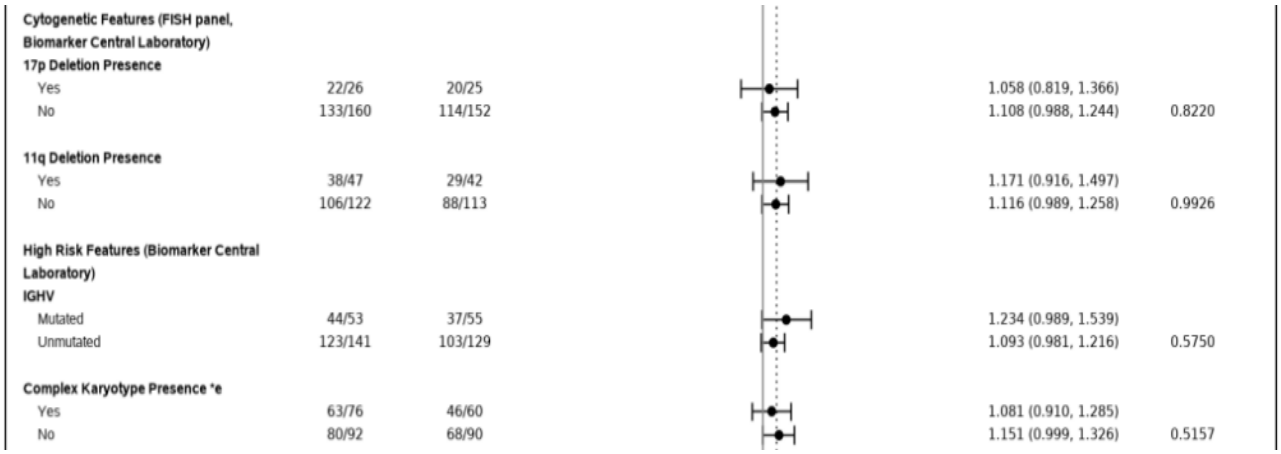


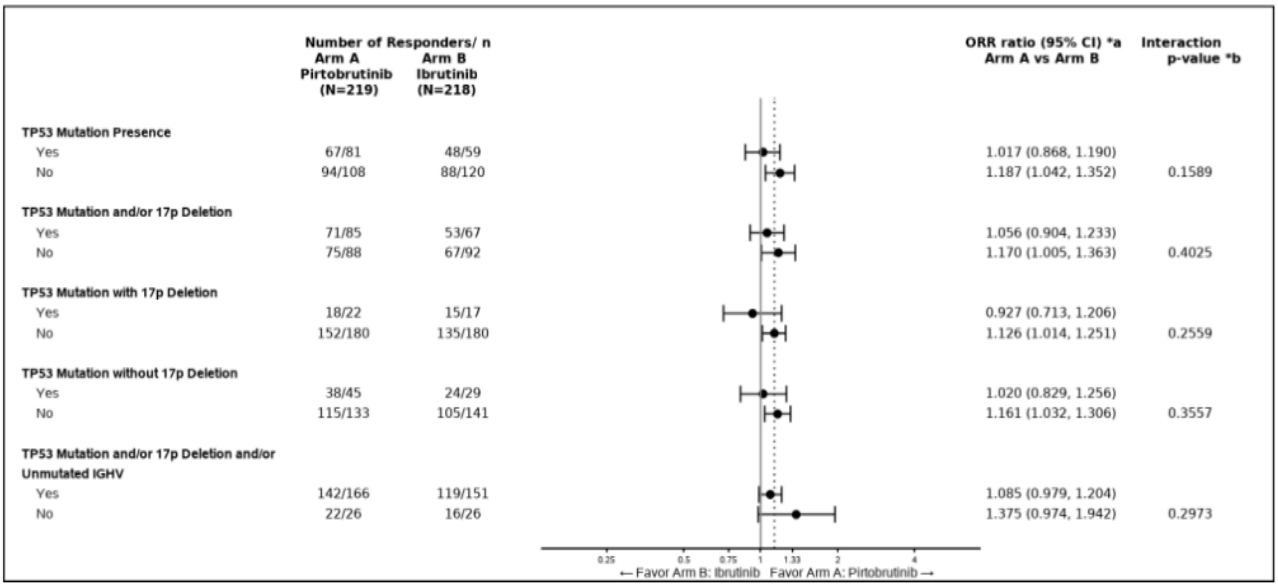
	Number of Responders/ n Arm A Pirtobrutinib (N=331)	Arm B Ibrutinib (N=331)	ORR ratio (95% CI) *a Arm A vs Arm B	Interaction p-value *b
Prior Lines of Systemic Therapies by EDC				
0	104/112	97/113	1.082 (0.988, 1.185)	
1	128/148	112/150	1.158 (1.035, 1.297)	
>=2	56/71	51/68	1.052 (0.876, 1.262)	0.5104
Receipt of Prior BCL2 inhibitor				
Yes	17/22	12/17	1.095 (0.748, 1.603)	
No	271/309	248/314	1.110 (1.035, 1.192)	0.7037
Bulky Disease *d				
<5 cm	193/224	169/215	1.096 (1.005, 1.196)	
>=5 cm	95/107	91/116	1.132 (1.007, 1.272)	0.5860
<10 cm	266/308	241/306	1.097 (1.019, 1.180)	
>=10 cm	22/23	19/25	1.259 (0.993, 1.595)	0.2206
ß2 Microglobulin (mg/L) Group at Baseline				
<=3.5 mg/L	95/107	90/118	1.164 (1.031, 1.314)	
>3.5 mg/L	183/213	165/207	1.078 (0.987, 1.177)	0.3133
17p Deletion Presence by EDC				
Yes	40/50	39/52	1.067 (0.865, 1.315)	
No	248/281	221/279	1.114 (1.035, 1.199)	0.4623
Cytogenetic Features (FISH panel, Biomarker Central Laboratory)				
17p Deletion Presence				
Yes	31/37	26/36	1.160 (0.906, 1.485)	
No	211/243	175/222	1.102 (1.013, 1.198)	0.8555
11q Deletion Presence				
Yes	48/57	34/48	1.189 (0.960, 1.472)	
No	176/198	142/178	1.114 (1.019, 1.218)	0.8880
High Risk Features (Biomarker Central Laboratory)				
IGHV				
Mutated	82/94	71/94	1.155 (1.005, 1.327)	
Unmutated	177/199	148/183	1.100 (1.009, 1.198)	0.7571
Complex Karyotype Presence *e				
Yes	88/104	61/78	1.082 (0.938, 1.248)	
No	140/155	118/149	1.141 (1.035, 1.257)	0.3602
TP53 Mutation Presence				
Yes	76/92	63/78	1.023 (0.886, 1.180)	
No	174/192	156/195	1.133 (1.042, 1.232)	0.1300
TP53 Mutation and/or 17p Deletion				
Yes	85/102	70/90	1.071 (0.931, 1.233)	
No	142/159	114/145	1.136 (1.027, 1.256)	0.3456
TP53 Mutation with 17p Deletion				
Yes	22/27	19/24	1.029 (0.783, 1.352)	
No	243/276	217/272	1.104 (1.025, 1.188)	0.5218
TP53 Mutation without 17p Deletion				
Yes	40/47	29/34	0.998 (0.830, 1.199)	
No	202/226	179/226	1.128 (1.041, 1.223)	0.2415
TP53 Mutation and/or 17p Deletion and/or Unmutated IGHV				
Yes	202/230	173/217	1.102 (1.014, 1.196)	
No	48/55	36/48	1.164 (0.960, 1.410)	0.7079

Figure 10. Subgroup analysis of ORR based on IRC assessments in study 20030, pretreated ITT population



	Number of Responders/ n Arm A Pirtobrutinib (N=219)	Number of Responders/ n Arm B Ibrutinib (N=218)	ORR ratio (95% CI) *a Arm A vs Arm B	Interaction p-value *b
Overall	184/219	163/218	1.124 (1.020, 1.237)	-
Age at Enrollment (years)				
<65	77/93	68/85	1.035 (0.899, 1.192)	
>=65	107/126	95/133	1.189 (1.044, 1.354)	0.2077
<75	148/175	127/169	1.125 (1.011, 1.253)	
>=75	36/44	36/49	1.114 (0.895, 1.385)	0.8497
Sex				
Male	125/145	110/144	1.129 (1.009, 1.262)	
Female	59/74	53/74	1.113 (0.926, 1.338)	0.6654
Race				
White	145/168	123/162	1.137 (1.023, 1.263)	
Asian	21/28	22/32	1.091 (0.795, 1.497)	
Black or African American	3/4	8/8	0.750 (0.426, 1.321)	0.8399
Ethnicity				
Hispanic or Latino	34/42	33/46	1.128 (0.894, 1.425)	
Not Hispanic or Latino	144/170	125/163	1.105 (0.993, 1.228)	0.9923
Region				
North America	9/12	9/13	1.083 (0.665, 1.765)	
Europe	96/107	85/108	1.140 (1.014, 1.282)	
Asia	20/27	22/32	1.077 (0.780, 1.488)	
South America	46/58	41/57	1.103 (0.895, 1.359)	
Australia/New Zealand	4/5	3/3	0.800 (0.516, 1.240)	
Middle East	9/10	3/5	1.500 (0.712, 3.159)	0.8732
Disease Type				
CLL	174/208	142/189	1.113 (1.006, 1.233)	
SLL	10/11	21/29	1.255 (0.937, 1.681)	0.4833
Rai Stage *c				
low/intermediate (0-II)	97/112	77/104	1.170 (1.022, 1.339)	
high (III-IV)	75/94	64/82	1.022 (0.877, 1.192)	0.1647
ECOG PS at Baseline				
0	102/118	77/107	1.201 (1.046, 1.379)	
1	77/94	83/104	1.026 (0.896, 1.175)	
2	5/7	3/7	1.667 (0.628, 4.420)	0.2571
Prior Lines of Systemic Therapies by EDC				
1	128/148	112/150	1.158 (1.035, 1.297)	
>=2	56/71	51/68	1.052 (0.876, 1.262)	0.2712
Receipt of Prior BCL2 inhibitor				
Yes	17/22	12/17	1.095 (0.748, 1.603)	
No	167/197	151/201	1.128 (1.022, 1.246)	0.7357
Bulky Disease *d				
<5 cm	124/150	97/135	1.151 (1.012, 1.308)	
>=5 cm	60/69	66/83	1.094 (0.948, 1.261)	0.8744
<10 cm	171/205	147/197	1.118 (1.010, 1.238)	
>=10 cm	13/14	16/21	1.219 (0.921, 1.612)	0.4655
ß2 Microglobulin (mg/L) Group at Baseline				
<=3.5 mg/L	54/66	52/76	1.196 (0.988, 1.447)	
>3.5 mg/L	122/145	106/136	1.080 (0.963, 1.210)	0.5221
17p Deletion Presence by EDC				
Yes	29/36	28/35	1.007 (0.800, 1.268)	
No	155/183	135/183	1.148 (1.033, 1.277)	0.3254





PFS

PFS interim analyses conducted at the time of the ORR final analysis were descriptive. Additional follow-up is ongoing to further characterize the PFS benefit.

Study 20030 showed a favourable trend in IRC-assessed PFS with pirtobrutinib monotherapy compared with ibrutinib in both the ITT and Pretreated populations, with an information fraction of 51% in both populations.

The concordance rate between IRC and Investigator PD assessments was high in both arms in the ITT and in the Pretreated populations, indicating agreement of disease response assessments using the iwCLL criteria (**Table 23**). Kaplan-Meier plot of PFS based on IRC assessments for the ITT, treatment naïve and pretreated populations are shown in **Figure 11**-**Figure 13**.

Table 23. Summary of PFS, ITT and pretreated populations-study 20030

	ITT Population N = 662		**Pretreated Population N = 437**	
Parameter	**Pirtobrutinib N = 331**	**Ibrutinib N = 331**	**Pirtobrutinib N = 219**	**Ibrutinib N = 218**
IRC-Assessed PFS				

Parameter	ITT Population N = 662		Pretreated Population N = 437	
	Pirtobrutinib N = 331	**Ibrutinib N = 331**	**Pirtobrutinib N = 219**	**Ibrutinib N = 218**
Number of Events, n (%)	58 (17.5)	69 (20.8)	48 (21.9)	50 (22.9)
PD	39 (11.8)	51 (15.4)	30 (13.7)	35 (16.1)
Death	19 (5.7)	18 (5.4)	18 (8.2)	15 (6.9)
Number of Participants Censored, n (%)	273 (82.5)	262 (79.2)	171 (78.1)	168 (77.1)
Event after 2 or more consecutively missed disease assessment visits	0	1 (0.3)	0	0
Event after subsequent anticancer therapy	3 (0.9)	3 (0.9)	1 (0.5)	3 (1.4)
No adequate disease assessment at postbaseline	0	2 (0.6)	0	0
No documented disease progression or death on or before data cutoff	254 (76.7)	218 (65.9)	161 (73.5)	142 (65.1)
Study exit	9 (2.7)	22 (6.6)	4 (1.8)	14 (6.4)
Subsequent anticancer therapy without event	2 (0.6)	9 (2.7)	2 (0.9)	6 (2.8)
Two or more consecutively missed disease assessment visits without event	5 (1.5)	7 (2.1)	3 (1.4)	3 (1.4)
Progression-free Survival, (months)				
Median (95% CI)	28.58 (28.06, NE)	NR (NE, NE)	28.06 (28.06, NE)	NR (22.47, NE)
Min, Max[a]	0.03+, 33.08+	0.03+, 29.21+	0.03+, 30.39+	0.03+, 28.09+
Stratified Analysis (versus Arm B)[b]				
Hazard Ratio (95% CI)	0.755 (0.531, 1.075)		0.845 (0.566, 1.262)	
p-value[c]	0.1185		0.4102	
PFS Follow-up Time (months)				
Median (95% CI)	21.98 (18.73, 22.11)	18.96 (18.43, 22.05)	18.43 (15.80, 18.46)	17.41 (14.92, 18.40)
Min, Max[a]	0.03+, 33.08+	0.03+, 29.21+	0.03+, 30.39+	0.03+, 28.09+
PFS Rate, % (95% CI)				
At 6 months	96.0 (93.2, 97.6)	96.2 (93.4, 97.8)	94.0 (89.9, 96.5)	95.1 (91.2, 97.4)
At 12 months	88.6 (84.5, 91.6)	86.7 (82.2, 90.0)	85.3 (79.7, 89.4)	83.6 (77.6, 88.1)
At 18 months	84.7 (80.1, 88.4)	80.2 (75.0, 84.4)	79.4 (72.8, 84.6	76.5 (69.3, 82.2)
INV-Assessed PFS				
Progression-free Survival, (months)				
Median (95% CI)	NR (NE, NE)	NR (27.70, NE)	NR (NE, NE)	NR (22.47, NE)
Stratified Analysis (versus Arm B)[b]				
Hazard Ratio (95% CI)	0.569 (0.388, 0.834)		0.729 (0.471, 1.128)	
PFS Follow-up Time (months)				
Median (95% CI)	21.98 (18.86, 22.11)	19.65 (18.46, 22.05)	18.37 (16.62, 18.50)	15.84 (14.92, 18.40)

Parameter	ITT Population N = 662		Pretreated Population N = 437	
	Pirtobrutinib N = 331	Ibrutinib N = 331	Pirtobrutinib N = 219	Ibrutinib N = 218
PFS Rate, % (95% CI)				
At 18 months	86.9 (82.4, 90.3)	82.3 (77.3, 86.3)	81.7 (75.1, 86.7)	79.2 (72.3, 84.6)

Although the treatment effect was often consistent across subgroups, some variability was observed, potentially due to the immaturity of the PFS data in both the ITT and Pretreated populations at this time and small patient numbers in some subgroups, limiting interpretation.

Figure 11. Kaplan-Meier plot of PFS based on IRC assessments, ITT population study 20030

Figure 12. Kaplan-Meier plot of PFS based on IRC assessments, treatment-naïve population, study 20030

Figure 13. Kaplan-Meier plot of PFS based on IRC assessments, pretreated population, study 20030

Duration of response

DOR was determined according to both IRC and investigator assessment for participants with a best overall response of PR or better.

At the time of data cutoff, DOR data were not yet mature.

ITT population

- The HR comparing IRC-assessed DOR between the Pirtobrutinib Arm and the Ibrutinib Arm was 0.717 (95% CI: 0.458, 1.121).
- The median DOR was 24.67 months (95% CI: 24.38, NE) in the Pirtobrutinib Arm and was not reached in the Ibrutinib Arm.
- The 12-month IRC-assessed DOR rate was 88.1% (95% CI 83.3, 91.6) for pirtobrutinib and 85.0% (95% CI: 79.5, 89.1) for ibrutinib.
- The median duration of follow-up among responders was 14.8 months (95% CI: 14.7, 15.1) in the Pirtobrutinib Arm and 14.8 months (95% CI: 14.4, 15.0) in the Ibrutinib Arm.
- The HR comparing investigator-assessed DOR between the Pirtobrutinib Arm and the Ibrutinib Arm was 0.565 (95% CI: 0.346, 0.922).

Pretreated population

- The HR comparing IRC-assessed DOR between the Pirtobrutinib Arm and the Ibrutinib Arm was 0.805 (95% CI: 0.476, 1.362).
- The median DOR was 24.38 months (95% CI: 24.38, NE) in the Pirtobrutinib Arm and was not reached in the Ibrutinib Arm.
- The 12-month IRC-assessed DOR rate was 83.9% (95% CI 76.5, 89.2) for pirtobrutinib and 82.8% (95% CI 75.1, 88.4) for ibrutinib.
- The median duration of follow-up among responders was 11.1 months (95% CI: 11.1, 14.3) in the Pirtobrutinib Arm and 11.1 months (95% CI: 11.1, 14.6) in the Ibrutinib Arm.
- The HR comparing investigator-assessed DOR between the Pirtobrutinib Arm and the Ibrutinib Arm was 0.804 (95% CI: 0.443, 1.459).

Although the treatment effect was often consistent across subgroups, some variability was observed, potentially due to the immaturity of the DOR data in both the ITT and Pretreated populations at this time, as well as small participant numbers in some subgroups, which limited interpretation.

OS

At the time of the primary analysis, the OS data in both the ITT and Pretreated populations remain immature. No OS detriment was observed for pirtobrutinib monotherapy compared with ibrutinib in the ITT and Pretreated populations.

ITT population

- The HR comparing OS between pirtobrutinib and ibrutinib was 0.961 (95% CI: 0.548, 1.686).
- The 18-month OS rate was 93.3% (95% CI: 90.0, 95.6) in the Pirtobrutinib Arm and 92.5% (95% CI: 88.9, 94.9) in the Ibrutinib Arm.
- The median OS was not reached in either arm.
- The median OS follow-up time was 22.57 months (95% CI: 21.13, 25.17) in the Pirtobrutinib Arm and 21.91 months (95% CI: 20.53, 22.77) in the Ibrutinib Arm.

Pretreated population

- The HR comparing OS between pirtobrutinib and ibrutinib was 0.964 (95% CI 0.528, 1.757).
- The 18-month OS rate was 91.5% (95% CI: 86.9, 94.6) in the Pirtobrutinib Arm and 89.7% (95% CI: 84.3, 93.3) in the Ibrutinib Arm.
- The median OS was not reached in either arm.
- The median OS follow-up time was 19.38 months (95% CI: 18.37, 20.21) in the Pirtobrutinib Arm and 18.43 months (95% CI: 17.45, 19.15) in the Ibrutinib Arm.
- The prespecified OS monitoring boundary for potential harm (HR = 1.42) was not crossed.

Patient-reported outcomes

Analysis of all PRO endpoints in this study were not controlled for type I error and any p-value reported is nominal.

The overall PRO completion rate at baseline was 85% and ranged between 63% and 82% during postbaseline assessment timepoints in the Pirtobrutinib Arm while it was 83% at baseline and ranged between 59% and 79% during postbaseline assessment timepoints in the Ibrutinib Arm among the ITT population. These rates were also similar among the Pretreated population.

Time-to-worsening in PROs: In both ITT and pretreated ITT populations, while there was no difference in TTW of PF within first 3 months of randomisation [ITT HR (95% CI): 1.23 (0.61, 2.48); pretreated ITT HR (95% CI): 1.11 (0.46, 2.68)] between arms, the risk of worsening of PF was lower after 3 months [ITT HR (95% CI): 0.47 (0.27, 0.82); pretreated ITT HR (95% CI): 0.52 (0.28, 0.97)] in the Pirtobrutinib Arm compared to the Ibrutinib Arm. In both ITT and pretreated ITT populations, there was no difference in TTW of CLL/SLL-related symptoms [ITT HR (95% CI): 0.875 (0.620, 1.234); pretreated ITT HR (95% CI): 0.762 (0.498, 1.167)], overall QoL [ITT HR (95% CI): 1.051 (0.699, 1.580); pretreated ITT HR (95% CI): 1.018 (0.625, 1.656)], or fatigue [ITT HR (95% CI): 0.851 (0.572, 1.268); pretreated ITT HR (95% CI): 0.748 (0.459, 1.218)] between the treatment arms.

Within-arm and Between-arm change from baseline in PROs: In both ITT and pretreated ITT populations, participants in both arms demonstrated within-arm reductions in CLL/SLL-related

symptoms and fatigue as well as improvements in PF and overall QoL, however, no clinically meaningful between-arm differences were observed in longitudinal analyses of these PROs.

Treatment-naïve population

Efficacy analyses in the treatment-naïve population are exploratory and are not controlled for the overall type I error rate. All p-values reported in this section are nominal. Results for this subpopulation are summarised in **Table 24**.

Table 24. Summary of Efficacy Results, Treatment naive population, study 20030

		TN population N=225	
		Pirtobrutinib N=112	Ibrutinib N=113
ORR IRC	ORR (PR or better), n (%)	104 (92.9)	97 (85.8)
	95% CI[a]	86.41, 96.87	78.03, 91.68
	p-value[b]	0.0886	
ORR INV	ORR (PR or better), n (%)	103 (92.0)	97 (85.8)
	95% CI[a]	85.29, 96.26	78.03, 91.68
	p-value[b]	0.1480	
DOR IRC	Number of Responders	104	97
	Number of Events, n (%)	8 (7.7)	14 (14.4)
	Median DOR (95% CI), months	24.67 (24.67, NE)	NR (NE, NE)
	HR (95% CI)[c]	0.504 (0.211, 1.205)	
	p-value[d]	0.1164	
	Median FU time (95% CI), months	18.43 (18.20, 18.46)	18.43 (18.30, 18.66)
PFS IRC	Number of events, n (%)	10 (8.9)	19 (16.8)
	Median PFS (95% CI), months	28.58 (28.58, NE)	NR (NE, NE)
	HR (95% CI)[c]	0.501 (0.233, 1.079)	
	p-value[d]	0.0718	
	Median FU time (95% CI), months	22.41 (22.31, 22.80)	22.37 (22.18, 22.54)
PFS INV	Number of events, n (%)	6 (5.4)	24 (21.2)
	Median PFS (95% CI), months	NR (NE, NE)	NR (NE, NE)
	HR (95% CI)[c]	0.239 (0.098, 0.586)	
	p-value[d]	0.0007	
	Median FU time (95% CI)	22.54 (22.31, 22.80)	22.44 (22.21, 22.87)
OS	Number of Deaths, n (%)	3 (2.7)	3 (2.7)
	Median OS (95% CI), months	NR (NE, NE)	NR (NE, NE)
	HR (95% CI)	0.987 (0.199, 4.890)	
	p-value	0.9870	
	Median FU time (95% CI), months	27.01 (26.61, 27.40)	26.64 (26.15, 27.10)
EFS IRC	Number of Events, n (%)	14 (12.5)	40 (35.4)
	Median EFS (95% CI), months	28.58 (28.58, NE)	NR (27.60, NE)
	HR (95% CI) [c]	0.301 (0.163, 0.554)	
	p-value [d]	<0.0001	
	Median FU time (95% CI), months	22.44 (22.31, 22.80)	22.37 (22.21, 22.54)
TTNT	Number of Events, n (%)	3 (2.7)	13 (11.5)
	Median TTNT (95% CI), months	NR (NE, NE)	NR (NE, NE)
	HR (95% CI)[c]	0.226 (0.064, 0.794)	
	p-value [d]	0.0111	
	Median FU time (95% CI), months	27.01 (26.61, 27.40)	26.64 (26.18, 27.10)

Summary of main studies

The following tables summarise the efficacy results from the two main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25. Summary of Efficacy for trial LOXO-BTK-20023

Title: A Phase 3 Open-Label, Randomised Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (BRUIN-CLL-313)			
Study identifier	LOXO-BTK-20023 (also Study 20023, J2N-OX-JZNP) EudraCT No: 2021-001234-20		
Design	A Phase 3 global, randomised, open-label active-controlled study in participants with untreated CLL/SLL with no evidence of 17p deletion. Eligible patients were randomly assigned in 1:1 ratio to Arm A (pirtobrutinib) and Arm B (BendaR), based on stratification factors of IGHV mutation status (mutated versus unmutated) and Rai stage (low/intermediate versus high). Participants randomly assigned to Arm B were allowed to cross over to receive pirtobrutinib monotherapy upon confirmation of PD by IRC and if they met the eligibility criteria for crossover.		
	Duration of main phase:		FPET: 06 December 2021 LPET: 13 April 2023 Data cutoff date: 11 July 2025
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	The primary hypothesis is that the treatment with pirtobrutinib monotherapy will provide superior PFS (assessed by IRC) over treatment with BendaR in untreated participants with CLL/SLL and no evidence of 17p deletion.		
Treatments groups	***Arm A***		Pirtobrutinib 200 mg Oral QD in 28-day continuous cycles Number of participants randomised: 141 Number of participants randomised and treated: 140
	Arm B		• Bendamustine IV 90 mg/m^2 on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6 • Rituximab IV 375 mg/m^2 on C1D1 and then 500 mg/m^2 given on Day 1 of each 28-day cycle, Cycles 2 to 6. Number of participants randomised: 141 Number of participants randomised and treated: 132
Endpoints and definitions	***Primary endpoint***	PFS by IRC	PFS is defined as the time from randomisation until the occurrence of documented PD by IRC, per iwCLL 2018 criteria, or death from any cause in the absence of documented PD.
	Key secondary endpoint	OS	OS is defined as the time measured from the date of randomisation to the date of death due to any cause.
	Supportive secondary endpoints	PFS by Investigator	PFS is defined as the time from randomisation until the occurrence of documented PD by Investigator, per iwCLL 2018 criteria, or death from any cause in the absence of documented PD.
		ORR by IRC and by Investigator	ORR is defined as the proportion of patients who achieve a BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anticancer therapy.

		DOR by IRC and by Investigator	DOR is defined as the time from the date of the first documented response of CR, CRi, nPR, or PR until the first date of the documentation of definitive PD by IRC or Investigator, per iwCLL 2018 criteria, or the date of death from any cause, whichever occurs first.
		TTNT by Investigator	TTNT is defined as time from the date of randomisation to the date of initiation of the subsequent anticancer therapy for CLL/SLL including therapy of pirtobrutinib for Arm B participants who crossover, or death due to any cause, whichever occurs first.
	Supportive secondary PRO endpoints	TTW of CLL/SLL-related symptoms	TTW of CLL/SLL-related symptoms as measured by 13 items of the EORTC IL87.
		TTW of physical functioning	TTW of physical functioning as measured by the physical function domain of the EORTC-QLQ-C30.
Database lock	Data cutoff date 11 July 2025 (PFS final analysis)		
Results and Analysis			
Analysis population and time point description	**ITT** All randomised participants, even if a participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analysed according to the treatment group they were assigned to regardless of what actual treatment they receive. Unless otherwise specified, all analyses using the ITT population include only data collected prior to crossover for Arm B patients who crossed over to Arm A, except for OS related analyses. Timepoint: Data cutoff as of 11 July 2025 (PFS final analysis)		
	Treatment group	**Arm A: Pirtobrutinib**	**Arm B: BendaR**
	Number of participants	141	141
	Number of participants who crossed over to Arm A	NA	18
Analysis description	**Primary Analysis**		
Descriptive statistics and estimate variability	Primary endpoint: ***PFS by IRC***		
	Number of participants	141	141
	Number of events, n (%)	13 (9.2)	48 (34.0)
	PFS Summary Median, months (95% CI)	 NR (NE, NE)	 33.54 (32.72, NE)
	24-month PFS rate, % (95% CI)	93.4 (87.6, 96.5)	70.7 (61.5, 78.1)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B[a]	
	Stratified Hazard Ratio (95% CI)	0.199 (0.107, 0.367)	
	Superiority p-value (2-sided)	<0.0001	
Analysis description	**Secondary Analyses**		
Descriptive statistics and estimate variability	Key secondary endpoint: ***OS***		
	Number of participants	141	141
	Number of events, n (%)	3 (2.1)	10 (7.1)
	OS Summary Median, months	NR	NR

	(95% CI)	(NE, NE)	(NE, NE)
	24-month OS rate, % (95% CI)	97.8 (93.3, 99.3)	93.0 (87.0, 96.3)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B[a]	
	Stratified Hazard Ratio (95% CI)	0.257 (0.070, 0.934)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***PFS by Investigator***		
	Number of participants	141	141
	Number of events, n (%)	11 (7.8)	42 (29.8)
	PFS Summary Median, months (95% CI)	NR (35.19, NE)	NR (33.38, NE)
	24-month PFS rate, % (95% CI)	92.7 (86.8, 96.0)	72.6 (63.7, 79.7)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B[a]	
	Stratified Hazard Ratio (95% CI)	0.186 (0.093, 0.371)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***ORR (PR or better) by IRC***		
	Number of participants	141	141
	ORR n (%) (95% CI)[b]	133 (94.3) (89.13, 97.52)	114 (80.9) (73.38, 86.99)
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***ORR (PR or better) by Investigator***		
	Number of participants	141	141
	ORR n (%) (95% CI)[b]	133 (94.3) (89.13, 97.52)	116 (82.3) (74.95, 88.18)
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***DOR by IRC***		
	Number of responders	133	114
	Number of events, n (%)	10 (7.5)	41 (36.0)
	DOR Summary Median, months (95% CI)	NR (NE, NE)	29.86 (28.32, NE)
	12-month DOR rate, % (95% CI)	97.7 (93.1, 99.3)	88.1 (80.4, 92.9)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B[a]	
	Stratified Hazard Ratio (95% CI)	0.178 (0.089, 0.356)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***DOR by Investigator***		
	Number of responders	133	116
	Number of events, n (%)	9 (6.8)	33 (28.4)
	DOR Summary Median, months (95% CI)	NR (31.21, NE)	NR (29.86, NE)
	12-month DOR rate, % (95% CI)	95.5 (90.2, 97.9)	89.0 (81.5, 93.6)

Effect estimate per comparison	Comparison groups	Arm A versus Arm B[a]
	Stratified Hazard Ratio (95% CI)	0.193 (0.089, 0.418)

Table 26. Summary of Efficacy for trial LOXO-BTK-20030

Title: A Phase 3 Open-Label, Randomised Study of Pirtobrutinib (LOXO-305) versus Ibrutinib in Patients with Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (BRUIN-CLL-314)			
Study identifier	LOXO-BTK-20030 (also Study 20030, J2N-OX-JZNU) EudraCT No: 2021-003206-41		
Design	A two-part, Phase 3, global, randomised, open-label active-controlled study. Part 1 compared pirtobrutinib as continuous monotherapy (Arm A) to ibrutinib continuous monotherapy (Arm B) in patients with CLL/SLL. Patients were treatment-naïve or previously treated, but they were BTK inhibitor-naïve. Part 1 enrolled approximately 30% untreated patients. Eligible patients were randomly assigned in a 1:1 ratio to Arm A or Arm B and were stratified based on del(17p) status (present versus not present), and number of prior lines of therapy (0 versus 1 versus ≥ 2). No crossover between treatment arms was permitted. Part 2 evaluates pirtobrutinib monotherapy in treatment-naïve patients with CLL/SLL with 17p deletions. No participants had been enrolled in Part 2 as of the time of the data cutoff date (10 June 2025), therefore Part 2 is not part of this submission.		
	Duration of main phase:		FPET: 18 Aug 2022 LPET: 24 June 2024 Data cutoff date: 10 June 2025
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	**Part 1**		
	The primary hypothesis is that ORR with treatment of pirtobrutinib (Arm A) will be non-inferior to the ORR with treatment of ibrutinib (Arm B) in CLL/SLL patients. The statistical hypothesis will be evaluated based on ORR ratio comparing Arm A versus Arm B. The primary hypothesis will be tested in 2 populations: the pretreated population and the ITT population.		
Treatments groups	**Part 1**		
	Arm A		Pirtobrutinib 200 mg Oral QD 28-day continuous cycles Number of participants randomised: 331 Number of participants randomised and treated: 330
	Arm B		Ibrutinib 420 mg Oral QD 28-day continuous cycles Number of participants randomised: 331 Number of participants randomised and treated: 325
Endpoints and definitions	**Part 1**		
	Primary endpoint	ORR by IRC in • pretreated population and • ITT population.	ORR by IRC is defined as the proportion of patients who achieve a BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anticancer therapy.
	Key secondary endpoint	PFS by IRC in • pretreated population and • ITT population	PFS is defined as the time from randomisation until the occurrence of documented PD by IRC, per iwCLL 2018 criteria, or death from any cause in the absence of documented PD, whichever occurs first.

	Supportive secondary endpoints	ORR by Investigator in • pretreated population and • ITT population	ORR by Investigator is defined as the proportion of patients who achieve a BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anticancer therapy.
		PFS by Investigator in • pretreated population and • ITT population	PFS is defined as the time from randomisation until the occurrence of documented PD by Investigator, per iwCLL 2018 criteria, or death from any cause in the absence of documented PD.
		DOR by IRC and Investigator in • pretreated population and • ITT population.	DOR is defined as the time from the date of the first documented response of CR, CRi, nPR, or PR to the earlier of the documentation of definitive PD, per iwCLL 2018 criteria, or death from any cause.
		OS in • pretreated population and • ITT population	OS is defined as the time from randomisation until death from any cause.
		EFS by IRC and Investigator in • pretreated population and • ITT population.	EFS is defined as the time from the date of randomisation to the first occurrence of • treatment discontinuation due to AE or toxicity • treatment-emergent atrial fibrillation or atrial flutter of any grade (assessed by Investigator) • PD (per iwCLL 2018 criteria), or • death.
Database lock	Data cutoff date 10 June 2025 (ORR final analysis)		

Results and Analysis

Analysis population and time point description

ITT
All randomised patients, even if a participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analysed according to the treatment group to which they were assigned to regardless of what actual treatment they receive.

Pretreated
Patients in the ITT population who were previously treated.

Timepoint: Data cutoff as of 10 June 2025 (ORR final analysis)

Analysis population	**ITT Population**		**Pretreated Population**	
Number of participants	662		437	
Treatment groups	**Arm A: Pirtobrutinib**	**Arm B: Ibrutinib**	**Arm A: Pirtobrutinib**	**Arm B: Ibrutinib**
Number of participants	331	331	219	218

Analysis description

Primary Analysis

Descriptive statistics and

Primary endpoint:
ORR by IRC (PR or better)

	ITT Population		**Pretreated Population**	

estimate variability	Number of participants	331	331	219	218
	ORR n (%) (95% CI)[a]	288 (87.0) (82.90, 90.44)	260 (78.5) (73.73, 82.85)	184 (84.0) (78.48, 88.61)	163 (74.8) (68.46, 80.39)
Effect estimate per comparison	***ORR Ratio Stratified Analysis*** ORR ratio (95% CI)	1.1080 (1.034, 1.187)	-	1.1233 (1.020, 1.237)	-
	Non-inferiority p-value (2-sided)[b]	<0.0001		<0.0001	
	Superiority nominal p-value (2-sided)[c]	0.0035		0.0175	
Analysis description	**Secondary Analyses**				
Descriptive statistics and estimate variability	Key secondary endpoint: ***PFS by IRC***	**ITT Population**		**Pretreated Population**	
	Number of participants	331	331	219	218
	Number of events, n (%)	58 (17.5)	69 (20.8)	48 (21.9)	50 (22.9)
	PFS Summary Median, months (95% CI)	28.58 (28.06, NE)	NR (NE, NE)	28.06 (28.06, NE)	NR (22.47, NE)
	18-month PFS rate, % (95% CI)	84.7 (80.1, 88.4)	80.2 (75.0, 84.4)	79.4 (72.8, 84.6)	76.5 (69.3, 82.2)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B		Arm A versus Arm B	
	Stratified Hazard Ratio (95% CI)	0.755 (0.531, 1.075)		0.845 (0.566, 1.262)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***ORR (PR or better) by Investigator***	**ITT Population**		**Pretreated Population**	
	Number of participants	331	331	219	218
	ORR n (%) (95% CI)[a]	295 (89.1) (85.26, 92.27)	261 (78.9) (74.05, 83.13)	192 (87.7) (82.57, 91.72)	164 (75.2) (68.95, 80.81)
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***PFS by Investigator***	**ITT Population**		**Pretreated Population**	
	Number of participants	331	331	219	218
	PFS Summary Median, months (95%, CI)	NR (NE, NE)	NR (27.70, NE)	NR (NE, NE)	NR (22.47, NE)
	18-month PFS rate, % (95% CI)	86.9 (82.4, 90.3)	82.3 (77.3, 86.3)	81.7 (75.1, 86.7)	79.2 (72.3, 84.6)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B		Arm A versus Arm B	
	Stratified Hazard Ratio (95% CI)	0.569 (0.388, 0.834)		0.729 (0.471, 1.128)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***DOR by IRC***	**ITT Population**		**Pretreated Population**	
	Number of responders	288	260	184	163
	DOR Summary Median, months (95% CI)	24.67 (24.38, NE)	NR (NE, NE)	24.38 (24.38, NE)	NR (18.79, NE)
	12-month DOR rate, % (95% CI)	88.1 (83.3, 91.6)	85.0 (79.5, 89.1)	83.9 (76.5, 89.2)	82.8 (75.1, 88.4)

Effect estimate per comparison	Comparison groups	Arm A versus Arm B		Arm A versus Arm B	
	Stratified Hazard Ratio (95% CI)	0.717 (0.458, 1.121)		0.805 (0.476, 1.362)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***DOR by Investigator***	**ITT Population**		**Pretreated Population**	
	Number of responders	295	261	192	164
	DOR Summary				
	Median, months (95% CI)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)	NR (18.79, NE)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B		Arm A versus Arm B	
	Stratified Hazard Ratio (95% CI)	0.565 (0.346, 0.922)		0.804 (0.443, 1.459)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***OS***	**ITT Population**		**Pretreated Population**	
	Number of participants	331	331	219	218
	Number of events, n (%)	25 (7.6)	24 (7.3)	22 (10.0)	21 (9.6)
	OS Summary				
	Median, months (95% CI)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B		Arm A versus Arm B	
	Stratified Hazard Ratio (95% CI)	0.961 (0.548, 1.686)		0.964 (0.528, 1.757)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***EFS by IRC***	**ITT Population**		**Pretreated Population**	
	Number of participants	331	331	219	218
	Number of events, n (%)	66 (19.9)	109 (32.9)	52 (23.7)	69 (31.7)
	EFS Summary				
	Median, months (95% CI)	28.58 (28.06, NE)	NR (27.60, NE)	28.06 (23.03, NE)	NR (22.18, NE)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B		Arm A versus Arm B	
	Stratified Hazard Ratio (95% CI)	0.510 (0.374, 0.695)		0.632 (0.439, 0.910)	
Descriptive statistics and estimate variability	Supportive secondary endpoint: ***EFS by Investigator***	**ITT Population**		**Pretreated Population**	
	Number of participants	331	331	219	218
	Number of events, n (%)	55 (16.6)	104 (31.4)	42 (19.2)	62 (28.4)
	EFS Summary				
	Median, months (95% CI)	NR (NE, NE)	NR (27.43, NE)	NR (NE, NE)	NR (NE, NE)
Effect estimate per comparison	Comparison groups	Arm A versus Arm B		Arm A versus Arm B	
	Stratified Hazard Ratio (95% CI)	0.456 (0.329, 0.633)		0.580 (0.392, 0.859)	

2.4.3. Discussion on clinical efficacy

This application to extend the marketing authorisation of pirtobrutinib for the treatment of adult patients with CLL is based on efficacy data from two phase 3 clinical trials (20023 and 20030).

Study 20023 (BRUIN-CLL-313)

Design and conduct

Study 20023 was a phase 3 global, randomised, open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to time-limited bendamustine plus rituximab (BendaR) (Arm B) in participants with TN CLL/SLL and no evidence of del(17p).

Eligible participants were randomly assigned 1:1 to Arm A:Arm B, based on the stratification factors of IGHV mutation status (mutated vs. unmutated) and Rai stage (low/intermediate vs. high). Participants randomly assigned to the BendaR arm were allowed to cross over to pirtobrutinib monotherapy treatment upon confirmation of PD by IRC, if also meeting crossover eligibility criteria. Although IGHV status and Rai stage are relevant prognostic factors, stratification does not account for TP53 mutation status. However, TP53 mutation in the absence of 17p deletion is rare, occurring in approximately 5% of TN CLL patients (Malcikova et al. 2018) and thus is unlikely to impact significantly the reported results.

Considering the differences between the study treatments used as comparators, the open-label design is considered acceptable. However, the lack of blinding represents a limitation, particularly for the assessment of quality of life. While BendaR was still included as a treatment option in first-line CLL at the study start date (first patient enrolled in December 2021), targeted therapies such as ibrutinib had already been authorized in the first-line CLL setting since 2016 and were widely used in clinical practice. Therefore, the absence of an optimal comparator reflecting current practices and SoC in first-line CLL is a limitation of the study but the totality of evidence provided (see Efficacy data and additional analyses) supports a clinically meaningful benefit.

The inclusion criteria in the global protocol are broadly aligned with international standards for first-line CLL clinical trials, notably through the use of iwCLL 2018 criteria for diagnosis and treatment initiation. However, restrictions related to performance status and organ function result in a selected study population, which may limit generalisability to frailer patients commonly encountered in routine clinical practice. The exclusion criteria are generally appropriate to ensure a homogeneous first-line CLL population and to minimise confounding factors.

Although the proposed indication is restricted to CLL, the study was conducted in a mixed CLL/SLL population. While CLL and SLL are generally considered manifestations of the same disease entity, this may limit the direct applicability of the results to the target population. Given that PFS is the primary endpoint, the inclusion of SLL patients is not expected to materially affect endpoint applicability.

Study 20023 was adequately powered for an event-driven primary analysis, targeting 53 events to reach approximately 90% power at a two-sided 5% alpha-level at a hazard ratio of 0.41. While the primary analysis achieved statistical significance, it is noteworthy that the sample size strategy relies on an optimistic effect size and a limited number of events. Consequently, although the study is adequate to demonstrate a potential treatment effect, the interpretation of the benefit over extended follow-up remains uncertain and should be considered when contextualising the results.

The primary endpoint is PFS assessed by an independent review committee, which is methodologically robust but consistency with investigator-assessed PFS is essential to support the relevance of the observed treatment effect. The primary estimand for IRC-assessed PFS is considered appropriate to address the primary objective.

Secondary endpoints such as investigator-assessed PFS, OS and TTNT are considered clinically meaningful, although OS data are immature. In contrast, ORR and DOR provide supportive information but are considered exploratory in this context and of limited clinical relevance for differentiating

treatment benefit in first-line CLL. Patient-reported outcomes and healthcare resource utilisation outcomes are exploratory and should be interpreted with caution given the open-label design and limited follow-up. The secondary estimand for overall survival applies a treatment policy strategy for intercurrent events, including treatment discontinuation and subsequent anticancer therapy, and reflects clinical practice.

A sequential gatekeeping strategy is implemented to control the family-wise type I error at a two-sided 5% level, with OS formally tested only if the primary IRC-assessed PFS endpoint is statistically significant. This approach is methodologically appropriate.

The hierarchical testing strategy further specifies an interim analysis of OS conducted at the time of the final PFS analysis, using a very conservative two-sided alpha level (0.000001), with the remaining alpha preserved for the final OS analysis at study completion. This approach appropriately controls the overall type I error. However, given the extremely small alpha allocated to the interim OS analysis and the expected impact of subsequent therapies and crossover, the interim OS analysis was unlikely to be informative, and OS is expected to remain largely exploratory until the final analysis.

The number of protocol deviations was low and comparable between treatment arms.

A protocol amendment was implemented in 2023 to introduce exploratory objective for HRQoL analyses, and provide clarifications related to sample acquisition and safety reporting. These changes are considered non-substantial in the context of this assessment.

Efficacy data and additional analyses

A total of 282 participants were randomised, 141 in each arm. 3.5% of randomised participants did not initiate the assigned treatment, with a lower rate of non-treated participants in the pirtobrutinib arm (0.7% vs 6.4% in the BendaR arm), primarily due to withdrawal of consent. In addition, treatment discontinuation patterns differed between arms, with a higher proportion of participants in the BendaR arm discontinuing treatment prior to completion of the planned regimen (11.3% in the pirtobrutinib arm vs 21.3% in the BendaR arm). Furthermore, a total of 18 (12,8%) participants crossed over from the BendaR arm to pirtobrutinib arm after IRC-assessed PD. Those patients are included in the BendaR arm for efficacy analyses. At data cut-off, all 18 patients were still receiving pirtobrutinib. Whilst the differential early attrition rate and the crossover could affect the comparability of the treatment arms and the interpretation of the ITT analyses this seems unlikely to have given the treatment effect difference between arms.

Baseline demographic and clinical characteristics, including age, performance status and Rai stage, were comparable between arms. The study population predominantly consisted of patients with ECOG PS 0-1 and a broad distribution of Rai stages, consistent with a first-line CLL population.

Baseline disease characteristics of the ITT population were generally well-balanced between treatment arms with respect to key prognostic factors (Rai stage, performance status, IGHV mutation status and PT53 mutation status). Of note, complex karyotype (defined as ≥3 abnormalities), a recognised adverse prognostic factor in CLL, was numerically more frequent in the pirtobrutinib arm (11.3% vs 7.8%), which reinforces the robustness of the observed PFS benefit.

The primary endpoint of the study was PFS assessed by an independent review committee. The results showed a marked and statistically robust PFS benefit in favour of pirtobrutinib, with an 80.1% decrease in the risk of progression or death and a clear separation of the PFS curves over time. This effect is supported by a concordance rate of 89.4% between IRC-assessed and investigator-assessed progression events, as well as by consistent hazard ratio estimates across assessment methods (0.199

[95% CI 0.107, 0.367] for IRC-assessed PFS vs 0.186 [95% CI 0.093, 0.371] for investigator-assessed PFS), which supports the clinical interpretability of the findings.

However, at the time of data cut-off, follow-up remains limited for a first-line CLL setting, and the number of events is still low (13 in the pirtobrutinib arm, 48 in the BendaR arm), resulting in 90.8% of censored observations in the pirtobrutinib arm.

PFS results demonstrate clear antitumour activity for pirtobrutinib, but some uncertainties remain regarding the durability and generalisability of the benefit in the intended first-line indication.

Subgroup analyses of IRC-assessed PFS showed treatment effects consistently favouring pirtobrutinib across all pre-specified subgroups. These analyses were descriptive in nature. Nevertheless, no subgroup showed a signal of reduced or reversed treatment effect, including clinically relevant subgroups in the first-line CLL setting. Overall, the subgroup analyses support the consistency of the observed PFS benefit.

OS data remain immature, with median OS not reached in either treatment arm and a very limited number of events observed (3 vs 10 events). Although a stratified hazard ratio numerically favours pirtobrutinib, the wide confidence interval and high survival rates in both arms preclude any firm conclusion regarding an OS benefit at this stage. Moreover, interpretation of OS is further complicated by the protocol-defined cross-over from arm B to arm A following disease progression. Given the immaturity of the data, the CHMP recommended that the MAH submit extended follow-up data for PFS and OS from study 20023.

Similarly, median time to next treatment was not reached for either the pirtobrutinib arm or the BendaR arm. ORR and DOR were numerically in favour of the pirtobrutinib arm (ORR: 94.3% in the pirtobrutinib arm vs 80.9% in the BendaR arm; 12-month DOR rates: 97.7% [93.1, 99.3] in the pirto arm vs 88.1 [80.4, 92.9] in the BendaR arm). However, these endpoints are considered of limited clinical relevance for differentiating long-term treatment benefit.

Patient-reported outcome completion rates were incomplete at baseline and declined substantially over time in both treatment arms, with consistently lower completion rates observed in the BendaR arm. While pirtobrutinib reduced the risk of worsening of CLL/SLL-related symptoms (HR: 0.501), fatigue (HR: 0.560), physical functioning (HR: 0.578) and QoL (HR:0.561), these results should be considered exploratory.

Study 20030 (BRUIN-CLL-314)

Design and conduct

Study 20030 was a phase 3, randomised, open-label study comparing pirtobrutinib as continuous monotherapy to ibrutinib as continuous monotherapy in participants with CLL/SLL.

Participants in Arm A and Arm B were treatment-naïve or previously treated, but must have been BTKi-naïve. The study was to enrol approximately 30% untreated participants. Eligible participants were randomly assigned 1:1 to Arm A:Arm B and were stratified based on del(17p) status (present versus not present) and number of prior lines of therapy (0 versus 1 versus ≥2).

No crossover between treatment arms was permitted.

Given the differences between the study treatments, an open-label design is considered acceptable.

Study 20030 included a heterogeneous population comprising both treatment-naïve and previously treated but BTKi-naïve patients, which is considered appropriate in the context of a CLL indication across all lines of therapy.

Overall, the inclusion criteria are aligned with international standards, relying on iwCLL 2018 criteria for diagnosis and treatment initiation, thereby ensuring enrolment of patients with active disease requiring therapy. Eligibility restrictions related to organ function and performance status (ECOG 0–2) result in a selected study population, which may limit representativeness of frailer patients commonly seen in routine practice. Exclusion criteria are consistent with those applied in study 20023 and are generally standard for clinical trials in CLL. In particular, exclusion of patients with prior BTK inhibitor exposure, Richter's transformation or central nervous system involvement is considered appropriate.

The number of protocol deviations was low and comparable between treatment arms.

Protocol amendment 6 (Nov 2024) introduced substantial changes to the study objectives and analysis strategy, including separate efficacy analyses in the pre-treated population, and modifications to the schedule of interim and final analyses. These changes were implemented during the conduct of the study and thus it is not possible to exclude that they were data driven. However, results were also reported for the overall population which are not impacted by this amendment.

The study uses ORR, assessed by an IRC according to iwCLL 2018 criteria, as the primary endpoint. While independent central review and standardised response criteria reduce possible bias, the choice of ORR as the primary endpoint represents a limitation in the context of CLL, where response rates are generally high and of limited clinical relevance. This is mitigated by the choice of the comparator in the trial, which is an established treatment option in this condition and demonstration of non-inferiority even in ORR should be expected to translate in a meaningful clinical benefit. The primary and secondary estimands are conservative and avoid bias introduced by post-randomisation therapies. However, the chosen strategy for ORR does not capture the durability of response beyond treatment discontinuation. The ORR estimand therefore primarily reflects short-term anti-tumour activity. The estimand for PFS is considered adequate but the use of hypothetical strategy may limit the interpretability of long-term PFS data.

OS and TTNT as secondary endpoints are considered meaningful, however OS data are immature at the time of the primary analysis for ORR.

The study is adequately powered to demonstrate non-inferiority of pirtobrutinib versus ibrutinib for ORR. For time-to-event secondary endpoints, the planned number of events is quite ambitious but acceptable from a statistical point of view.

The choice of ibrutinib as a comparator is considered clinically relevant as it represents an established therapy in CLL and a standard of care for BTKi-naïve patients.

Stratification by del(17p) status and number of prior lines of therapy is relevant to account for differences in prognosis and treatment history. Although IGHV and TP53 mutation status were not used as stratification factors, stratification by del(17p) status captures a major component of biological risk, and the overall stratification approach is considered acceptable.

The hypothesis testing strategy prioritises demonstration of non-inferiority on ORR in both the pre-treated and ITT populations. Testing in both populations increases the reliance on consistency across populations with different prior treatment histories. As PFS superiority is evaluated only as a secondary objective, any finding establishing superiority over the comparator remain supportive.

Overall, the hypothesis framework is methodologically acceptable.

Efficacy data and additional analyses

A total of 662 participants (437 pre-treated, 225 treatment-naïve) were randomised, 331 in each arm (219 and 218 pre-treated in each arm, respectively).

In the ITT population, treatment initiation rates were high and comparable between pirtobrutinib and ibrutinib arms (99.7% vs 98.2%, respectively). Median time on study was similar between the pirtobrutinib and ibrutinib arms (21.85 vs 20.93 months, respectively), indicating balanced follow-up across treatment groups. Treatment discontinuation due to disease progression occurred more frequently in the ibrutinib arm (10.9% in the ibrutinib arm vs 4.5% in the pirtobrutinib arm).

Overall, no major imbalance in participant flow at treatment initiation or during follow-up was identified that would be expected to affect the interpretation of efficacy results.

Overall, the demographic and baseline disease characteristics of the study population are consistent with a real-world CLL population requiring treatment. The proportion of patients with advanced disease was relatively high, with approximately 40% of participants presenting with Rai stage III–IV, suggesting an enrichment for more advanced disease. The study included both treatment-naïve and previously treated patients, with around 30% of participants being treatment-naïve, nearly 50% having received one prior line of therapy, and approximately 20% having received two or more prior lines, with a balanced distribution between treatment arms. Prior systemic therapies were balanced between arms, with more than 90% of pretreated patients having received prior chemotherapy, approximately 75% having received prior anti-CD20 antibody and approximately 10% having received prior venetoclax (9.6% in the pirtobrutinib arm and 7.8% in the ibrutinib arm).

Baseline imbalances between treatment arms were limited. Notably, complex karyotype, a recognised adverse prognostic factor in CLL, was more frequent in the pirtobrutinib arm and thus any impact from this would be unlikely to favour pirtobrutinib.

The primary endpoint analysis demonstrated a statistically significant difference in ORR in favour of pirtobrutinib compared with ibrutinib, both in the ITT population (87.0% [95% CI 82.90, 90.44] in the pirtobrutinib arm and 78.5% [95% CI 73.73, 82.85] in the ibrutinib arm) and in previously treated patients (84.0% [78.48, 88.61] in the pirtobrutinib arm and 74.8% [68.46, 80.39] in the ibrutinib arm). In treatment-naïve patients, efficacy results consistently numerically favoured pirtobrutinib (92.9% [86.41, 96.87] for pirtobrutinib and 85.8% [78.03, 91.68] for ibrutinib) but the difference did not reach statistical significance. Response rates were high in both treatment arms, and the observed difference was mainly driven by partial responses, while complete remission rates remained low and comparable between arms (15 patients achieved CR in the pirtobrutinib arm vs 8 patients in the ibrutinib arm). ORR results assessed by IRC according to iwCLL 2018 criteria were consistent with investigator-assessed responses.

Subgroup analyses of ORR did not show a consistent effect across all categories. Several subgroup estimates were close to unity with wide confidence intervals, and some subgroups (Asian and Black or African-American race and Asian region) numerically favoured ibrutinib. Given the high overall response rates, the exploratory nature of subgroup analyses, and the limited numbers of patients in the concerned subgroups, these findings are considered imprecise and do not allow any conclusion regarding differential treatment effects.

IRC-assessed PFS showed a numerical trend in favour of pirtobrutinib compared with ibrutinib across populations. In the treatment-naïve subgroup, a more pronounced reduction in the risk of progression was observed, with a hazard ratio close to 0.5, suggesting potentially meaningful clinical activity in this setting. While statistical significance was not reached and confidence intervals were wide, these findings are consistent with an emerging treatment effect. Interpretation of PFS results is influenced by

the limited number of events and the immaturity of the data at the time of analysis, which is expected in the context of a relatively short follow-up in CLL. Investigator-assessed PFS showed a more pronounced treatment effect across populations, providing additional supportive evidence of disease control with pirtobrutinib. Overall, the available PFS data suggest a favourable trend in efficacy, although longer follow-up will be required to confirm the durability of the observed benefit.

Overall, the primary endpoint was met but the evidence of pirtobrutinib effect in time to event endpoints from this study is limited. However, an effect of pirtobrutinib in PFS on treatment naïve patients has already been shown in study 20023. The non-inferiority to ibrutinib in terms of ORR is reassuring and expected to translate in a clinical benefit of pirtobrutinib treatment in terms of PFS and OS. The CHMP recommended that the MAH submit extended follow-up data for PFS and OS from study 20030 when available in order to confirm this.

No clinically meaningful between-arm differences were observed in longitudinal analyses of symptoms, fatigue or global quality of life. For physical functioning, a lower risk of worsening after 3 months was reported in the pirtobrutinib arm (HR=0.47 [0.27, 0.82]). Given the open-label design and the exploratory nature of these analyses, the interpretability of the PRO results is limited.

Overall efficacy assessment

Study 20023 demonstrated a clear and statistically robust improvement in IRC-assessed PFS with a marked reduction in the risk of progression or death and a consistent effect when compared with investigator-assessed PFS. The direction and magnitude of benefit are supported by PFS rates over time and by largely comparable baseline characteristics. However, the interpretation of this data is constrained by data immaturity, reflected by a low number of events and a high proportion of censored observations which limits assessment of effect durability.

Study 20030 is less compelling for demonstration of durable clinical benefit, as the primary endpoint is ORR, an endpoint of limited clinical relevance in CLL. Although the primary endpoint was met the observed differences are mainly driven by PR with low CR rates. The key secondary endpoint IRC-assessed PFS does not yet provide conclusive evidence of benefit over ibrutinib, showing only a numerical trend with confidence intervals crossing unity and discordance between IRC and investigator-assessed PFS. A potentially favourable signal in treatment-naïve patients was observed but is based on small numbers of events and is not considered robust at this stage.

As data from studies 20023 and 20030 are immature, especially with regards to PFS and OS, the CHMP recommended that the MAH submits extended follow-up data from these studies when available.

2.4.4. Conclusions on the clinical efficacy

Overall, the submitted package demonstrates antitumour activity of pirtobrutinib in CLL. While some uncertainties remain regarding the long-term durability of effect, the totality of the data is considered sufficient to support the efficacy of pirtobrutinib for the treatment of adult patients with CLL.

2.5. Clinical safety

Introduction

Pirtobrutinib as monotherapy is indicated since October 2023 in Europe for the treatment of adult patients with relapsed or refractory MCL who have been previously treated with a BTK inhibitor and later for the treatment of relapsed or refractory CLL in patients who have been previously treated with

a BTK inhibitor. The most common adverse reactions for pirtobrutinib listed in the EU SmPC are neutropenia, thrombocytopenia, anaemia, haemorrhage, bruising, contusion, diarrhoea, abdominal pain, nausea, rash, arthralgia and fatigue.

Patient exposure

In Studies 20023 and 20030, all safety analyses were performed using the safety population and summarized by treatment arms:

Participants treated in Study 20023

- **Safety Population (N=272):** 140 participants with TN CLL who received pirtobrutinib 200 mg monotherapy and 132 participants who received BendaR.

Participants treated in Study 20030

- **Safety Population (N=655):** 330 participants with either pretreated (BTKi-naïve) or TN CLL who received pirtobrutinib 200 mg monotherapy and 325 participants who received ibrutinib
- **Pretreated Safety Population (N=434):** 218 participants with pretreated CLL, but not previously treated with a BTKi, who received pirtobrutinib 200 mg monotherapy, and 216 participants who received ibrutinib; and
- **Treatment-Naïve Safety Population (N=221):** 112 participants with TN CLL who received pirtobrutinib 200 mg monotherapy and 109 participants who received ibrutinib.

Safety data from an integrated safety set is also reported including 1153 participants with hematologic malignancies, including CLL, and other NHL from studies including pirtobrutinib monotherapy: J2N-OX-JZNA (Study 18001, OMTSAS-200 population in MCL), J2N-OX-JZNN (Study 20020 in CLL patients), J2N-OX-JZNP (Study 20023 in CLL Patients), and J2N-OX-JZNU (Study 20030 in CLL patients) who received pirtobrutinib 200 mg monotherapy. Safety data from the Integrated Safety Set were used for the identification of ADRs, as it represents the most comprehensive safety dataset for pirtobrutinib available. Notably, Study 18001 (OMTSAS-200) is the only study to include participants with NHL in addition to those with CLL. These NHL participants were retained in the overall safety population, as the safety profile of pirtobrutinib is not anticipated to be influenced by malignancy type.

Table 27 provides a summary of exposure, dose intensities, and dose adjustment in the Studies 20023 and 20030 safety populations. Dose adjustments include dose hold and dose reduction and infusion interruption.

Table 28 provides a summary of concomitant therapy information for participants enrolled in the safety populations in Studies 20023 and 20030

Table 27. Summary of Exposure, Dose Intensities, and Dose Adjustments-Study 20023 and Study 20030 Safety Populations

Category	Study 20023			Study 20030					
	Arm A Pirtobrutinib N = 140	Arm B BendaR N = 132		Arm A Pirtobrutinib N = 330	Arm B Ibrutinib N = 325	Arm A Pirtobrutinib N = 218	Arm B Ibrutinib N = 216	Arm A Pirtobrutinib N = 112	Arm B Ibrutinib N = 109
	Pirtobrutinib	Bendamustine	Rituximab	Safety Population		Pretreated Safety Population[a]		Treatment-Naïve Safety Population[a]	
Duration of therapy (months)									
Median (min–max)	32.30 (1.0 – 40.6)	5.59 (0.2 – 11.3)		20.53 (0.16 - 33.77)	19.25 (0.03 - 32.03)	17.86 (0.16 – 32.43)	16.33 (0.03 – 31.70)	26.73 (0.26 – 33.77)	26.19 (0.66 – 32.03)
Relative dose intensity[b]									
Median (Q1 - Q3)	99.4 (98.1, 100.0)	100 (92.7, 100.0)	100 (100.0, 100.0)	98.93 (96.1, 100.0)	97.94 (92.9, 99.8)	98.85 (95.8, 100.0)	98.29 (92.7, 99.8)	99.09 (96.52, 99.88)	97.83 (93.36, 99.63)
>100%	0	0	1 (0.8)	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)	0	0
90% to ≤100%	134 (95.7)	110 (83.3)	111 (84.1)	286 (86.7)	260 (80.0)	184 (84.4)	176 (81.5)	102 (91.1)	84 (77.1)
75% to ≤90%	3 (2.1)	17 (12.9)	11 (8.3)	24 (7.3)	34 (10.5)	19 (8.7)	24 (11.1)	5 (4.5)	10 (9.2
50% to ≤75%	1 (0.7)	4 (3.0)	6 (4.5)	16 (4.8)	28 (8.6)	12 (5.5)	15 (6.9)	4 (3.6)	13 (11.9)
≤50%	2 (1.4)	1 (0.8)	3 (2.3)	3 (0.9)	2 (0.6)	2 (0.9)	0	1 (0.9)	2 (1.8)
Dose hold/delay[c], n (%)									
	97 (69.3)	21 (15.9)		247 (74.8)	257 (79.1)	157 (72.0)	169 (78.2)	90 (80.4)	88 (80.7)
Primary reason for dose hold/delay, n (%)									
Participant error	62 (44.3)	0		117 (35.5)	113 (34.8)	71 (32.6)	77 (35.6)	46 (41.1)	36 (33.0)
Procedure	33 (23.6)	0		61 (18.5)	57 (17.5)	29 (13.3)	35 (16.2)	32 (28.6)	22 (20.2)
AE	49 (35.0)	20 (15.2)		162 (49.1)	168 (51.7)	107 (49.1)	101 (46.8)	55 (49.1)	67 (61.5)
Other	15 (10.7)	1 (0.8)		41 (12.4)	67 (20.6)	30 (13.8)	49 (22.7)	11 (9.8)	18 (16.5)
Dose reductions, n (%)									
	10 (7.1)	45 (34.1)		35 (10.6)	81 (24.9)	26 (11.9)	49 (22.7)	9 (8.0)	32 (29.4)
Primary reason for dose reductions, n (%)									
Participant error	4 (2.9)	0		8 (2.4)	23 (7.1)	6 (2.8)	16 (7.4)	2 (1.8)	7 (6.4)
Procedure	0	0		1 (0.3)	1 (0.3)	0	1 (0.5)	1 (0.9)	0

Category	Study 20023			Study 20030					
	Arm A Pirtobrutinib N = 140	Arm B BendaR N = 132		Arm A Pirtobrutinib N = 330	Arm B Ibrutinib N = 325	Arm A Pirtobrutinib N = 218	Arm B Ibrutinib N = 216	Arm A Pirtobrutinib N = 112	Arm B Ibrutinib N = 109
	Pirtobrutinib	Bendamustine	Rituximab	Safety Population		Pretreated Safety Population[a]		Treatment-Naïve Safety Population[a]	
AE	5 (3.6)	20 (15.2)		26 (7.9)	59 (18.2)	20 (9.2)	32 (14.8)	6 (5.4)	27 (24.8)
Other	2 (1.4)	1 (0.8)		2 (0.6)	5 (1.5)	2 (0.9)	5 (2.3)	0	0
Infusion interruption, n (%)									
	NA	43 (32.6)		NA	NA	NA	NA	NA	NA
Primary reason for infusion interruption, n (%)									
AE	NA	38 (28.8)		NA	NA	NA	NA	NA	NA
Dose administration error	NA	4 (3.0)		NA	NA	NA	NA	NA	NA
Equipment failure	NA	0		NA	NA	NA	NA	NA	NA
Other	NA	7 (5.3)		NA	NA	NA	NA	NA	NA

Abbreviations: AE = adverse event; BendaR = bendamustine plus rituximab; n = number of participants in the specific category; N = number of participants; NA = not applicable; Q1/3 = Quartile 1/3.

[a] The Pretreated Safety Population and Treatment-Naïve Safety Population are subsets of the Safety Population

[b] Relative dose intensity (%) = (actual cumulative dose intensity / planned dose intensity) × 100 for pirtobrutinib and ibrutinib; relative dose intensity (%) = (cumulative dose received / total dose prescribed) ×100 for bendamustine and rituximab.

[c] Dose hold is applicable to pirtobrutinib and ibrutinib in the respective arms, dose delay is applicable to bendamustine in the BendaR Arm.

Note: Participants may be counted in more than 1 category. The reason of 'participant error' is applicable to the Pirtobrutinib Arm and Ibrutinib Arm.

Data cutoff: 11 July 2025 (Study 20023), 10 June 2025 (Study 20030)

Table 28. Categories of Selected Concomitant Therapy Study 20023 and Study 20030 Safety Populations

	Study 20023		Study 20030	
	Arm A Pirtobrutinib N = 140 n (%)	**Arm B BendaR N = 132 n (%)**	**Arm A Pirtobrutinib N = 330 n (%)**	**Arm B Ibrutinib N = 325 n (%)**
	Safety Population		**Safety Population**	
Number of participants that received at least 1 form of concomitant therapy[a]	**134 (95.7)**	**131 (99.2)**	**220 (66.7)**	**217 (66.8)**
Antibacterials for systemic use	75 (53.6)	92 (69.7)	220 (66.7)	217 (66.8)
Antivirals for systemic use	48 (34.3)	78 (59.1)	119 (36.1)	111 (34.2)
Antithrombotic agents	38(27.1)	33 (25.0)	91 (27.6)	113 (34.8)
Systemic corticosteroids	17 (12.1)	108 (81.8)	60 (18.2)	62 (19.1)
Analgesics	52 (37.1)	101 (76.5)	148 (44.8)	149 (45.8)
Antihistamines for systemic use	24 (17.1)	110 (83.3)	73 (22.1)	62 (19.1)
Anti-inflammatory and antirheumatic products	42 (30.0)	11 (8.3)	71 (21.5)	78 (24.0)
Cough and cold preparation	25 (17.9)	7 (5.3)	66 (20.0)	69 (21.2)
Blood substitutes and perfusion solutions	15 (10.7)	33 (25.0)	33 (10.0)	26 (8.0)
Immunostimulants	13 (9.3)	75 (56.8)	56 (16.4)	45 (13.8)
Antiemetics and antinauseants Immunostimulants	7 (5.0)	94 (71.2)	22 (6.7)	15 (4.6)

Abbreviations: ATC = anatomical, therapeutic, chemical; BendaR = bendamustine plus rituximab; n = number of participants in the specified category; N = number of participants.

[a] A participant is counted only once for each ATC class and standardized medication name.

Data cutoff: 11 July 2025 (Study 20023), 10 June 2025 (Study 20030)

Adverse events

Study 20023

Table 29. Overview of Treatment-Emergent Adverse Events (Pirtobrutinib Arm versus BendaR Arm) Study 20023 Safety Population

Number of Subjects*a	Arm A: Pirtobrutinib (N=140) n (%)	Arm B: BendaR (N=132) n (%)	Total (N=272) n (%)
Subjects with >=1 TEAE	131 (93.6)	117 (88.6)	248 (91.2)
Maximum CTCAE Grade 3/4	55 (39.3)	85 (64.4)	140 (51.5)
Maximum CTCAE Grade 5	1 (0.7)	4 (3.0)	5 (1.8)
Maximum CTCAE Grade 3/4/5	56 (40.0)	89 (67.4)	145 (53.3)
Subjects with >=1 TEAE Related to Study Treatment*b	83 (59.3)	113 (85.6)	196 (72.1)
Maximum CTCAE Grade 3/4	31 (22.1)	79 (59.8)	110 (40.4)
Maximum CTCAE Grade 5	0	1 (0.8)	1 (0.4)
Maximum CTCAE Grade 3/4/5	31 (22.1)	80 (60.6)	111 (40.8)
Subjects with >=1 Treatment-Emergent SAE	39 (27.9)	37 (28.0)	76 (27.9)
Related to Any Study Treatment*b	15 (10.7)	31 (23.5)	46 (16.9)
Subjects who discontinued study treatment due to TEAE*c	6 (4.3)	20 (15.2)	26 (9.6)
Related to Any Study Treatment*b	3 (2.1)	17 (12.9)	20 (7.4)
Subjects who discontinued study treatment due to Treatment-Emergent SAE*c	3 (2.1)	10 (7.6)	13 (4.8)
Related to Any Study Treatment*b	1 (0.7)	8 (6.1)	9 (3.3)
Subjects who died due to TEAE on study treatment	0	0	0
Related to Any Study Treatment*b	0	0	0
Subjects who died due to TEAE within 30 days of last dose of study drug	1 (0.7)	3 (2.3)	4 (1.5)

Abbreviations: BendaR = Bendamustine plus Rituximab; CTCAE = common terminology criteria for adverse events; MedDRA = medical dictionary for regulatory activities; N = number of subjects in population; n = number of subjects within category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
**a - Subjects may be counted in more than one category.*
**b - Includes events considered related to study treatment by the investigator.*
**c - Deaths due to adverse events included.*
MedDRA Version 28.0; CTCAE Version 5.0

Any grade TEAEs occurred with a higher frequency in the Pirtobrutinib Arm than in the BendaR Arm. However, to reflect the differences in drug exposure between both arms, Exposure-Adjusted Incidence Rates (EAIRs) are provided in **Table 30** . TEAEs of any grade were lower in the Pirtobrutinib Arm (196.7 per 100 PY) compared to the BendaR Arm (844.6 per 100 PY).

Table 30. Overview of Treatment-Emergent Adverse Events (Pirtobrutinib Arm versus BendaR Arm) with Exposure-Adjusted Incidence Rates Study 20023 Safety Population

	Arm A: Pirtobrutinib (N=140, PY*a=366.680)			Arm B: BendaR (N=132, PY*a=60.435)			Incidence Rate Ratio	
Number of Subjects	n(%)	PYE*b	IR*c	n(%)	PYE*b	IR*c	IRR*d*e(95% CI)	p-value*e
Subjects with >=1 TEAE	131 (93.6)	66.601	196.7	117 (88.6)	13.854	844.6	0.23 (0.18,0.30)	<0.0001
Maximum CTCAE Grade 3/4	55 (39.3)	273.270	20.1	85 (64.4)	34.642	245.4	0.08 (0.06,0.12)	<0.0001
Maximum CTCAE Grade 5	1 (0.7)	366.680	0.3	4 (3.0)	60.367	6.6	0.04 (0.00,0.37)	0.0043
Maximum CTCAE Grade 3/4/5	56 (40.0)	272.903	20.5	89 (67.4)	33.785	263.4	0.08 (0.06,0.11)	<0.0001
Subjects with >=1 TEAE Related to Study Treatment	83 (59.3)	194.494	42.7	113 (85.6)	16.397	689.2	0.06 (0.05,0.08)	<0.0001
Maximum CTCAE Grade 3/4	31 (22.1)	314.634	9.9	79 (59.8)	35.688	221.4	0.04 (0.03,0.07)	<0.0001
Maximum CTCAE Grade 5	0	366.680	0	1 (0.8)	60.433	1.7	0	0
Maximum CTCAE Grade 3/4/5	31 (22.1)	314.634	9.9	80 (60.6)	35.685	224.2	0.04 (0.03,0.07)	<0.0001
Subjects with >=1 Treatment-Emergent SAE	39 (27.9)	315.636	12.4	37 (28.0)	50.114	73.8	0.17 (0.11,0.26)	<0.0001
Related to Any Study Treatment	15 (10.7)	352.320	4.3	31 (23.5)	50.965	60.8	0.07 (0.04,0.13)	<0.0001
Subjects who discontinued study treatment due to TEAE*f	6 (4.3)	366.034	1.6	20 (15.2)	58.363	34.3	0.05 (0.02,0.12)	<0.0001
Related to Any Study Treatment	3 (2.1)	366.278	0.8	17 (12.9)	58.401	29.1	0.03 (0.01,0.10)	<0.0001
Subjects who discontinued study treatment due to Treatment-Emergent SAE*f	3 (2.1)	366.404	0.8	10 (7.6)	59.964	16.7	0.05 (0.01,0.18)	<0.0001
Related to Any Study Treatment	1 (0.7)	366.530	0.3	8 (6.1)	59.970	13.3	0.02 (0.00,0.16)	0.0002
Subjects who died due to TEAE on study treatment	0	366.680	0	0	60.435	0		
Related to Any Study Treatment	0	366.680	0	0	60.435	0		
Subjects who died due to TEAE within 30 days of last dose of study drug	1 (0.7)	366.680	0.3	3 (2.3)	60.427	5.0	0.05 (0.01,0.53)	0.0120
Related to Any Study Treatment	0	366.680	0	1 (0.8)	60.433	1.7		

Abbreviations: BendaR = Bendamustine plus Rituximab; CTCAE = common terminology criteria for adverse events; MedDRA = medical
dictionary for regulatory activities; N = number of subjects in population; n = number of subjects within category; SAE = serious
adverse event; TEAE = treatment-emergent adverse event.
*a - Subjects may be counted in more than one category.
*b - Includes events considered related to study treatment by the investigator.
*c - Deaths due to adverse events included.
MedDRA Version 28.0; CTCAE Version 5.0

The most common study drug-related TEAEs (reported in ≥5% of participants) reported in Arm A were Neutropenia, Hypertension, and Urinary tract infection. The most common study drug-related TEAEs (reported in ≥5% of participants) in Arm B were Neutropenia, Neutrophil count decreased, Nausea, Pyrexia, Anaemia, Thrombocytopenia, Infusion related reaction, Vomiting, White blood cell count decreased, Chills, Rash, Lymphocyte count decreased, and Febrile neutropenia.

The most common study drug-related Grade 3 or 4 TEAE (reported in ≥5% of participants) in Arm A was Neutropenia. The most common study drug-related Grade 3 or 4 TEAE (reported in ≥5% of participants) in Arm B were Neutropenia, Neutrophil count decreased, Thrombocytopenia, Febrile neutropenia, Anaemia, and Lymphocyte count decreased. One Grade 5 study drug-related TEAE of Tumour lysis syndrome was reported in Arm B.

Common Adverse Events

Study 20023

Table 31. Treatment-Emergent Adverse Events of Any Grade by System Organ Class in ≥30% of Participants in Arm A or Arm B, or Preferred Term in ≥10% of Participants in Arm A or Arm B, by Decreasing Order of Frequency safety Population in study 20023

MedDRA System Organ Class MedDRA Preferred Term	Arm A: Pirtobrutinib N=140	Arm B: BendaR N=132
	n (%)	n (%)
Subjects with ≥1 TEAE	131 (93.6)	117 (88.6)
SOC and PT		
Blood and lymphatic system disorders	40 (28.6)	79 (59.8)
Neutropenia	17 (12.1)	51 (38.6)
Anaemia	13 (9.3)	21 (15.9)
Thrombocytopenia	11 (7.9)	17 (12.9)
Infections and infestations	80 (57.1)	44 (33.3)
COVID-19	30 (21.4)	12 (9.1)
Upper respiratory tract infection	25 (17.9)	9 (6.8)
Skin and subcutaneous tissue disorders	58 (41.4)	47 (35.6)
Rash	15 (10.7)	18 (13.6)
Gastrointestinal disorders	45 (32.1)	52 (39.4)
Vomiting	10 (7.1)	15 (11.4)
Nausea	3 (2.1)	31 (23.5)
General disorders and administration site conditions	37 (26.4)	45 (34.1)
Pyrexia	12 (8.6)	25 (18.9)
Musculoskeletal and connective tissue disorders	41 (29.3)	11 (8.3)
Arthralgia	17 (12.1)	1 (0.8)
Back pain	15 (10.7)	5 (3.8)
Injury, poisoning and procedural complications	26 (18.6)	21 (15.9)
Infusion related reaction	0	20 (15.2)
Investigations	32 (22.9)	30 (22.7)
Neutrophil count decreased	2 (1.4)	14 (10.6)

Abbreviations: BendaR = bendamustine plus rituximab; MedDRA = medical dictionary for regulatory activities; N = number of subjects in population; n = number of subjects within category; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Table 32 summarises TEAEs reported in at least 10% of the participants in the Pirtobrutinib Arm or the BendaR Arm for the Safety Population.

Table 32. Summary of Treatment-Emergent Adverse Events by Preferred Term and Maximum CTCAE Grade Categories in at least 10% of Participants in Either Arm Study 20023 Safety Population

	Arm A Pirtobrutinib N = 140		Arm B BendaR N = 132		Exposure-Adjusted IR		
MedDRA preferred term	**Any Grade n (%)**	**Grade 3+ n (%)**	**Any Grade n (%)**	**Grade 3+ n (%)**	**Any Grade Pirtobrutinib Arm IR[a]**	**Any Grade BendaR Arm IR[a]**	**Arm A:B IRR (95% CI)[b,c]**
Participants with at least 1 TEAE	131 (93.6)	56 (40.0)	117 (88.6)	89 (67.4)	196.7	844.6	0.23 (0.18, 0.30)
COVID-19	30 (21.4)	1 (0.7)	12 (9.1)	2 (1.5)	9.9	20.9	0.47 (0.24, 0.92)
Upper respiratory tract infection	25 (17.9)	1 (0.7)	9 (6.8)	0	7.7	15.7	0.49 (0.32,1.05)
Arthralgia	17 (12.1)	1 (0.7)	1 (0.8)	0	5.1	1.7	3.05 (0.41, 22.89)
Neutropenia	17 (12.1)	10 (7.1)	51 (38.6)	46 (34.8)	5.2	110.0	0.05 (0.03, 0.08)
Back pain	15 (10.7)	1 (0.7)	5 (3.8)	0	4.4	8.5	0.52 (0.19, 1.42)
Rash	15 (10.7)	0	18 (13.6)	2 (1.5)	4.4	34.0	0.13 (0.07, 0.26)
Anemia	13 (9.3)	6 (4.3)	21 (15.9)	10 (7.6)	3.8	37.7	0.10 (0.05, 0.20)
Pyrexia	12 (8.6)	0	25 (18.9)	0	3.5	49.1	0.07 (0.04, 0.14)
Thrombocytopenia	11 (7.9)	4 (2.9)	17 (12.9)	7 (5.3)	3.2	30.7	0.10 (0.05, 0.22)
Vomiting	10 (7.1)	0	15 (11.4)	0	2.8	27.4	0.10 (0.05, 0.23)
Nausea	3 (2.1)	0 (0)	31 (23.5)	1 (0.8)	0.8	65.1	0.01 (0.00, 0.04)
Neutrophil count decreased	2 (1.4)	1 (0.7)	14 (10.6)	10 (7.6)	0.5	25.1	0.02 (0.00, 0.14)
Infusion-related reaction	0	0	20 (15.2)	4 (3.0)	0	39	-

Abbreviations: BendaR = bendamustine plus rituximab; CI = confidence interval; CTCAE = Common Terminology Criteria in Adverse Events; IR = incidence rate per 100 PYE; IRR = incidence rate ratio; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in population; n = number of participants within category; PYE = person years exposure; TEAE = treatment-emergent adverse event.

[a] IR is for the first occurrence of the event and is calculated as n divided by PYE times 100.

[b] IRR is based on Pirtobrutinib Arm IR relative to the BendaR Arm IR.

[c] The 95% CI for IRR is based on Poisson regression.

Note: MedDRA Version 28.0; CTCAE Version 5.0.

Study 20030

Treatment-Emergent Adverse Events

Table 33. Overview of Adverse Events Study 20030 Safety Populations

	Study 20030					
	Safety Population		**Pretreated Safety Population**		**Treatment-Naïve Safety Population**	
Number of Participants[a]	**Arm A Pirtobrutinib N = 330**	**Arm B Ibrutinib N = 325**	**Arm A Pirtobrutinib N = 218**	**Arm B Ibrutinib N = 216**	**Arm A Pirtobrutinib N = 112**	**Arm B Ibrutinib N = 109**
Participants with at least 1 TEAE	**320 (97.0)**	**318 (97.8)**	**210 (96.3)**	**210 (97.2)**	**110 (98.2)**	**108 (99.1)**
Related to any study drug[b]	254 (77.0)	270 (83.1)	172 (78.9)	178 (82.4)	82 (73.2)	92 (84.4)
Participants with at least 1 TEAE Maximum CTCAE Grade 3/4	**163 (49.4)**	**158 (48.6)**	**105 (48.02)**	**103 (47.7)**	**58 (51.8)**	**55 (50.5)**
Related to any study drug[b]	113 (34.2)	123 (37.8)	78 (35.8)	81 (37.5)	35 (31.3)	42 (38.5)
Participants with at least 1 TE-SAE	**107 (32.4)**	**108 (33.2)**	**72 (33.0)**	**74 (34.3)**	**35 (31.3)**	**34 (31.2)**
Related to any study drug[b]	46 (13.9)	54 (16.6)	32 (14.7)	37 (17.1)	14 (12.5)	17 (15.6)
Participants who discontinued treatment due to TEAE[c]	**31 (9.4)**	**35 (10.8)**	**25 (11.5)**	**23 (10.6)**	**6 (5.4)**	**12 (11.0)**
Related to any study drug[b]	14 (4.2)	21 (6.5)	13 (6.0)	11 (5.1)	1 (0.9)	10 (9.2)
Participants who died due to TEAE on study treatment	**1 (0.3)**	**1 (0.3)**	**1 (0.5)**	**1 (0.5)**	**0**	**0**
Related to any study drug[b]	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)	0	0
Participants who died within 30 days of last dose due to TEAE	**16 (4.8)**	**12 (3.7)**	**15 (6.9)**	**10 (4.6)**	**1 (0.9)**	**2 (1.8)**
Related to any study drug[b]	5(1.5)	4(1.2)	5 (2.3)	3 (1.4)	0	1 (0.9)

Abbreviations: CTCAE = Common Terminology Criteria in Adverse Events; N = number of participants; TE-SAE = treatment-emergent-serious adverse event; TEAE = treatment-emergent adverse event.

[a] Participants may be counted in more than 1 category.

[b] Includes events considered related to study treatment by the investigator.

[c] Deaths due to adverse events included.

Common adverse events

Table 34 summarises TEAEs reported in at least 10% of the participants in the pirtobrutinib Arm or the BendaR Arm for the Safety Populations in study 20030.

Table 34. Summary of Treatment-Emergent Adverse Events by Preferred Term and Maximum CTCAE Grade Categories in at least 10% of Participants Study 20030 Safety Populations

	Safety Population				**Pretreated Safety Population**				**Treatment-Naïve Safety Population**			
	Arm A Pirtobrutinib N = 330		**Arm B Ibrutinib N = 325**		**Arm A Pirtobrutinib N = 218**		**Arm B Ibrutinib N = 216**		**Arm A Pirtobrutinib N = 112**		**Arm B Ibrutinib N = 109**	
	Any grade n (%)	**Grade 3+ n (%)**	**Any grade n (%)**	**Grade 3+ n (%)**	**Any grade n (%)**	**Grade 3+ n (%)**	**Any grade n (%)**	**Grade 3+ n (%)**	**Any grade n (%)**	**Grade 3+ n (%)**	**Any grade n (%)**	**Grade 3+ n (%)**
Participants with at least 1 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)	210 (96.3)	122 (56.0)	210 (97.2)	117 (54.2)	110 (98.2)	59 (52.7)	108 (99.1)	57 (52.3)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)	56 (25.7)	42 (19.3)	42 (19.4)	32 (14.8)	19 (17.0)	15 (13.4)	16 (14.7)	11 (10.1)
Upper respiratory tract infection	59 (17.9)	2 (0.6)	63 (19.4)	0 (0)	41 (18.8)	2 (0.9)	37 (17.1)	0	18 (16.1)	0	26 (23.9)	0
Anemia	50 (15.2)	19 (5.8)	46 (14.2)	12 (3.7)	31 (14.2)	13 (6.0)	29 (13.4)	9 (4.2)	19 (17.0)	6 (5.4)	17 (15.6)	3 (2.8)
Pneumonia	45 (13.6)	21 (6.4)	49 (15.1)	28 (8.6)	36 (16.5)	16 (7.3)	36 (16.7)	20 (9.3)	9 (8.0)	5 (4.5)	13 (11.9)	8 (7.3)
Diarrhea	44(13.3)	1(0.3)	62(19.1)	4(1.2	27 (12.4)	0	39 (18.1)	4 (1.9)	17 (15.2)	1 (0.9)	23 (21.1)	0
COVID-19	40 (12.1)	4 (1.2)	33 (10.2)	5 (1.5)	18 (8.3)	2 (0.9)	16 (7.4)	4 (1.9)	22 (19.6)	2 (1.8)	17 (15.6)	1 (0.9)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)	19 (8.7)	5 (2.3)	29 (13.4)	6 (2.8)	16 (14.3)	6 (5.4)	20 (18.3)	10 (9.2)
Contusion	33 (10.0)	0 (0)	30 (9.2)	0 (0)	19 (8.7)	0	14 (6.5)	0	14 (12.5)	0	16 (14.7)	0
Arthralgia	26 (7.9)	0 (0)	41 (12.6)	0 (0)	17 (7.8)	0	22 (10.2)	0	9 (8.0)	0	19 (17.4)	0
Thrombocytopenia	26 (7.9)	9 (2.7)	37 (11.4)	10 (3.1)	19 (8.7)	8 (3.7)	29 (13.4)	8 (3.7)	7 (6.3)	1 (0.9	8 (7.3)	2 (1.8)
Urinary tract infection	26 (7.9)	3 (0.9)	40 (12.3)	3 (0.9)	16 (7.3)	1 (0.5)	24 (11.0)	3 (1.4)	10 (8.9)	2 (1.8)	16 (14.7)	0
Atrial fibrillation	8 (2.4)	3 (0.9)	41 (12.6)	12 (3.7)	3 (1.4)	1 (0.5)	20 (.9.3)	8 (3.7)	5 (4.5)	2 (1.8	21 (19.3)	4 (3.7)
Cough	31 (9.4)	1 (0.3)	31 (9.5)	0	23 (10.6)	1 (0.5)	21 (9.7)	0	8 (7.1)	0	10 (9.2)	0
Constipation	31 (9.4)	0	16 (4.9)	0	17 (7.8)	0	11 (5.1)	0	14 (12.5)	0	5 (4.6)	0

	Safety Population				Pretreated Safety Population				Treatment-Naïve Safety Population			
	Arm A Pirtobrutinib N = 330		Arm B Ibrutinib N = 325		Arm A Pirtobrutinib N = 218		Arm B Ibrutinib N = 216		Arm A Pirtobrutinib N = 112		Arm B Ibrutinib N = 109	
	Any grade n (%)	Grade 3+ n (%)	Any grade n (%)	Grade 3+ n (%)	Any grade n (%)	Grade 3+ n (%)	Any grade n (%)	Grade 3+ n (%)	Any grade n (%)	Grade 3+ n (%)	Any grade n (%)	Grade 3+ n (%)
Haematuria	22 (6.7)	1 (0.3)	18 (5.5)	1 (0.3)	9 (4.1)	1 (0.5)	8 (3.7)	1 (0.5)	13 (11.6)	0	10 (9.2)	0
Back pain	29 (8.8)	0	21 (6.5)	1 (0.3)	17 (7.8)	0	9 (4.2)	0	12 (10.7)	0	12 (11.0)	1 (0.9)
Muscle spasms	11 (3.3)	0	32 (9.8)	0	9 (4.1)	0	20 (9.3)	0	2 (1.8)	0	12 (11.0)	0

Abbreviations: CTCAE = Common Terminology Criteria in Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants within category; N = number of participants in population; TEAE = treatment-emergent adverse event.
Note: MedDRA Version 28.0; CTCAE Version 5.0.
Data cutoff: 10 June 2025

Integrated safety set (ISS)

In the ISS, 1105 participants experienced at least 1 TEAE (95.8%). Treatment-related AEs occurred in 768 participants (66.6%). Grade 3 or Grade 4 TEAEs occurred in 600 participants (52.0%). TE-SAEs occurred in 487 participants (42.2%). (**Table 35**).

Table 35. Overview of Adverse Events Integrated Safety Set, Study 20023 and Study 20030 Safety Populations

Number of participants[a]	Integrated Safety Set N = 1153 n (%)	Study 20023 Safety Population N = 140 n (%)	Study 20030 Safety Population N = 330 n (%)
Participants with at least TEAE	**1105 (95.8)**	**131 (93.6)**	**320 (97.0)**
Related to any study drug[b]	768 (66.6)	83 (59.3)	254 (77.0)
Participants with at least 1 TEAE maximum CTCAE Grade 3 or Grade 4	**600 (52.0)**	**55 (39.3)**	**163 (49.4)**
Related to any study drug[b]	330 (28.6)	31 (22.1)	113 (34.2)
Participants with at least 1 TE-SAE	**487 (42.2)**	**39 (27.9)**	**107 (32.4)**
Related to any study drug[b]	121 (10.5)	15 (10.7)	46 (13.9)
Participants who discontinued treatment due to TEAE[c]	**127 (11.0)**	**6 (4.3)**	**31 (9.4)**
Related to any study drug[b]	44 (3.8)	3 (2.1)	14 (4.2)
Participants who died due to TEAE on study treatment	**4 (0.3)**	**0**	**1(0.3)**
Related to any study drug[b]	1 (0.1)	0	1(0.3)
Participants who died within 30 days of last dose due to TEAE	**70 (6.1)**	**1 (0.7)**	**16(4.8)**
Related to any study drug[b]	11 (1.0)	0	5(1.5)

Abbreviations: CTCAE = Common Terminology Criteria in Adverse Events; n = number of participants within category; N = number of participants in population; TE-SAE = treatment-emergent-serious adverse event; TEAE = treatment-emergent adverse event.

a Participants may be counted in more than 1 category.

b Includes events considered related to study treatment by the investigator.

c Deaths due to adverse events included.

Data cutoff: 11 July 2025 (Study 20023), 10 June 2025 (Study 20030)

Serious adverse event/deaths/other significant events

Serious adverse events

Table 36 provides a summary of TE-SAEs in the Safety Population in study 20023 and **Table 37** summarises TE-SAEs by PT and maximum CTCAE grade categories reported in at least 1% of participants in either arm in study 20030.

Table 36. Summary of Treatment-Emergent SAEs by Preferred Term and Maximum CTCAE Grade Categories in at least 2 Participants in the Pirtobrutinib Arm Study 20023 Safety Population

	Arm A Pirtobrutinib N = 140		Arm B BendaR N = 132		Exposure-Adjusted IR		
MedDRA Preferred Term	**Any grade n (%)**	**Grade 3+ n (%)**	**Any grade n (%)**	**Grade 3+ n (%)**	**Any grade Pirtobrutinib Arm IR[a]**	**Any grade BendaR Arm IR[a]**	**Arm A:B IRR (95% CI)[b,c]**
Participants with at least 1 TE-SAE	39 (27.9)	30 (21.4)	37 (28.0)	31 (23.5)	12.4	73.8	0.17 (0.11, 0.26)-
Pneumonia	7 (5.0)	6 (4.3)	4 (3.0)	3 (2.3)	2.0	6.6	0.30 (0.09, 1.01)
Prostate cancer	2 (1.4)	1 (1.2)	0	0	0.5	0	-
Anemia	3 (2.1)	3 (2.1)	4 (3.0)	4 (3.0)	0.8	6.7	0.12 (0.03, 0.55)
COVID-19	2 (1.4)	1 (0.7)	4 (3.0)	2 (1.5)	0.6	6.7	0.08 (0.02, 0.22)
Febrile neutropenia	2 (1.4)	2 (1.4)	7 (5.3)	7 (5.3)	0.6	12.1	0.05 (0.01,0.22)

Table 37. Summary of Treatment-Emergent SAEs by Preferred Term and Maximum CTCAE Grade Categories in at least 1% of Participants in Either Arm in study 20030

	Arm A Pirtobrutinib N = 330		Arm B Ibrutinib N = 325	
MedDRA Preferred Term	**Any grade n (%)**	**Grade 3+ n (%)**	**Any grade n (%)**	**Grade 3+ n (%)**
Participants with at least 1 TE-SAE	107 (32.4)	95 (28.8)	108 (33.2)	88 (27.1)
Pneumonia	23 (7.0)	20 (6.1)	29 (8.9)	25 (7.7)
Anemia	7 (2.1)	6 (1.8)	1 (0.3)	1 (0.3)
Acute kidney injury	5 (1.5)	5 (1.5)	0	0
Febrile neutropenia	5 (1.5)	5 (1.5)	4 (1.2)	4 (1.2)
COVID-19	4 (1.2)	4 (1.2)	5 (1.5)	5 (1.5)
Atrial fibrillation	2 (0.6)	2 (0.6)	10 (3.1)	8 (2.5)

Abbreviations: CTCAE = Common Terminology Criteria in Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants within category; N = number of participants; SAE = serious adverse event; TE-SAE = treatment-emergent-serious adverse event; TEAE = treatment-emergent adverse event.

Note: MedDRA Version 28.0; CTCAE Version 5.0.

Data cutoff: 10 June 2025

Treatment naïve safety population

SAEs occurred with a similar frequency in the Pirtobrutinib Arm (35 participants, 31.3%) and in the Ibrutinib Arm (34 participants, 31.2%). Treatment-related SAEs occurred in 14 participants (12.5%) in the Pirtobrutinib Arm and in 17 participants (15.6%) in the Ibrutinib Arm.

The most reported SOC for any grade TE-SAEs reported in at least 10% of participants in either treatment arm was Infections and infestations (Pirtobrutinib Arm: 14 participants: 12.5%; Ibrutinib Arm: 14 participants, 12.5%).

The most common any grade TE-SAEs reported in at least 2% of participants in either treatment arm were pneumonia (4.5%) and anaemia (2.7%) in the Pirtobrutinib Arm and pneumonia (7.3%) and atrial fibrillation (2.8%) in the Ibrutinib Arm.

Integrated safety set

A total of 487 participants experienced at least 1 SAE (42.2%). Treatment-related SAEs occurred in 121 participants (10.5%). Grade 3 or Grade 4 SAEs occurred in 355 participants (30.8%). A total of 84 participants (7.3%) discontinued pirtobrutinib due to a SAE. There were 80 participants (6.9%) who had a fatal SAE. Twelve fatal SAEs (1.0%) were considered related to pirtobrutinib treatment. Most SAEs were observed in the SOC of Infections and infestations (265 participants; 23.0%). Pneumonia was the most commonly reported SAE in the ISS as well as in Study 20023 and Study 20030.

Deaths

In study 20023, one participant in the ITT Population died before receiving treatment and was, therefore, not included in the Safety Population.

Participant deaths due to all causes (including PD, AE, and other) occurred in 3 participants (2.1%) in Arm A and 9 participants (6.8%) in Arm B. One participant death in Arm B did not receive treatment and was not included in the safety population. No deaths occurred in the crossover population.

Only a few deaths occurred in the Pirtobrutinib Arm and the BendaR Arm within 30 days of the last dose of study drug. There were no deaths during treatment.

Deaths due to AEs within 30 days of last dose of study drug:

- In the Pirtobrutinib Arm, 1 death (0.7%) was due to septic shock, which was considered not related to treatment.
- In the BendaR Arm, 3 deaths (2.3%) were due to cardio-respiratory arrest, ischemic stroke, and TLS. TLS was considered treatment related.

Deaths after 30 days of last dose of study drug:

- In the Pirtobrutinib Arm, there were 2 deaths due to unknown reasons.
- In the BendaR Arm, 6 deaths (4.5%) occurred including
    - 1 death due to PD
    - 2 deaths due to AEs, namely pneumonia and hepatocellular carcinoma.

Both deaths were considered non treatment related.

o 3 deaths due to other reasons not reported as AEs: acute on chronic liver failure, pneumonia, and death due to unknown cause.

<u>Safety Population</u>

Overall. in study 200230, deaths occurred in 25 participants (7.6%) in Arm A and 24 participants (7.4%) in Arm B. Most of the deaths in both arms occurred in the pretreated population.

Deaths on therapy or within 30 days of the last study drug dose occurred in 17 participants in Arm A (5.2%) and 13 participants (4.0%) in Arm B. All were due to AEs, and most commonly were due to Infections and infestations-related AEs (11 participants [3.3%] Arm A, 8 participants [2.5%] Arm B). The most frequent AE leading to death on therapy or within 30 days of last study drug dose in both treatment arms was pneumonia-related events

Deaths on therapy or within 30 days of the last study drug dose due to treatment-related AEs occurred in 6 participants (1.8%) in Arm A and 5 participants (1.5%) in Arm B.

These treatment-related AEs in Arm A were: pneumonia in 2 participants (0.6%), septic shock in 2 participants (0.6%), pulmonary sepsis in 1 participant (0.3%), and pneumonia cryptococcal in 1 participant (0.3%).

Treatment-related AEs in Arm B were pneumonia in 1 participant (0.3%), septic shock in 1 participant (0.3%), death in 1 participant (0.3%), ventricular fibrillation in 1 participant (0.3%), and atrial fibrillation in 1 participant (0.3%).

Pretreated Safety Population

Overall, deaths occurred in 22 participants (10.1%) in Arm A and 21 participants (9.7%) in Arm B. Deaths on therapy or within 30 days of the last study drug dose occurred in 16 participants (7.3%) in Arm A and 11 participants (5.1%) in Arm B. All were due to AEs, and most commonly were infections and infestations-related AEs (10 participants [4.6%] Arm A, 6 participants [2.8%] Arm B). The most frequent AE leading to death on therapy or within 30 days of last study drug dose in both treatment arms was pneumonia. Deaths on therapy or within 30 days of the last dose of study drug due to treatment-related AEs occurred in 6 participants (2.8%) in Arm A and 4 participants (1.9%) in Arm B.

These treatment-related AEs in Arm A were pneumonia in 2 participants (0.9%), septic shock in 2 participants (0.9%), pulmonary sepsis in 1 participant (0.5%), and pneumonia cryptococcal in 1 participant (0.5%).

These treatment-related AEs in Arm B were septic shock in 1 participant (0.5%), death in 1 participant (0.5%), ventricular fibrillation in 1 participant (0.5%), and atrial fibrillation in 1 participant (0.5%).

Deaths after 30 days of the last study drug dose occurred in 6 participants (2.8%) in Arm A (2 due to disease progression, and 4 due to AEs with 1 treatment-related AE of Pneumonia) and in 10 participants (4.6%) in Arm B (3 due to disease progression, 1 due to "other", and 6 due to AEs, with 1 treatment-related AE of Disseminated cryptococcosis and 1 treatment-related AE of Sepsis).

Treatment-naïve safety population

Deaths within 30 days of the last dose of study drug occurred with a similar frequency in the Pirtobrutinib Arm (1 participant, 0.9%) and the Ibrutinib Arm (2 participants, 1.8%). No deaths occurred during treatment in either arm.

In the Pirtobrutinib Arm, 1 death was due to an AE of pneumonia and was considered non-treatment related.

In the Ibrutinib Arm, both deaths were due to AEs. One death was due to COVID-19, and the other was due to pneumonia. Both were considered treatment related.

Integrated safety set

A total of 6 participants (0.5%) died on therapy. Four deaths (0.3%) on therapy were due to AEs, of which 1 was related to study treatment. Two deaths on therapy (0.2%) were attributed to disease progression.

A total of 101 deaths (8.8%) occurred within 30 days of the last dose of study drug. Seventy deaths (6.1%) were due to AEs, of which 11 deaths (1.0%) were considered related to study treatment. Deaths were mainly caused by COVID-19 pneumonia (11 participants, 1%) or the result of an underlying infection. Thirty-one deaths within 30 days of the last dose of study drug (2.7%) were attributed to disease progression.

Other Significant Adverse Events

Adverse events of special interest (AESIs) were identified based on the known safety profile of BTKi therapies, nonclinical toxicology, and safety data generated by the pirtobrutinib development program.

AESIs include the following composite terms:

- Infections (including COVID-19 and subcategory "without COVID-19")
- Bleeding (including bruising, petechiae and purpura, and haemorrhage)
- Atrial fibrillation and Atrial flutter, and
- Cytopenias (specifically anaemia, neutropenia, and thrombocytopenia).

Infections

Study 20023

Aggregate analysis of infections was conducted using all terms within the SOC of Infections and infestations due to the degree of variation of PTs that exist within the category of infection. An additional aggregate analysis was conducted, removing component PTs related to COVID-19 events from the broader SOC, to better assess the impact of COVID-19 specifically.

<u>Infections including COVID-19</u>

Infections of any grade were reported more frequently in Arm A (80 participants [57.1%]) than in Arm B (44 participants [33.3%]). Exposure-adjusted incidence rates of infections of any grade were lower in Arm A (38.3 participants per 100 PY) compared to Arm B (89.7 participants per 100 PY). Treatment-related infections of any grade were similarly reported in Arm A (26 participants [18.6%]) and in Arm B (28 participants [21.2%]). In Arm A, the most common (reported in >5% of participants) infections included COVID-19, upper respiratory tract infection, urinary tract infection, nasopharyngitis, and pneumonia. In Arm B, the most common (reported in >5% of participants) infections included COVID-19 and upper respiratory tract infection. Most infections were managed without dose modification in each treatment arm. Grade 3 or 4 infections were reported in a higher frequency in Arm A (18 participants [12.9%]) compared to Arm B (10 participants [7.6%]). Grade 3 or 4 treatment-related infections were similar between both arms (8 participants in Arm A [5.7%] and 9 participants in Arm B [6.8%]). SAEs of infections and treatment-related SAEs of infections were reported in a similar frequency in Arm A (20 participants [14.3%] and 7 participants [5.0%], respectively) and Arm B (16 participants [12.1%] and 12 participants [9.1%], respectively). Grade 5 infections were reported by 1 participant in both arms, and the events were considered not related to study drug.

Infections excluding COVID-19

When COVID-19 was excluded, infections of any grade were reported more frequently in Arm A (72 participants [51.4%]) than in Arm B (38 participants [28.8%]). Exposure-adjusted incidence rates of any grade infections were lower in Arm A (30.9 participants per 100 PY) compared to Arm B (74.9 participants per 100 PY). Treatment-related infections of any grade were similarly reported in Arm A (25 participants [17.9%]) and in Arm B (23 participants [17.4%])

Table 38. Summary of Infections AESIs Study 20023 Safety Population

	Arm A Pirtobrutinib N=140	**Arm B BendaR N=132**	**Total N=272**
Infections			
Participants with any TEAEs, n (%)	**80 (57.1)**	**44 (33.3)**	**124 (45.6)**
Highest Grade, n (%)			
Grade 1	15 (10.7)	10 (7.6)	25 (9.2)
Grade 2	46 (32.9)	23 (17.4)	69 (25.4)
Grade 3	18 (12.9)	9 (6.8)	27 (9.9)
Grade 4	0	1 (0.8)	1 (0.4)
Grade 5	1 (0.7)	1 (0.8)	2 (0.7)
Participants with any study drug related TEAEs, n (%)	**26 (18.6)**	**28 (21.2)**	**54 (19.9)**
Highest Grade, n (%)			
Grade 1	5 (3.6)	3 (2.3)	8 (2.9)
Grade 2	13 (9.3)	16 (12.1)	29 (10.7)
Grade 3	8 (5.7)	8 (6.1)	16 (5.9)
Grade 4	0	1 (0.8)	1 (0.4)
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**20 (14.3)**	**16 (12.1)**	**36 (13.2)**
Participants with any study drug related TE-SAE, n (%)	**7 (5.0)**	**12 (9.1)**	**19 (7.0)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	27 (19.3)	4 (3.0)	31 (11.4)
TEAEs Leading to Dose Reduction	0	1 (0.8)	1 (0.4)
TEAEs Leading to Study Drug Discontinuation[a]	0	6 (4.5)	6 (2.2)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	12 (8.6)	2 (1.5)	14 (5.1)
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	5 (3.8)	5 (1.8)
Infections without COVID-19			
Participants with any TEAEs, n (%)	**72 (51.4)**	**38 (28.8)**	**110 (40.4)**
Highest Grade, n (%)			
Grade 1	14 (10.0)	9 (6.8)	23 (8.5)
Grade 2	39 (27.9)	20 (15.2)	59 (21.7)
Grade 3	18 (12.9)	7 (5.3)	25 (9.2)
Grade 4	0	1 (0.8)	1 (0.4)
Grade 5	1 (0.7)	1 (0.8)	2 (0.7)
Participants with any study drug related TEAEs, n (%)	**25 (17.9)**	**23 (17.4)**	**48 (17.6)**

	Arm A Pirtobrutinib N=140	Arm B BendaR N=132	Total N=272
Highest Grade, n (%)			
Grade 1	4 (2.9)	3 (2.3)	7 (2.6)
Grade 2	13 (9.3)	13 (9.8)	26 (9.6)
Grade 3	8 (5.7)	6 (4.5)	14 (5.1)
Grade 4	0	1 (0.8)	1 (0.4)
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**19 (13.6)**	**11 (8.3)**	**30 (11.0)**
Participants with any study drug related TE-SAE, n (%)	**7 (5.0)**	**8 (6.1)**	**15 (5.5)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	17 (12.1)	4 (3.0)	21 (7.7)
TEAEs Leading to Dose Reduction	0	1 (0.8)	1 (0.4)
TEAEs Leading to Study Drug Discontinuation[a]	0	5 (3.8)	5 (1.8)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	10 (7.1)	2 (1.5)	12 (4.4)
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	5 (3.8)	5 (1.8)

Abbreviations: AESI = adverse event of special interest; BendaR = bendamustine plus rituximab; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants within category; N = number of participants in population; TE-SAE = treatment-emergent-serious adverse event; TEAE = treatment-emergent adverse event.

[a] Deaths due to adverse events are included.

Data cutoff: 11 July 2025

Study 20030

Table 39 provides a summary of infections, including and not including COVID-19, in the safety [opulation.

In the pirtobrutinib Arm, the most common any grade infections reported in at least 10% of participants were upper respiratory tract infections and pneumonia.

In the ibrutinib Arm, the most common any grade infections reported in at least 10% of participants were upper respiratory tract infection, pneumonia, and urinary tract infection.

Table 39. Summary of Infections AESIs Study 20030 Safety Population

	Arm A Pirtobrutinib N=330	Arm B Ibrutinib N=325	Total N=655
Infections			
Participants with any TEAEs, n (%)	**226 (68.5)**	**241 (74.2)**	**467 (71.3)**
Highest Grade, n (%)			
Grade 1	37 (11.2)	33 (10.2)	70 (10.7)
Grade 2	133 (40.3)	154 (47.4)	287 (43.8)
Grade 3	38 (11.5)	44 (13.5)	82 (12.5)

	Arm A Pirtobrutinib N=330	Arm B Ibrutinib N=325	Total N=655
Grade 4	7 (2.1)	2 (0.6)	9 (1.4)
Grade 5	11 (3.3)	8 (2.5)	19 (2.9)
Participants with any study drug related TEAEs, n (%)	**81 (24.5)**	**91 (28.0)**	**172 (26.3)**
Highest Grade, n (%)			
Grade 1	8 (2.4)	11 (3.4)	19 (2.9)
Grade 2	45 (13.6)	51 (15.7)	96 (14.7)
Grade 3	19 (5.8)	25 (7.7)	44 (6.7)
Grade 4	3 (0.9)	1 (0.3)	4 (0.6)
Grade 5	6 (1.8)	3 (0.9)	9 (1.4)
Participants with TE-SAE, n (%)	**56 (17.0)**	**56 (17.2)**	**112 (17.1)**
Participants with any study drug related TE-SAE, n (%)	**27 (8.2)**	**26 (8.0)**	**53 (8.1)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	72 (21.8)	85 (26.2)	157 (24.0)
TEAEs Leading to Dose Reduction	4 (1.2)	6 (1.8)	10 (1.5)
TEAEs Leading to Study Drug Discontinuation[a]	10 (3.0)	9 (2.8)	19 (2.9)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	32 (9.7)	33 (10.2)	65 (9.9)
Study Drug Related TEAEs Leading to Dose Reduction	1 (0.3)	5 (1.5)	6 (0.9)
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	6 (1.8)	4 (1.2)	10 (1.5)
Infections without COVID-19[b]			
Participants with any TEAEs, n (%)	214 (64.8)	234 (72.0)	448 (68.4)
Highest Grade, n (%)			
Grade 1	38 (11.5)	34 (10.5)	72 (11.0)
Grade 2	123 (37.3)	151 (46.5)	274 (41.8)
Grade 3	36 (10.9)	40 (12.3)	76 (11.6)
Grade 4	7 (2.1)	2 (0.6)	9 (1.4)
Grade 5	10 (3.0)	7 (2.2)	17 (2.6)
Participants with any study drug related TEAEs, n (%)	**76 (23.0)**	**89 (27.4)**	**165 (25.2)**
Highest Grade, n (%)			
Grade 1	6 (1.8)	10 (3.1)	16 (2.4)
Grade 2	43 (13.0)	51 (15.7)	94 (14.4)
Grade 3	18 (5.5)	24 (7.4)	42 (6.4)
Grade 4	3 (0.9)	1 (0.3)	4 (0.6)
Grade 5	6 (1.8)	3 (0.9)	9 (1.4)
Participants with TE-SAE, n (%)	**52 (15.8)**	**50 (15.4)**	**102 (15.6)**
Participants with any study drug related TE-SAE, n (%)	**26 (7.9)**	**25 (7.7)**	**51 (7.8)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	58 (17.6)	75 (23.1)	133 (20.3)
TEAEs Leading to Dose Reduction	3 (0.9)	6 (1.8)	9 (1.4)
TEAEs Leading to Study Drug Discontinuation[a]	9 (2.7)	8 (2.5)	17 (2.6)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	27 (8.2)	31 (9.5)	58 (8.9)

	Arm A Pirtobrutinib N=330	Arm B Ibrutinib N=325	Total N=655
Study Drug Related TEAEs Leading to Dose Reduction	1 (0.3)	5 (1.5)	6 (0.9)
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	6 (1.8)	4 (1.2)	10 (1.5)

Pretreated Safety Population

Infections of any grade were reported at a similar frequency in Arm A (155 participants [71.1%]) and Arm B (157 participants [72.7%]). Treatment-related infections of any grade were reported at a similar frequency in Arm A (55 participants [25.2%]) and Arm B (63 participants [29.2%] respectively). In Arm A, the most common infections included upper respiratory tract infection and pneumonia.

In Arm B the most common infections included upper respiratory tract infection, pneumonia, and urinary tract infection. Most infections were managed without dose modification.

Grade 3 or 4 infections and treatment-related Grade 3 or 4 infections were reported at a similar frequency in Arm A (30 participants [13.8%] and 15 participants [6.9%], respectively) and Arm B (36 participants [16.7%] and 19 participants [8.8%], respectively).

SAEs of infections and treatment-related SAEs of infections were reported at a similar frequency in Arm A (42 participants [19.3%] and 19 participants [8.7%], respectively) and Arm B (43 participants [19.9%] and 19 participants [8.8%], respectively).

Grade 5 infections were reported in 10 participants (4.6%) in Arm A and 6 participants (2.8%) in Arm B. Treatment-related Grade 5 infections AESI were reported in 6 participants (2.8%) in Arm A and 2 participants (0.9%) in Arm B.

Treatment naïve safety population

Any grade infection occurred with a lower frequency in the pirtobrutinib Arm (71 participants, 63.4%) compared to the ibrutinib Arm (84 participants, 77.1%).

The most common AESIs of infection reported in at least 10% of participants were COVID 19 and upper respiratory tract infection in the pirtobrutinib Arm, and COVID-19, upper respiratory tract infection, urinary tract infection, and pneumonia in the ibrutinib Arm.

Serious infection AESIs occurred with a similar frequency in the pirtobrutinib Arm (14 participants, 12.5%) and the ibrutinib Arm (13 participants, 11.9%).

Grade 5 infection occurred with a similar frequency in the pirtobrutinib Arm (1 participant, 0.9%) and the ibrutinib Arm (2 participants, 1.8%). Treatment related Grade 5 of infection occurred 1 participant (0.9%) in the ibrutinib Arm.

Integrated safety set

Infections occurred in 719 participants (62.4%), treatment-related infections occurred in 209 participants (18.1%), and 220 participants (19.1%) had Grade 3 or Grade 4 infections. Serious infections occurred in 265 participants (23.0%). There were 50 participants (4.3%) who had a fatal infection, and 9 participants (0.8%) had fatal infections considered related to pirtobrutinib treatment. Most of the infections were upper respiratory tract infections.

Infections, excluding COVID-19, occurred in 647 participants (56.1%), 193 participants (16.7%) had treatment-related AESIs, and 193 participants (16.8%) had Grade 3 or Grade 4 infections. Serious

infections (without COVID-19) occurred in 211 participants (18.3%). A total of 30 participants (2.6%) experienced fatal infection without COVID-19. In 7 participants (0.6%) fatal infection was considered related to pirtobrutinib treatment.

Bleedings Including Bruising, Petechiae and Purpura, and Haemorrhage

Study 20023

Table 40. Summary of Bleedings AESIs Including Bruising, Petechiae and Purpura, and Haemorrhage Study 20023 Safety Population

	Arm A Pirtobrutinib N=140	**Arm B BendaR N=132**	**Total N=272**
Bleeding			
Participants with any TEAEs, n (%)	**36 (25.7)**	**2 (1.5)**	**38 (14.0)**
Highest Grade, n (%)			
Grade 1	29 (20.7)	1 (0.8)	30 (11.0)
Grade 2	6 (4.3)	1 (0.8)	7 (2.6)
Grade 3	1 (0.7)	0	1 (0.4)
Grade 4	0	0	0
Grade 5	0	0	0
Participants with any study drug related TEAEs, n (%)	**29 (20.7)**	**0**	**29 (10.7)**
Highest Grade, n (%)			
Grade 1	24 (17.1)	0	24 (8.8)
Grade 2	4 (2.9)	0	4 (1.5)
Grade 3	1 (0.7)	0	1 (0.4)
Grade 4	0	0	0
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**1 (0.7)**	**0**	**1 (0.4)**
Participants with any study drug related TE-SAE, n (%)	**1 (0.7)**	**0**	**1 (0.4)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	1 (0.7)	0	1 (0.4)
TEAEs Leading to Dose Reduction	0	0	0
TEAEs Leading to Study Drug Discontinuation[a]	1 (0.7)	0	1 (0.4)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	1 (0.7)	0	1 (0.4)
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	1 (0.7)	0	1 (0.4)
Hemorrhage[b]			
Participants with any TEAEs, n (%)	17 (12.1)	2 (1.5)	19 (7.0)
Highest Grade, n (%)			
Grade 1	14 (10.0)	1 (0.8)	15 (5.5)
Grade 2	2 (1.4)	1 (0.8)	3 (1.1)
Grade 3	1 (0.7)	0	1 (0.4)
Grade 4	0	0	0
Grade 5	0	0	0

	Arm A Pirtobrutinib N=140	Arm B BendaR N=132	Total N=272
Participants with any study drug related TEAEs, n (%)	**14 (10.0)**	**0**	**14 (5.1)**
Highest Grade, n (%)			
Grade 1	12 (8.6)	0	12 (4.4)
Grade 2	1 (0.7)	0	1 (0.4)
Grade 3	1 (0.7)	0	1 (0.4)
Grade 4	0	0	0
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**1 (0.7)**	**0**	**1 (0.4)**
Participants with any study drug related TE-SAE, n (%)	**1 (0.7)**	**0**	**1 (0.4)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	0	0	0
TEAEs Leading to Dose Reduction	0	0	0
TEAEs Leading to Study Drug Discontinuation[a]	0	0	0
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	0	0	0
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	0	0
Bruising[b]			
Participants with any TEAEs, n (%)	**16 (11.4)**	**0**	**16 (5.9)**
Highest Grade, n (%)			
Grade 1	13 (9.3)	0	13 (4.8)
Grade 2	3 (2.1)	0	3 (1.1)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with any study drug related TEAEs, n (%)	**11 (7.9)**	**0**	**11 (4.0**
Highest Grade, n (%)			
Grade 1	9 (6.4)	0	9 (3.3)
Grade 2	2 (1.4)	0	2 (0.7)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**0**	**0**	**0**
Participants with any study drug related TE-SAE, n (%)	**0**	**0**	**0**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	1 (0.7)	0	1 (0.4)
TEAEs Leading to Dose Reduction	0	0	0
TEAEs Leading to Study Drug Discontinuation[a]	1 (0.7)	0	1 (0.4)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	1 (0.7)	0	1 (0.4)

	Arm A Pirtobrutinib N=140	Arm B BendaR N=132	Total N=272
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	1 (0.7)	0	1 (0.4)
Petechiae and Purpura[b]			
Participants with any TEAEs, n (%)	**8 (5.7)**	**0**	**8 (2.9)**
Highest Grade, n (%)			
Grade 1	7 (5.0)	0	7 (2.6)
Grade 2	1 (0.7)	0	1 (0.4)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with any study drug related TEAEs, n (%)	**8 (5.7)**	**0**	**8 (2.9)**
Highest Grade, n (%)			
Grade 1	7 (5.0)	0	7 (2.6)
Grade 2	1 (0.7)	0	1 (0.4)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**0**	**0**	**0**
Participants with any study drug related TE-SAE, n (%)	**0**	**0**	**0**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	0	0	0
TEAEs Leading to Dose Reduction	0	0	0
TEAEs Leading to Study Drug Discontinuation[a]	0	0	0
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	0	0	0
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	0	0

Abbreviations: AESI = adverse event of special interest; BendaR = bendamustine plus rituximab; n = number of participants within category; N = number of participants in population; TE-SAE = treatment-emergent-serious adverse event; TEAE = treatment-emergent adverse event.

a Deaths due to adverse events are included.

b Subcategory of bleeding.

Data cutoff: 11 July 2025

In the pirtobrutinib Arm the most common bleeding event reported in at least 5% of participants was contusion. One participant (0.7%) experienced one SAE Grade 3 of haematoma.

In the BendaR Arm 2 participants (1.5%) reported 2 nonserious, non-treatment-related AESI of bleedings (Grade 2 conjunctival haemorrhage, and Grade 1 eye haemorrhage). Events, greater than or equal to Grade 3 of bleeding were not reported.

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In the Pirtobrutinib Arm, the most common any grade bleedings AESIs reported in at least 5% of participants were contusion (10.0%) and haematuria (6.7%).

In the Ibrutinib Arm, the most common any grade bleedings AESIs reported in at least 5% of participants were contusion (9.2%), petechiae (6.5%), haematuria (5.5%), haematoma (5.5%), and epistaxis (5.5%).

There were two Grade 5 bleedings AESIs, both in the Pirtobrutinib Arm and both considered as non-treatment related. **Table 41** summarises the bleedings AESIs observed in Study 20030.

Table 41. Summary of Bleeding Including Bruising, Petechiae and Purpura, and Haemorrhage AESI Study 20030 Safety Population

	Arm A Pirtobrutinib N=330	**Arm B Ibrutinib N=325**	**Total N=655)**
Bleeding			
Participants with any TEAEs, n (%)	**115 (34.8)**	**118 (36.3)**	**233 (35.6)**
Highest Grade, n (%)			
Grade 1	76 (23.0)	85 (26.2)	161 (24.6)
Grade 2	28 (8.5)	24 (7.4)	52 (7.9)
Grade 3	7 (2.1)	6 (1.8)	13 (2.0)
Grade 4	2 (0.6)	1 (0.3)	3 (0.5)
Grade 5	2 (0.6)	2 (0.6)	4 (0.6)
Participants with any study drug related TEAEs, n (%)	**82 (24.8)**	**94 (28.9)**	**176 (26.9)**
Highest Grade, n (%)			
Grade 1	57 (17.3)	72 (22.2)	129 (19.7)
Grade 2	21 (6.4)	18 (5.5)	39 (6.0)
Grade 3	3 (0.9)	3 (0.9)	6 (0.9)
Grade 4	1 (0.3)	1 (0.3)	2 (0.3)
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**11 (3.3)**	**10 (3.1)**	**21 (3.2)**
Participants with any study drug related TE-SAE, n (%)	**3 (0.9)**	**5 (1.5)**	**8 (1.2)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	18 (5.5)	14 (4.3)	32 (4.9)
TEAEs Leading to Dose Reduction	2 (0.6)	6 (1.8)	8 (1.2)
TEAEs Leading to Study Drug Discontinuation[a]	2 (0.6)	3 (0.9)	5 (0.8)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	15 (4.5)	9 (2.8)	24 (3.7)
Study Drug Related TEAEs Leading to Dose Reduction	1 (0.3)	5 (1.5)	6 (0.9)
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	2 (0.6)	2 (0.3)
Hemorrhage[b]			
Participants with any TEAEs, n (%)	78 (23.6)	81 (24.9)	159 (24.3)
Highest Grade, n (%)			
Grade 1	44 (13.3)	56 (17.2)	100 (15.3)
Grade 2	23 (7.0)	16 (4.9)	39 (6.0)
Grade 3	7 (2.1)	6 (1.8)	13 (2.0)
Grade 4	2 (0.6)	1 (0.3)	3 (0.5)
Grade 5	2 (0.6)	2 (0.6)	4 (0.6)

	Arm A Pirtobrutinib N=330	Arm B Ibrutinib N=325	Total N=655)
Participants with any study drug related TEAEs, n (%)	**42 (12.7)**	**61 (18.8)**	**103 (15.7)**
Highest Grade, n (%)			
Grade 1	22 (6.7)	44 (13.5)	66 (10.1)
Grade 2	16 (4.8)	13 (4.0)	29 (4.4)
Grade 3	3 (0.9)	3 (0.9)	6 (0.9)
Grade 4	1 (0.3)	1 (0.3)	2 (0.3)
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**11 (3.3)**	**10 (3.1)**	**21 (3.2)**
Participants with any study drug related TE-SAE, n (%)	**3 (0.9)**	**5 (1.5)**	**8 (1.2)**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	15 (4.5)	13 (4.0)	28 (4.3)
TEAEs Leading to Dose Reduction	2 (0.6)	6 (1.8)	8 (1.2)
TEAEs Leading to Study Drug Discontinuation[a]	2 (0.6)	3 (0.9)	5 (0.8)
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	12 (3.6)	8 (2.5)	20 (3.1)
Study Drug Related TEAEs Leading to Dose Reduction	1 (0.3)	5 (1.5)	6 (0.9)
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	2 (0.6)	2 (0.3)
Bruising[b]			
Participants with any TEAEs, n (%)	**45 (13.6)**	**39 (12.0)**	**84 (12.8)**
Highest Grade, n (%)			
Grade 1	38 (11.5)	31 (9.5)	69 (10.5)
Grade 2	7 (2.1)	8 (2.5)	15 (2.3)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with any study drug related TEAEs, n (%)	**38 (11.5)**	**28 (8.6)**	**66 (10.1)**
Highest Grade, n (%)			
Grade 1	32 (9.7)	23 (7.1)	55 (8.4)
Grade 2	6 (1.8)	5 (1.5)	11 (1.7)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**0**	**0**	**0**
Participants with any study drug related TE-SAE, n (%)	**0**	**0**	**0**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	2 (0.6)	1 (0.3)	3 (0.5)
TEAEs Leading to Dose Reduction	0	0	0
TEAEs Leading to Study Drug Discontinuation[a]	0	0	0
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	2 (0.6)	1 (0.3)	3 (0.5)
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0

	Arm A Pirtobrutinib N=330	Arm B Ibrutinib N=325	Total N=655)
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	0	0
Petechiae and Purpura[b]			
Participants with any TEAEs, n (%)	**17 (5.2)**	**25 (7.7)**	**42 (6.4)**
Highest Grade, n (%)			
Grade 1	15 (4.5)	22 (6.8)	37 (5.6)
Grade 2	2 (0.6)	3 (0.9)	5 (0.8)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with any study drug related TEAEs, n (%)	**15 (4.5)**	**21 (6.5)**	**36 (5.5)**
Highest Grade, n (%)			
Grade 1	13 (3.9)	18 (5.5)	31 (4.7)
Grade 2	2 (0.6)	3 (0.9)	5 (0.8)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Participants with TE-SAE, n (%)	**0**	**0**	**0**
Participants with any study drug related TE-SAE, n (%)	**0**	**0**	**0**
Number of Participants with, n (%)			
TEAEs Leading to Dose Hold	1 (0.3)	0	1 (0.2)
TEAEs Leading to Dose Reduction	0	0	0
TEAEs Leading to Study Drug Discontinuation[a]	0	0	0
Number of Participants with, n (%)			
Study Drug Related TEAEs Leading to Dose Hold	1 (0.3)	0	1 (0.2)
Study Drug Related TEAEs Leading to Dose Reduction	0	0	0
Study Drug Related TEAEs Leading to Study Drug Discontinuation[a]	0	0	0

Abbreviations: AESI = adverse event of special interest; n = number of participants within category; N = number of participants in population; TE-SAE = treatment-emergent-serious adverse event; TEAE = treatment-emergent adverse event.

[a] Deaths due to adverse events are included.

[b] Subcategory of Bleeding.

Data cutoff: 10 June 2025

Pretreated Safety Population

Bleeding of any grade were reported at a similar frequency in Arm A (68 participants [31.2%]) and Arm B (71 participants [32.9%]).

Most of the bleeding events were Grade 1 or 2 in either treatment arm.

Grade 3 or 4 bleeding and treatment-related Grade 3 or 4 bleeding were reported at a similar frequency in Arm A (4 participants [1.8%] and 2 participants [0.9%], respectively) and Arm B (7 participants [3.2%] and 4 participants [1.9%], respectively).

SAEs of bleeding and treatment-related SAEs of bleeding were reported at a similar frequency in Arm A (6 participants [2.8%] and 1 participant [0.5%], respectively) and Arm B (9 participants [4.2%] and 4 participants [1.9%], respectively).

Grade 5 Bleeding was reported by 2 participants (0.9%) in each treatment arm, and all instances were considered not treatment related.

Treatment naïve safety population

Any grade bleedings AESIs occurred with a similar frequency in the Pirtobrutinib Arm (47 participants, 42%) and the Ibrutinib Arm (47 participants, 43.1%).

Grade 3 or Grade 4 bleedings occurred with a higher frequency in the pirtobrutinib Arm (5 participants, 4.5%) compared to the ibrutinib Arm (no events reported).

Serious bleedings occurred with a higher frequency in the pirtobrutinib Arm (5 participants, 4.5%) compared to the ibrutinib Arm (1 participant, 0.9%).

No fatal bleeding occurred in either arm.

Integrated safety set

Bleedings occurred in 397 participants (34.4%); treatment-related bleeding occurred in 245 participants (21.2%), and Grade 3 or Grade 4 bleeding occurred in 32 participants (2.8%). Serious bleeding occurred in 34 participants (2.9%). There were 4 participants (0.3%) who had a fatal bleeding event. None of the fatal bleeding events was considered related to pirtobrutinib treatment. Most of bleedings were mucocutaneous bleedings of Grade 1 or Grade 2.

Atrial Fibrillation and Atrial Flutter

Study 20023

Participants with a past medical history for atrial fibrillation or atrial flutter were included in Study 20023 (Baseline rates for atrial fibrillation: Pirtobrutinib Arm: 4.3%, BendaR Arm: 3.8%; baseline rates for atrial flutter: BendaR Arm: 1.5%).

Atrial fibrillation of any grade occurred in 2 participants in the Pirtobrutinib Arm and in 2 participants in the BendaR Arm (1.4% and 1.5%, respectively). After adjusting for exposure, the incidence rate was 0.5 per 100 PY in the Pirtobrutinib Arm and 3.3 per 100 PY in the BendaR Arm.

Study 20030

Atrial fibrillation and Atrial flutter of any grade were reported at a lower frequency in Arm A (8 participants [2.4%]) compared to Arm B (44 participants [13.5%]). Most of the atrial fibrillation and atrial flutter were Grade 2 or 3 in each treatment arm.

Grade 3 or 4 atrial fibrillation and atrial flutter and treatment-related Grade 3 or 4 atrial fibrillation and atrial flutter were reported at a lower frequency in Arm A (3 participants [0.9%] and 0 participants [0.0%], respectively) compared to Arm B (12 participants [3.7%] and 11 participants [3.4%], respectively).

In Arm A, most of the AESI of Atrial fibrillation and Atrial flutter were managed without dose modification, and no discontinuations of study drug or Grade 5 events were reported. In Arm B, 5 treatment-related discontinuations of study drug were reported, and 1 treatment-related Grade 5 event was reported.

<u>Pretreated Safety Population</u>

Atrial fibrillation of any grade were reported at a lower frequency in Arm A (3 participants [1.4%]) compared to Arm B (22 participants [10.2%]). Grade 3 and 4 atrial fibrillation and atrial flutter were

reported by 1 participant (0.5%) in Arm A and 7 participants (3.2%) in Arm B. No treatment-related Grade 3 and 4 atrial fibrillation and atrial flutter I were reported in Arm A. Treatment-related Grade 3 and 4 atrial fibrillation and atrial flutter were reported by 6 participants (2.8%) in Arm B.

In Arm A, most AESI were managed without dose modification, and no discontinuations or Grade 5 events were reported. In Arm B, 2 treatment-related discontinuations of study drug were reported, and 1 treatment-related Grade 5 atrial fibrillation and atrial flutter was reported.

Treatment naïve safety population

Medical history of atrial fibrillation was reported in 6 participants (5.4%) in the pirtobrutinib Arm and in 5 participants (4.6%) in the ibrutinib Arm.

Any grade atrial fibrillation occurred with a lower frequency in the pirtobrutinib Arm (5 participants, 4.5%) compared to the ibrutinib Arm (22 participants, 20.2%). Treatment-related atrial fibrillation of any grade occurred with a lower frequency in the pirtobrutinib Arm (3 participants, 2.7%) compared to the ibrutinib Arm (20 participants, 18.3%).

Serious atrial fibrillation occurred in 1 participant (0.9%) in the pirtobrutinib Arm and in 3 participants (2.8%) in the ibrutinib Arm.

Integrated safety set

Atrial fibrillation and atrial flutter occurred in 36 participants (3.1%); treatment-related atrial fibrillation and atrial flutter occurred in 14 participants (1.2%), and Grade 3 or Grade 4 atrial fibrillation or atrial flutter occurred in 18 participants (1.6%). Serious atrial fibrillation and atrial flutter occurred in 13 participants (1.1%). None of the participants experienced a fatal atrial fibrillation or atrial flutter event.

Cytopenias Including Neutropenia, Anaemia, and Thrombocytopenia

Study 20023

The predominant cytopenia reported in both arms was neutropenia, followed by anaemia in the Pirtobrutinib Arm and by thrombocytopenia in the BendaR Arm.

Neutropenia

Neutropenia of any grade occurred with a lower frequency in the pirtobrutinib Arm (21 participants, 15%) compared to the BendaR Arm (68 participants, 51.5%). Grade 3 or Grade 4 neutropenia occurred with a lower frequency in the pirtobrutinib Arm (13 participants, 9.3%) compared to the BendaR Arm (60 participants, 45.5%). SAEs occurred with a lower frequency in the pirtobrutinib Arm (2 participants, 1.4%) compared to the BendaR Arm (7 participants, 5.3%). Most of the neutropenia were manageable without dose adjustments in the pirtobrutinib Arm and were a maximum of Grade 3 or Grade 4 in each treatment arm.

Anaemia

Anaemia of any grade occurred with a similar frequency in the pirtobrutinib Arm (14 participants, 10.0%) compared to the BendaR Arm (21 participants,15.9%). Anaemia of Grade 3 or Grade 4 occurred with a similar frequency in the pirtobrutinib Arm (6 participants, 4.3%) compared to BendaR Arm (10 participants, 7.6%). SAEs occurred with a similar frequency in the pirtobrutinib Arm (3 participants, 2.1%) compared to the BendaR Arm (4 participants, 3.0%). Most of the anaemia were manageable without dose adjustments and were Grade 1 or Grade 2 in each treatment arm.

Thrombocytopenia

Thrombocytopenia of any grade occurred with lower frequency in the pirtobrutinib Arm (12 participants, 8.6%) compared to the BendaR Arm (23 participants, 17.4%). Grade 3 or Grade 4 thrombocytopenia occurred with a similar frequency in the pirtobrutinib Arm (4 participants, 2.9%) and the BendaR Arm (9 participants, 6.8%). Most of the thrombocytopenia were manageable without dose adjustments and were Grade 1 or Grade 2 in each treatment arm. No SAEs of thrombocytopenia occurred in the pirtobrutinib Arm. One participant (0.8%) reported a treatment-related SAE of thrombocytopenia in the BendaR Arm.

Study 20030

Neutropenia

Neutropenia AESIs of any grade and Grade 3 or Grade 4 occurred with a higher frequency in the Pirtobrutinib Arm (31.2% and 25.1%, respectively) compared to the Ibrutinib Arm (23.4% and 17.5%, respectively). SAEs of neutropenia occurred in 1.5% of participants in each arm. Most neutropenia AESIs were Grade 3 or Grade 4 in either treatment arm.

Anaemia

Anaemia of any grade occurred with a similar frequency in the Pirtobrutinib Arm and the Ibrutinib Arm (15.5% and 15.7%, respectively). Most of the anaemia were Grade 1 or 2 in either treatment arm. Anaemia of Grade 3 or Grade 4 and SAEs of anaemia occurred in 6.1% and 2.1% of participants, respectively in the Pirtobrutinib Arm, and in 3.7% and 0.3% of participants, respectively, in the Ibrutinib Arm.

Thrombocytopenia

Thrombocytopenia of any grade occurred with a lower frequency in the pirtobrutinib Arm (11.8%) compared to the ibrutinib Arm (17.5%). Most of the thrombocytopenia were Grade 1 or Grade 2 in either treatment arm. Thrombocytopenia s of Grade 3 or Grade 4 occurred with a similar frequency in the pirtobrutinib Arm (3.6%) and the ibrutinib Arm (4.0%). SAEs of thrombocytopenia were only reported in the Ibrutinib Arm (1.4%). No Grade 5 thrombocytopenia occurred in either arm.

Pretreated Safety Population

Neutropenia of any grade were reported at a higher frequency in Arm A (78 participants [35.8%]) than in Arm B (55 participants [25.5%]). Grade 3 or 4 neutropenia and treatment-related Grade 3 or 4 neutropenia were reported at a higher frequency in Arm A (62 participants [28.4%] and 48 participants [22.0%], respectively) compared to Arm B (43 participants [19.9%] and 35 participants [16.2%], respectively). SAEs of neutropenia were reported by 4 participants (1.8%) in Arm A and 3 participants (1.4%) in Arm B. Treatment-related SAEs of neutropenia were reported by 4 participants (1.8%) in Arm A and 2 participants (0.9%) in Arm B.

Anaemia of any grade were reported at a similar frequency in Arm A (32 participants [14.7%]) and Arm B (31 participants [14.4%]). Grade 3 or 4 anaemia were reported at a similar frequency in Arm A (14 participants [6.4%]) and Arm B (9 participants [4.2%]). Treatment-related Grade 3 or 4 AESI of Anaemia were reported at a higher frequency in Arm A (12 participants [5.5%]) compared to Arm B (3 participants [1.4%]). SAEs of anaemia were reported by 4 participants (1.8%) in Arm A. Treatment-related SAEs of anaemia were reported by 3 participants (1.4%) in Arm A. No SAEs of anaemia were reported in Arm B.

Thrombocytopenia of any grade were reported in a lower frequency in Arm A (29 participants [13.3%]) compared to Arm B (42 participants [19.4%]). Grade 3 or 4 thrombocytopenia were reported at a similar

frequency in Arm A (11 participants [5.0%]) and Arm B (10 participants [4.6%]). Treatment-related Grade 3 or 4 of thrombocytopenia were reported by 5 participants (2.3%) in Arm A and 9 participants (4.2%) in Arm B. No SAEs of thrombocytopenia were reported in Arm A. SAEs of thrombocytopenia were reported by 3 participants (1.4%) in Arm B. Treatment-related SAEs of thrombocytopenia were reported by 2 participants (0.9%) in Arm B.

Treatment naïve safety population

Neutropenia of any grade occurred with a similar frequency in the Pirtobrutinib Arm (25 participants, 22.3%) and the Ibrutinib Arm (21 participants, 19.3%).

Neutropenia of Grade 3 or Grade 4 occurred with a higher frequency in the pirtobrutinib Arm (21 participants, 18.7%) compared to the ibrutinib Arm (14 participants, 12.8%).

SAEs of neutropenia occurred with a similar frequency in the pirtobrutinib Arm (1 participant, 0.9%) and the Ibrutinib Arms (2 participants, 1.8%).

Anaemia of any grade occurred with a similar frequency in the pirtobrutinib Arm (19 participants, 17%) and the ibrutinib Arm (20 participants, 18.3%).

Grade 3 or Grade 4 anaemia occurred with a higher frequency in pirtobrutinib Arm (6 participants, 5.4%) compared to the ibrutinib Arm (3 participants, 2.8%).

Serious anaemia occurred with a higher frequency in the pirtobrutinib Arm (3 participants, 2.7%) compared to the ibrutinib Arm (1 participant, 0.9%).

Thrombocytopenia of any grade occurred with a lower frequency in the pirtobrutinib Arm (10 participants, 8.9%) compared to the ibrutinib Arm (15 participants, 13.8%).

Thrombocytopenia of Grades 3 or Grade 4 occurred with a lower frequency in the pirtobrutinib Arm (1 participants, 0.9%) compared to the ibrutinib Arm (3 participants, 2.7%).

Integrated safety set

Neutropenia occurred in 316 participants (27.4%). Treatment-related neutropenia occurred in 227 participants (19.7%), and Grade 3 or Grade 4 neutropenia occurred in 263 participants (22.8%). Serious neutropenia occurred in 30 participants (2.6%). None of the participants experienced a fatal neutropenia event.

Anaemia occurred in 212 participants (18.4%). Treatment-related anaemia occurred in 83 participants (7.2%), and Grade 3 or Grade 4 anaemia occurred in 104 participants (9.0%). Serious anaemia occurred in 28 participants (2.4%). None of the participants experienced a fatal anaemia event.

Thrombocytopenia occurred in 170 participants (14.7%). Treatment-related thrombocytopenia occurred in 75 participants (6.5%), and Grade 3 or Grade 4 thrombocytopenia occurred in 83 participants (7.2%). Serious thrombocytopenia occurred in 6 participants (0.5%). None of the participants experienced a fatal thrombocytopenia event.

Adverse Events of Potential Clinical Significance

Adverse Events of Potential Clinical Significance (AEPCS) do not necessarily represent known on-target safety risks of the BTKi drug class but are potentially clinically significant based on general risks associated with anticancer treatment in this patient population, or on-target effects of the BTKi drug class that are potential, but not identified, risks. Aggregate analysis was conducted as part of the analysis of AEPCS and included the following composite terms: ventricular tachyarrhythmias (VT),

supraventricular tachyarrhythmias (SVT), cardiac failure, hypertension, second primary malignancies, Tumour lysis syndrome (TLS), lymphocytosis, and rash

Ventricular Tachyarrhythmias (VT)

Study 20023

Ventricular tachyarrhythmias of any grade occurred in 3 participants (2.1%) in the Pirtobrutinib Arm but not in the BendaR Arm.

Treatment-related events of any grade were reported by 2 participants (1.4%) in Arm A and included Ventricular extrasystoles (2 participants [1.4%]) and Ventricular arrhythmia (1 participant [0.7%]). There were no Grade 3 or higher VT, SAEs, or discontinuation due to VT.

Study 20030

Any grade VT occurred with a lower frequency in the pirtobrutinib Arm (7 participants, 2.1%) compared to the ibrutinib Arm (12 participants, 3.7%). All VT in the pirtobrutinib Arm were ventricular extrasystoles. Most participants experienced nonserious, treatment-related, Grade 1 or Grade 2 events, except for 1 participant who experienced a treatment-related Grade 3 SAE. No Grade 4 or 5 events occurred in the pirtobrutinib Arm.

In the ibrutinib Arm, most participants experienced nonserious, treatment-related Grade 1 or Grade 2 ventricular extrasystoles. One participant experienced a Grade 5 treatment-related SAE of ventricular fibrillation, and 1 participant had a Grade 1, treatment-related, nonserious event of ventricular arrhythmia.

Pretreated Safety Population

VT of any grade were reported at a lower frequency in Arm A (4 participants [1.8%]), compared to Arm B (8 participants [3.7%]). Treatment-related events of any grade were reported by 3 participants (1.4%) in Arm A and 8 participants (3.7%) in Arm B.

In Arm A, all events were of ventricular extrasystoles. Except for one participant who reported a treatment-related event with maximum severity of Grade 3, most participants experienced non-serious, and Grade 1 or 2 events. No Grade 4 or 5 events were reported in Arm A.

In Arm B, except for one participant with Grade 5 treatment-related SAE of ventricular fibrillation, most participants reported ventricular extrasystoles. Most participants experienced non-serious, and Grade 1 or 2 events that were considered treatment related. No Grade 3 or 4 events were reported in Arm B.

Treatment naïve safety population

Any grade VT occurred with a similar frequency in the pirtobrutinib Arm (3 participants, 2.7%) and the ibrutinib Arm (4 participants, 3.7%).

In the pirtobrutinib Arm, all events of VT were reported as ventricular extrasystoles. In the ibrutinib Arm, 2 events were reported as ventricular arrhythmia, and 2 as ventricular extrasystoles. In both arms, all events were Grade 1 or Grade 2 and did not require dose adjustments. No SAEs or discontinuations occurred in either treatment arm.

VT occurred in 18 participants (1.6%). Treatment-related VT occurred in 11 participants (1.0%), and Grade 3 or Grade 4 VT occurred in 1 participant (0.1%). Serious VT occurred in 1 participant (0.1%). None of the participants experienced a fatal VT event. Most of the VT were ventricular extrasystoles.

Integrated safety set

VT occurred in 18 participants (1.6%). Treatment-related VT occurred in 11 participants (1.0%), and Grade 3 or Grade 4 VT occurred in 1 participant (0.1%). Serious VT occurred in 1 participant (0.1%). None of the participants experienced a fatal VT event. Most of the VT were ventricular extrasystoles.

Supraventricular Tachyarrhythmias (SVT) excluding Atrial Fibrillation and Atrial Flutter

Study 20023

In the pirtobrutinib Arm, 6 participants (4.3%) experienced 6 non-serious events of supraventricular tachyarrhythmias (4 supraventricular extrasystoles, 1 arrhythmia supraventricular and 1 sinus tachycardia). Of these, 5 events of SVT were Grade 1 (3 related, 2 not related) and one was Grade 2 and treatment related. SAEs, events greater than or equal to Grade 3, dose adjustments, and treatment discontinuations were not reported.

In the BendaR Arm, no events of SVT occurred.

Study 20030

SVT of any grade occurred with at a similar frequency in the pirtobrutinib Arm (6 participants, 1.8%) and the ibrutinib Arm (7 participants, 2.2%).

In the pirtobrutinib Arm, 6 participants (1.8%) experienced 11 events of SVT. Five participants experienced sinus node (n=2), sinus tachycardia (n=1), supraventricular tachyarrhythmia (n=1), and supraventricular extrasystoles (n=1). One participant experienced 6 recurrent events of supraventricular extrasystoles. Most of the events were nonserious and Grade 1 or Grade 2. Dose adjustments or discontinuations were not reported.

In the ibrutinib Arm, 7 participants (2.2%) experienced 9 events of SVT. Three participants experienced 5 events: supraventricular extrasystoles (n=2), atrial tachycardia (n=1), arrhythmia supraventricular (n=1), nodal arrhythmia (n=1). The remaining 4 participants experienced 1 event of supraventricular extrasystole each. All events were nonserious and Grade 1 or Grade 2. Dose adjustments occurred in 3 participants. No drug discontinuations occurred.

Pretreated Safety

SVT occurred in 2 participants (0.9%) in each treatment arm. These events were Grade 1 or 2, not treatment related, and managed without dose modifications and discontinuations

Treatment naïve safety population

SVT and treatment-related SVT occurred with a similar frequency in the pirtobrutinib Arm (4 participants, 3.6% and 3 participants, 2.7%, respectively) and the ibrutinib Arm (5 participants, 4.6% and 2 participants, 1.8%, respectively). All events were nonserious Grade 1 or Grade 2.

Integrated safety set

SVT occurred in 40 participants (3.5%). Treatment-related SVT occurred in 9 participants (0.8%), and Grade 3 or Grade 4 SVT occurred in 5 participants (0.4%). Serious SVT occurred in 4 participants (0.3%). Most of the events were nonserious and Grade 1 or Grade 2.

Cardiac Failure

Study 20023

Cardiac failure of any grade occurred with a similar frequency in the pirtobrutinib Arm (2 participants, 1.4%) compared to the BendaR Arm (1 participant, 0.8%). Exposure adjusted incidence rates were 0.5 per 100 PY in the Pirtobrutinib Arm and 1.7 per 100 PY in the BendaR Arm.

Treatment-related of cardiac failure of any grade were reported by 2 participants (1.4%) in Arm A. Grade 3 or 4 of cardiac failure were reported by 2 participants (1.4%) in Arm A. One of the participants had more than 1 event of Cardiac failure reported, including a Grade 2 event considered related and a Grade 3 not treatment-related event months later. No treatment-related Grade 3 or 4 events were reported in Arm B. One participant (0.8%) reported a SAE of cardiac failure in Arm B, but it was not considered treatment related. Cardiac failure leading to dose reduction and dose discontinuation were reported by 1 participant each in Arm A. There were no events leading to dose modification in Arm B. No Grade 5 events were reported in either treatment arm.

Study 20030

Cardiac failure of any grade was reported at a lower frequency in Arm A (5 participants [1.5%], with no treatment-related events), compared to Arm B (9 participants, [2.8%], 3 of 9 with treatment-related events). Grade 3 or 4 cardiac failure was reported at a similar frequency in Arm A (2 participants [0.6%]) and Arm B (1 participant, [0.3%]). No treatment-related Grade 3 or 4 events were reported in either treatment arm. SAEs of cardiac failure were reported at a higher frequency in Arm A (3 participants [0.9%], with no treatment-related events, compared to Arm B (1 participant, [0.3%] with at least 1 treatment-related event).

In Arm A, most participants that reported events of cardiac failure reported events that were serious (3 in 5) and Grade 1 or 2 (3 in 5). No treatment-related events were reported. Most reported events were not associated with dose holds (4 in 5). No Grade 4 or 5 events of Cardiac failure, dose reductions, or discontinuations were reported.

In Arm B, most participants that reported events of cardiac failure reported events that were non-serious (8 in 9), Grade 1 or 2 (8 in 9), and not treatment related (6 in 9). Most reported events of were not associated with dose hold (7 in 9) and not associated with discontinuations (8 in 9). No dose reductions were reported.

In the ibrutinib Arm, all events were nonserious, mainly Grade 1 or Grade 2, and did not require dose holds, reductions, or discontinuations.

<u>Pretreated safety population</u>

Cardiac failure of any grade was reported at a lower frequency in Arm A (2 participants [0.9%]) than Arm B (5 participants [2.3%]). No treatment-related events of any grade were reported in Arm A. Treatment-related cardiac failure of any grade was reported by 2 participants (0.9%) in Arm B. SAEs of cardiac failure were reported by 2 participants (0.9%) in Arm A and by 1 participant (0.5%) in Arm B. Treatment-related SAEs of cardiac failure were reported by 1 participant (0.5%) in Arm B. No Grade 4 or 5 events were reported in either treatment arm.

In Arm A, 2 participants reported non-treatment-related SAEs (1 Grade 2, 1 Grade 3) of Cardiac failure. No dose holds, dose reductions, or discontinuations were reported.

In Arm B, most events of Cardiac failure were non-serious (4 in 5), all were Grade 1 or 2, and most were not treatment related (3 in 5). One participant reported a dose hold (1 in 5). No dose reductions or discontinuations were reported.

Treatment naïve safety population

Cardiac failure of any grade occurred with a similar frequency in the pirtobrutinib Arm (3 participants, 2.7%) and the ibrutinib Arm (4 participants, 3.7%). No treatment-related events of any grade cardiac failure occurred in the pirtobrutinib Arm. Treatment-related events of any grade cardiac failure occurred in 1 participant (0.9%) in the Ibrutinib Arm, resulting in discontinuation of study treatment. Most of the events of cardiac failure were nonserious, Grade 1 or Grade 2, and did not require dose adjustments. No Grade 5 events occurred in either treatment arm.

Integrated safety set

Cardiac failure occurred in 21 participants (1.8%). Treatment-related cardiac failures occurred in 6 participants (0.5%), and Grade 3 or Grade 4 cardiac failure occurred in 14 participants (1.2%). Serious cardiac failure occurred in 12 participants (1.0%). None of the participants experienced a fatal cardiac failure

Hypertension

Study 20023

Hypertension of any grade occurred with a higher frequency in the Pirtobrutinib Arm (14 participants, 10.0%) compared to the BendaR Arm (6 participants, 4.5%). After adjusting for exposure, the incidence rate was 4.1 per 100 PY in the Pirtobrutinib Arm and 10.2 per 100 PY in the BendaR Arm. Hypertension is not unexpected in an elderly and predominantly male population and medical history of hypertension was reported in 39.7% of participants in the Pirtobrutinib Arm and in 49.6% of participants in the BendaR Arm.

In the pirtobrutinib Arm, 8 participants (5.7%) experienced hypertension events of Grade 1 or Grade 2 (6 treatment related) and 6 participants (4.3%) experienced events of Grade 3 (1 treatment related). All hypertension AEPCS were nonserious.

In the BendaR Arm, 2 participants (1.6%) experienced hypertension AEPCS of Grade 1 or Grade 2 (1 treatment related) and 4 participants (3.0%) experienced events of Grade 3 (all non-treatment-related). All hypertension AEPCS were nonserious. Grade 4 or Grade 5 events, dose adjustments, or study drug discontinuations were not reported.

Study 20030

Medical history of hypertension was reported in 44.5% and 46.5% of the participants in the Pirtobrutinib Arm and the Ibrutinib Arms, respectively.

Any grade hypertension occurred with a lower frequency in the Pirtobrutinib Arm (36 participants, 10.9%) compared to the Ibrutinib Arm (55 participants, 16.9%).

In the pirtobrutinib Arm, 12 participants (3.6%) had Grade 3 hypertension, including 7 participants (2.1%) with Grade 3 treatment-related events. Most of the events did not require dose adjustments. SAEs, Grade 5 events, and study drug discontinuations were not reported.

In the ibrutinib Arm, 20 participants (6.2%) experienced Grade 3 hypertension, including 15 participants (4.6%) with Grade 3 treatment-related events. Most of the events did not require dose adjustments. SAEs, Grade 5 events, and study drug discontinuations were not reported.

<u>Pretreated safety population</u>

Hypertension of any grade were reported in a lower frequency in Arm A (20 participants [9.2%]) compared to Arm B (30 participants [13.9%]). Treatment-related hypertension of any grade were reported at a similar frequency in Arm A (13 participants [6.0%]) and Arm B (20 participants [9.3%]).

Grade 3 or 4 events of hypertension were reported at the same frequency (6 participants [2.8%]) in each treatment arm. Treatment-related Grade 3 events of hypertension were reported at a similar frequency in Arm A (5 participants [2.3%]) and Arm B (4 participants [1.9%]). No SAEs or Grade 4 or 5 events of hypertension were reported in either treatment arm. Dose hold was reported in 2 participants (0.9%) in each treatment arm. Dose reduction was reported in 1 participant (0.5%) in Arm A. Drug discontinuations were not reported in either treatment arm.

Treatment naïve safety population

Medical history of hypertension was reported in 49 participants (43.8%) in the pirtobrutinib Arm and in 55 participants (50.5%) in the ibrutinib Arm.

Any grade hypertension occurred with a lower frequency in the pirtobrutinib Arm (16 participants, 14.2%) compared to the ibrutinib Arm (25 participants, 22.9%). Treatment related hypertension occurred with a lower frequency in the pirtobrutinib Arm (7 participants, 6.3%) compared to the ibrutinib Arm (17 participants, 15.6%).

In the pirtobrutinib Arm, 10 participants (9.0%) experienced Grade 1 or Grade 2 hypertension, and 6 participants (5.4%) experienced Grade 3 events. Most participants (9 out of 16) experienced non-treatment-related events. No SAEs, Grade 4 or Grade 5 events, dose adjustments, or discontinuations occurred.

In the ibrutinib Arm, 11 participants reported Grade 1 or Grade 2 hypertension, and 14 participants experienced Grade 3 events. Most participants (17 out of 25) experienced treatment-related events. SAEs, Grade 4 and Grade 5 events, and discontinuations were not reported.

Integrated safety set

Hypertension occurred in 130 participants (11.3%). Treatment-related hypertension occurred in 52 participants (4.5%), and Grade 3 or Grade 4 hypertension occurred in 47 participants (4.1%). None of the participants experienced serious or fatal hypertension.

Second Primary Malignancy

Study 20023

Second Primary Malignancy Non-Melanoma Skin Cancer

Second primary malignancy non-melanoma skin cancer of any grade occurred in 8 participants (5.7%) in the Pirtobrutinib Arm and in 2 participants (1.5%) in the BendaR Arm. After adjusting for exposure, the incidence rate was 2.3 per 100 PY in the Pirtobrutinib Arm and 3.3 per 100 PY in the BendaR Arm. Treatment-related events of SPM non-melanoma skin cancer occurred in 3 participants (2.1%) in the Pirtobrutinib Arm and in no participant in the BendaR Arm.

Medical history of basal cell carcinoma was reported in 2.1% of participants in the Pirtobrutinib Arm and in 0.8% of participants in the BendaR Arm. Medical history of squamous cell carcinoma was reported in 0.7% of participants in the BendaR Arm.

In the Pirtobrutinib Arm, 8 participants experienced 21 events of non-melanoma skin cancer:

- 13 events of basal cell carcinoma (4 treatment related and 9 non-treatment-related) and8 events of squamous cell carcinoma (all non-treatment-related) One participant experienced a serious, Grade 2, non-treatment-related event of basal cell carcinoma. No events Grade 3 or higher, dose adjustments, or study drug discontinuations occurred following a diagnosis of non-melanoma skin cancer.

In the BendaR Arm, 2 participants experienced 2 events of non-melanoma skin cancer:

- One participant experienced a Grade 2, nonserious, non-treatment-related event of basal cell carcinoma. The other participant experienced a Grade 3, nonserious, non-treatment-related event of squamous cell carcinoma. No Grade 4 or Grade 5 events, dose adjustments, or study drug discontinuations occurred.

Second Primary Malignancy Excluding Non-Melanoma Skin Cancer

In the Pirtobrutinib Arm, 6 participants (4.3%) experienced 6 events of SPM excluding non-melanoma skin cancer: prostate cancer (n=4), colon cancer (n=1), and rectal adenocarcinoma (n=1).

Three events were Grade 2 (1 treatment related) and 3 events were Grade 3 (all non-treatment related). Three SAEs occurred, of which 1 was considered treatment related. No Grade 4 or Grade 5 events, dose adjustments, or study drug discontinuations occurred.

No events of SPM excluding non-melanoma skin cancer occurred in the BendaR Arm.

Study 20030

Second Primary Malignancy Non-Melanoma Skin Cancer

SPM non-melanoma skin cancer of any grade occurred with a higher frequency in the pirtobrutinib Arm (14 participants, 4.2%) compared to the ibrutinib Arm (9 participants, 2.8%).

In the pirtobrutinib Arm, 14 participants experienced 15 events of non-melanoma skin cancer:

- 5 participants experienced 1 event of basal cell carcinoma
- 8 participants experienced 1 event of squamous cell carcinoma, and
- 1 participant experienced 2 events (1 basal cell carcinoma and 1 squamous cell carcinoma).

Most of the participants (13 out of 14) experienced Grade 1 or Grade 2 events (only 1 event was treatment related). One participant experienced a Grade 3 treatment-related event of squamous cell carcinoma. Two SAEs of squamous cell carcinoma (one Grade 1 and the other Grade 2) occurred. Both were non-treatment-related, but the Grade 2 SAE led to pirtobrutinib being withheld. In addition, pirtobrutinib was withheld for Grade 2, nonserious, non-treatment-related event of basal cell carcinoma. Grade 4 and Grade 5 events and discontinuations were not reported.

In the ibrutinib Arm, 9 participants experienced 11 events of non-melanoma skin cancer

- 3 participants experienced 1 basal cell carcinoma
- 4 participants experienced 1 squamous cell carcinoma, and
- 2 participants experienced 2 events (1 basal cell carcinoma and 1 squamous cell carcinoma).

Most of the participants (8 out of 9 participants) experienced Grade 1 or Grade 2 events (only 2 events were treatment related). One participant experienced one Grade 3, nonserious, non-treatment related event of basal cell carcinoma, and one Grade 2, serious, non-treatment-related event of squamous cell carcinoma. No Grade 4 and Grade 5 events, dose adjustments, and discontinuations occurred.

Second Primary Malignancy Excluding Non-Melanoma Skin Cancer

SPM excluding non-melanoma skin cancer of any grade occurred with a similar frequency in the pirtobrutinib Arm (12 participants, 3.6%) and the Ibrutinib Arm (9 participants, 2.8%).

In the pirtobrutinib Arm, 12 participants experienced 13 events of SPM excluding non-melanoma skin cancer. One participant experienced 2 events (pancreatic carcinoma and vulvar cancer). Most of the

events (8 out of 13) were maximum Grade 3 or Grade 4. Six participants experienced SAEs and 4 participants discontinued study drug. No Grade 5 events occurred.

SMP excluding non-melanoma skin cancer reported were: vulvar cancer (n=1), malignant melanoma (n=2), prostate cancer (n=1), adenocarcinoma of colon (n=1), invasive breast carcinoma (n=1), keratoacanthoma (n=1), laryngeal cancer (n=1), lung adenocarcinoma (n=1), lung neoplasm malignant (n=1), malignant melanoma stage 0 (n=1), pancreatic carcinoma (n=1), squamous cell carcinoma of the tongue (n=1).

In the ibrutinib Arm, 9 participants experienced 11 events of SPM excluding non-melanoma skin cancer. Most of the events (8 out of 11) were Grade 3 or Grade 4 and non-treatment-related (9 out of 11). Five participants experienced SAEs, and 2 participants discontinued study drug. No Grade 5 events occurred.

SMP excluding non-melanoma skin cancer reported were: prostate cancer (n=1), invasive breast carcinoma (n=1), acute erythroid leukaemia (n=1), Bowen´s disease (n=1), clear cell renal cell carcinoma (n=1), glioblastoma (n=1), neoplasm malignant (n=1), non-small cell lung cancer (n=1), squamous cell carcinoma of lung (n=1), transitional cell carcinoma (n=1), tubular breast carcinoma (n=1).

Pretreated Safety Population

SPM non-melanoma skin cancer of any grade were reported at a higher frequency in Arm A (8 participants [3.7%]) compared to Arm B (4 participants [1.9%]). Few participants reported treatment-related events (1 participant [0.5%] in each treatment Arm). In Arm A, most of the participants reported non-serious, non-treatment-related, and Grade 1 or 2 events. No Grade 4 or 5 events were reported in Arm A. In Arm B, all reported events were non-serious, most were non-treatment-related, and most were Grade 2 events. No Grade 4 or 5 events were reported in Arm B.

SPM excluding non-melanoma skin cancer of any grade were reported at a similar frequency in Arm A (4 participants [1.8%]) and Arm B (6 participants [2.8%]). No treatment-related events of any grade were reported in Arm A. Treatment-related events of any grade were reported by 1 participant (0.5%) in Arm B. In the pretreated safety population, second primary malignancy excluding non-melanoma skin cancer of Grade 3 and SAEs were reported at a similar frequency in Arm A (3 participants [1.4%] and 3 participants [1.4%], respectively) compared to Arm B (3 participants [1.4%] and 4 participants [1.9%], respectively). In Arm A, most of the participants reported serious (3 in 4), Grade 3 events (3 in 4) that were not treatment related. No Grade 4 or 5 events were reported. In Arm B, most of the participants reported serious (4 in 6), Grade 3 or 4 (5 in 6) events, most of which were not treatment related. No Grade 5 events were reported.

Treatment naïve safety population

Any grade SPM non-melanoma skin cancer occurred with a similar frequency in the pirtobrutinib Arm (6 participants, 5.4%) and the Ibrutinib Arm (5 participants, 4.6%).

In the pirtobrutinib Arm, all 6 participants experienced Grade 1 or Grade 2 events. Most participants (5 out of 6 participants) experienced nonserious and non-treatment-related events. Grade 3 and Grade 4 events, dose adjustments, and study drug discontinuation were not reported.

In the Ibrutinib Arm, all 5 participants experienced Grade 1 or Grade 2 events. Most participants (4 out of 5) experienced nonserious and non-treatment-related events. Grade 3 or Grade 4 events, dose adjustments, and study drug discontinuation were not reported.

No Grade 5 events occurred in either treatment arm.

SPM excluding non-melanoma skin cancer of any grade occurred with a higher frequency in the Pirtobrutinib Arm (8 participants, 7.1%) compared to the Ibrutinib Arm (3 participants, 2.8%).

In the pirtobrutinib Arm, 8 participants experienced 8 events of SPM excluding non-melanoma skin cancer (one Grade 1, two Grade 2, four Grade 3, and one Grade 4). Three SAEs occurred. All events were deemed non-treatment related. Dose holds or study drug discontinuations occurred in 3 and 4 participants, respectively.

SPM excluding non-melanoma skin cancer reported were prostate cancer (n=1), adenocarcinoma of colon (n=1), invasive breast carcinoma (n=1), keratoacanthoma (n=1), laryngeal cancer (n=1), lung adenocarcinoma (n=1), malignant melanoma stage 0 (n=1), and squamous cell carcinoma of the tongue (n=1).

In the ibrutinib Arm, 3 participants experienced 3 events of SPM excluding non-melanoma skin cancer (one Grade 1, one Grade 2, and one Grade 4). One participant reported a SAE. All events were non-treatment-related, and 1 discontinuation occurred.

SPM excluding non-melanoma skin cancer reported were Bowen's disease (n=1), glioblastoma (n=1), and neoplasm malignant (n=1).

No Grade 5 events occurred in either treatment arm.

Integrated safety set

Second primary malignancy non-melanoma skin cancer occurred in 57 participants (4.9%). Treatment-related SPM non-melanoma skin cancer occurred in 10 participants (0.9%), and Grade 3 or Grade 4 SPM non-melanoma skin cancer occurred in 8 participants (0.7%). Serious SPM non-melanoma skin cancer occurred in 10 participants (0.9%). One fatal SPM non melanoma skin cancer occurred. This event was considered non-treatment related.

SPM excluding non-melanoma skin cancer occurred in 62 participants (5.4%). Treatment-related SPM excluding non-melanoma skin cancer occurred in 2 participants (0.2%), and Grade 3 or Grade 4 SPM excluding non-melanoma skin cancer occurred in 27 participants (2.4%). Serious SPM excluding non-melanoma skin cancer occurred in 28 participants (2.4%). Two fatal events of SPM excluding non-melanoma skin cancer occurred. Both were considered non-treatment related.

Tumour Lysis Syndrome

Study 20023

In the pirtobrutinib Arm, TLS was not reported. In the BendaR Arm, 4 participants reported 4 events of TLS. Of these, 3 were treatment-related SAEs including 1 fatal event; 1 was a treatment-related nonserious Grade 2 event.

Study 20030

TLS of any grade occurred in 1 participant (0.3%) in each treatment arm.

In the pirtobrutinib Arm, 1 participant experienced one Grade 4 SAE considered as treatment related and associated with dose hold and reduction. No Grade 5 events or discontinuations occurred.

In the ibrutinib Arm, 1 participant experienced one Grade 4 SAE, which was considered non-treatment related. No Grade 5 events, dose adjustments, or discontinuations occurred.

Both events of TLS described in the safety population were from the pretreated safety population.

Lymphocytosis

Study 20023

In the pirtobrutinib Arm, 4 participants (2.9%) experienced AEPCS of lymphocytosis. All events were nonserious, Grade 3, treatment-related, and recovered. One of these 4 events was associated with drug hold. In the BendaR Arm, no events of lymphocytosis occurred.

Study 20030

Lymphocytosis of any grade occurred with a similar frequency in the pirtobrutinib Arm (12 participants, 3.6%) and the ibrutinib Arm (19 participants, 5.8%).

In the pirtobrutinib Arm, all participants had events of Grade 3, and most participants (11 out of 12) had treatment-related events. No SAEs, dose adjustment, or discontinuations occurred.

In the ibrutinib Arm, all participants reported events of Grade 3, and most participants (18 out of 19) had treatment-related events. No SAEs, dose adjustments, or discontinuations occurred.

Pretreated Safety Population

Lymphocytosis of any grade was reported at a similar frequency in Arm A (6 participants [2.8%]) and Arm B (10 participants [4.6%]). All participants that reported events of lymphocytosis reported at least one event that was considered treatment related. Grade 3 events were reported at a similar frequency in Arm A (4 participants [1.8%]) and Arm B (6 participants [2.8%]). No SAEs or Grades 4 or 5 events were reported in either treatment arm. All events were managed without dose modification and discontinuation.

Treatment naïve safety population

Lymphocytosis of any grade occurred with a similar frequency in the pirtobrutinib Arm (6 participants, 5.4%) and the ibrutinib Arm (9 participants, 8.3%). Treatment-related of any grade lymphocytosis occurred in 5 participants (4.5%) in the pirtobrutinib Arm and in 8 participants (7.3%) in the ibrutinib Arm.

All events were nonserious and managed without dose adjustments. No Grade 5 events occurred in either treatment arm.

Integrated safety set

Lymphocytosis occurred in 58 participants (5.0%); treatment-related lymphocytosis occurred in 35 participants (3.0%), and Grade 3 or Grade 4 lymphocytosis occurred in 37 participants (3.2%). Serious lymphocytosis occurred in 5 participants (0.4%). None of the participants experienced fatal lymphocytosis events.

Rash

Study 20023

Any grade rash occurred with a similar frequency in the pirtobrutinib Arm (31 participants, 22%) and the BendaR Arm (34 participants 25.8%). After adjusting for exposure, the incidence rate was 10 per 100 PY in the pirtobrutinib Arm and 70.4 per 100 PY in the BendaR Arm. Treatment-related rash occurred with a lower frequency in the Pirtobrutinib Arm (9 participants, 6.4%) compared to the BendaR Arm (21 participants, 15.9%).

In the pirtobrutinib Arm, no SAEs of rash occurred. Thirty participants (21.4%) had Grade 1 or Grade 2 events; 1 participant had a Grade 3 event. Dose hold occurred in 2 participants. No Grade 4 or Grade 5 events, dose reductions, and discontinuations occurred in the pirtobrutinib Arm.

In the BendaR Arm, 33 out of 34 participants experienced nonserious rash. A total of 31 participants (23.5%) had Grade 1 or Grade 2 events; 3 participants had Grade 3 events. Dose hold occurred in 4 participants. No Grade 4 or Grade 5 events, nor dose reductions occurred in the BendaR Arm.

Study 20030

Rash of any grade occurred with a lower frequency in the pirtobrutinib Arm (58 participants, 17.6%) compared to the Ibrutinib Arm (70 participants, 21.5%).

In the pirtobrutinib Arm, 56 out of 58 participants experienced nonserious rash. A total of 53 participants (16.1%) experienced Grade 1 or Grade 2 events; 5 participants (1.5%) experienced Grade 3 rash. Most of the events were not associated with dose adjustments and drug discontinuations.

In the ibrutinib Arm, 68 out of 70 participants experienced nonserious rash. A total of 65 participants (20.0%) experienced Grade 1 or Grade 2 events; 5 participants experienced Grade 3 f rash. Most of the events were not associated with dose adjustments or drug discontinuations.

Pretreated Safety Population

Rash of any grade and treatment-related rash were reported at a lower frequency in Arm A (36 participants [16.5%] and 15 participants [6.9%], respectively) compared to Arm B (50 participants [23.1%] and 25 participants [11.6%], respectively). Grade 3 events were reported in 3 participants (1.4%) in Arm A and 4 participants (1.9%) in Arm B. Most were non-serious, Grade 1 and 2, and managed without dose modification. No Grade 4 or 5 events were reported in either treatment arm.

Treatment naïve safety population

Any grade rash occurred with a similar frequency in the pirtobrutinib Arm (22 participants, 19.6%) and the Ibrutinib Arm (20 participants, 18.3%). Treatment-related any grade rash occurred in 7 participants (6.3%) in the Pirtobrutinib Arm and in 12 participants (11.0%) in the Ibrutinib Arm.

Most of the events were nonserious, Grade 1 or Grade 2, and managed without dose adjustment. No Grade 4 or Grade 5 events occurred in either treatment arm.

Integrated safety set

Rash occurred in 221 participants (19.2%). Treatment-related rash occurred in 84 participants (7.3%), and Grade 3 or Grade 4 occurred in 14 participants (1.2%). Serious rash occurred in 3 participants (0.3%). None of the participants experienced fatal events of rash.

Laboratory findings

Haematology

Analyses of haematology laboratory values were consistent with analyses of the haematological AEs. No new safety findings were identified in Pirtobrutinib Arm.

Haemoglobin

In the Pirtobrutinib Arm, shift analysis for haemoglobin decreased for worst postbaseline values showed that 75.7% and 68.8% of participants in studies 20023 and 20030 respectively maintained their baseline grade throughout treatment. 2.9% of participants in study 20023 and 3.1% in study 20030 had a treatment-emergent downward shift of 2 grades or more.

Neutrophils

In the Pirtobrutinib Arm, shift analysis for neutrophils decreased for worst postbaseline values showed that 52.2% and 40.1% of participants in studies 20023 and 20030 respectively maintained their baseline

grade throughout treatment. 29.7% of participants in study 20023 and 38.8% in study 20030 had a treatment-emergent downward shift of 2 grades or more.

Lymphocytes

In the Pirtobrutinib Arm, shift analysis for lymphocyte decreased for worst postbaseline values showed that 89.7% and 81.8% of participants in studies 20023 and 20030 respectively maintained their baseline grade throughout treatment. 2.2% of participants in study 20023 and 7.1 % in study 20030 had a treatment-emergent downward shift of 2 grades or more.

Platelets

In the Pirtobrutinib Arm, shift analysis for platelets decreased for worst postbaseline values showed that 87.1% of participants maintained their baseline grade throughout treatment. 2.9% of participants in study 20023 and 2.4 % in study 20030 had a treatment-emergent downward shift of 2 grades or more.

Chemistry

In general, analyses of serum chemistry laboratory values were consistent with analyses of AE data and did not reveal any additional safety signals in the Pirtobrutinib Arm.

Creatinine

In the Pirtobrutinib Arm, shift analysis for creatinine increased for worst postbaseline values showed that 86.4% and 77.4% of participants of participants in studies 20023 and 20030 respectively maintained their baseline grade throughout treatment. 1.4% had a treatment-emergent downward shift of 2 grades or more. Most participants (95%) had maintained or improved their baseline grade by the time of the last measurement.

Electrolytes

Individual fluctuations of calcium, sodium, potassium and magnesium occurred in some participants in the Pirtobrutinib Arm, with most of them being of Grade 1. For all electrolytes analysed, more than 95% of participants had maintained or improved their baseline grade by the time of the last measurement.

Liver function tests

Individual fluctuations in ALT, AST, alkaline phosphatase, and total bilirubin were identified in some participants in the Pirtobrutinib Arms.

Shift analysis for AST and ALT increased for worst postbaseline values showed that 87.1% and 72.9% of participants in study 20023 and 89% and 79.5% of participants in study 20030 maintained their baseline grade throughout treatment, respectively. 2.9% and 3.6% of participants in study 20023 and 1.2% and 2.1% of participants in study 20030 had a treatment-emergent downward shift of 2 grades or more, respectively.

Shift analysis for bilirubin increased for worst postbaseline values showed that 70% and 82.3% of participants in studies 20023 and 20030 respectively maintained their baseline grade throughout treatment. 7.1% of participants in study 20023 and 1.5% of participants in study 20030 had a treatment-emergent downward shift of 2 grades or more, respectively.

In the pirtobrutinib Arm, no events were identified which met Hy’s Law criteria of drug-induced liver in neither study.

Safety in special populations

Intrinsic Factors

The safety profile of pirtobrutinib was reviewed based on TEAEs for the following intrinsic factors for Study 20023, Study 20030, and the Integrated Safety Set:

• Age: below 65 years versus 65 years and older, below 75 years versus 75 years and older, and below 85 years versus 85 years and older

• Sex: male versus female

• Race: Asian, White, Black or African American, and other; and

• Ethnicity: Hispanic or Latino, not Hispanic or Latino, and other.

Overall, the safety profile within each subgroup per treatment arm was consistent with the Safety Population. Notably, Grade 3 or higher TEAEs and SAEs were more frequent in participants aged 65 years or older as expected in an elderly population with multiple comorbidities. Although numerical differences were noted in the subpopulations by sex, ethnicity, and race, these differences are expected in the participant population and are not considered to be clinically significant. No specific safety concerns were identified.

Extrinsic Factors

Analysis of extrinsic factors were not performed on the Safety Analysis Population in Study 20023 and Study 20030. Approximately 404 participants (35%) were enrolled from North America, 473 participants were from Europe (41%), and 126 participants (10.9%) were from Asia.

In the ISS, the safety profile of pirtobrutinib was reviewed based on TEAEs for the extrinsic factor region (North America, Europe, Asia, Australia/New Zealand, South America, and Middle East).

In summary, the incidence of any grade TEAEs was consistent across regions. However, Grade 3 or higher TEAEs and TE-SAEs occurred more frequently among participants from North America. Additionally, the analysis of individual preferred terms indicated that nonspecific events tended to be reported more often by participants in North America.

Discontinuation due to adverse events

Study 2023

Table 42 summarises TEAEs leading to treatment discontinuation for participants in the Safety Population. The proportion of participants who experienced any grade TEAEs leading to treatment discontinuation was lower in the Pirtobrutinib Arm (6 participants, 4.3%) compared to the BendaR Arm (20 participants, 15.2%). The specific TEAEs that led to permanent discontinuation of study drug varied by study treatment. In both arms, cytopenia was the main cause of treatment discontinuation.

Table 42. Summary of Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug by Preferred Term and Maximum CTCAE Grade Categories Study 20023 Safety Population

	Arm A: Pirtobrutinib (N=140)								Arm B: BendaR (N=132)							
	Any grade		Grade 3/4		Grade 5		Grade 3/4/5		Any grade		Grade 3/4		Grade 5		Grade 3/4/5	
MedDRA Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with >= 1 TEAE	6	(4.3)	3	(2.1)	0		3	(2.1)	20	(15.2)	10	(7.6)	3	(2.3)	13	(9.8)
Anaemia	1	(0.7)	0		0		0		2	(1.5)	1	(0.8)	0		1	(0.8)
Chronic obstructive pulmonary disease	1	(0.7)	1	(0.7)	0		1	(0.7)	0		0		0		0	
Ecchymosis	1	(0.7)	0		0		0		0		0		0		0	
Femoral neck fracture	1	(0.7)	0		0		0		0		0		0		0	
Interstitial lung disease	1	(0.7)	0		0		0		1	(0.8)	1	(0.8)	0		1	(0.8)
Right ventricular failure	1	(0.7)	1	(0.7)	0		1	(0.7)	0		0		0		0	
Thrombocytopenia	1	(0.7)	1	(0.7)	0		1	(0.7)	0		0		0		0	
Back pain	0		0		0		0		1	(0.8)	0		0		0	
COVID-19	0		0		0		0		1	(0.8)	0		0		0	
Cardio-respiratory arrest	0		0		0		0		1	(0.8)	0		1	(0.8)	1	(0.8)
Erythema	0		0		0		0		1	(0.8)	0		0		0	
Flank pain	0		0		0		0		1	(0.8)	0		0		0	
Infection	0		0		0		0		1	(0.8)	1	(0.8)	0		1	(0.8)
Infusion related reaction	0		0		0		0		1	(0.8)	1	(0.8)	0		1	(0.8)
Ischaemic stroke	0		0		0		0		1	(0.8)	0		1	(0.8)	1	(0.8)
Myocardial ischaemia	0		0		0		0		1	(0.8)	1	(0.8)	0		1	(0.8)
Neutropenia	0		0		0		0		4	(3.0)	4	(3.0)	0		4	(3.0)
Pneumonia	0		0		0		0		1	(0.8)	0		0		0	
Rash erythematous	0		0		0		0		1	(0.8)	0		0		0	
Sepsis	0		0		0		0		1	(0.8)	0		0		0	
Skin toxicity	0		0		0		0		1	(0.8)	0		0		0	
Subcutaneous abscess	0		0		0		0		1	(0.8)	0		0		0	
Tumour lysis syndrome	0		0		0		0		1	(0.8)	0		1	(0.8)	1	(0.8)
Urosepsis	0		0		0		0		1	(0.8)	1	(0.8)	0		1	(0.8)
Vomiting	0		0		0		0		1	(0.8)	0		0		0	

Abbreviations: BendaR = Bendamustine plus Rituximab; CTCAE = common terminology criteria for adverse events; MedDRA = medical dictionary for regulatory activities; N = number of subjects in population; n = number of subjects within category; TEAE = treatment-emergent adverse event.
MedDRA Version 28.0; CTCAE Version 5.0.

Treatment-Emergent Adverse Events Leading to Drug Interruptions

In Study 20023, the definition of "drug interruption" varies based on the context in which it is used and may include drug hold, or infusion interruption:

- Drug interruption for pirtobrutinib only includes drug hold.
- Drug interruption for bendamustine treatment includes drug hold and/or infusion interruption.
- Drug interruption for rituximab only includes infusion interruption.

The proportion of participants who experienced any grade TEAEs leading to drug interruption was similar in the Pirtobrutinib Arm (49 participants, 35%) and BendaR Arm (45 participants, 34.1%).

The most common, any grade TEAEs leading to drug interruption was COVID-19 in the Pirtobrutinib Arm (10%) and infusion-related reaction in the BendaR Arm (12.1%).

Treatment-related AEs that led to dose hold of study drug were reported in fewer participants in Arm A (30 participants [21.4%]) than in Arm B (40 participants [30.3%]). Grade 3 or 4 TEAEs that led to dose hold of study drug were reported in more participants in Arm A (29 participants [20.7%]) than in Arm B (17 participants [12.9%]). Treatment-related Grade 3 or 4 TEAEs that led to dose hold of study drug were reported similarly in participants in Arm A (16 participants [11.4%]) and in Arm B (17 participants [12.9%]).

Treatment-Emergent Adverse Events Leading to Dose Reduction

Despite the longer exposure to pirtobrutinib, the proportion of participants who experienced any grade TEAEs leading to dose reduction was lower in the Pirtobrutinib Arm (5 participants, 3.6%) compared to the BendaR Arm (41 participants, 31.1%).

The most common any grade TEAE leading to dose reduction in the Pirtobrutinib Arm was pruritus (2 participants, 1.4%). The most common any grade TEAE leading to dose reduction in the BendaR Arm was neutropenia (21 participants, 15.9%).

Treatment-related AEs that led to dose reduction of study drug were reported in fewer participants in Arm A (4 participants [2.9%]) than in Arm B (39 participants [29.5%]).

Grade 3 or 4 TEAEs that led to dose reduction of study drug were reported in fewer participants in Arm A (2 participants [1.4%]) than in Arm B (32 participants [24.2%]). Treatment-related Grade 3 or 4 TEAEs that led to dose reduction of study drug were reported in 2 participants in Arm A (1.4%) and 31 participants in Arm B (23.5%)

Study 20030

The proportion of participants who experienced any grade and Grade 3 or Grade 4 TEAEs leading to treatment discontinuation was similar in the Pirtobrutinib Arm (9.4% and 3.3%, respectively) and the Ibrutinib Arm (10.8% and 3.7%, respectively).

Most any grade TEAEs leading to treatment discontinuation occurred in a single participant in the Pirtobrutinib Arm. In addition, pneumonia (3 participants; 0.9%) and pulmonary sepsis (2 participants; 0.6%) occurred. In the Ibrutinib Arm, the most common any grade TEAEs leading to treatment discontinuation were pneumonia (4 participants; 1.2%), unknown death (2 participants; 0.6%), and atrial fibrillation (5 participants; 1.5%); the remaining TEAEs occurred in a single participant.

Grade 5 TEAEs that led to permanent treatment discontinuation were reported at a similar frequency in Arm A (14 participants [4.2%]) and Arm B (13 participants [4.0.%]), with treatment-related Grade 5 events reported at a similar frequency in Arm A (4 participants [1.2%]) and Arm B (5 participants [1.5%]).

In the Pretreated Safety Population, TEAEs of any grade that led to permanent treatment discontinuation were reported at a similar frequency in Arm A (25 participants [11.5%]) and Arm B (23 participants [10.6%]), with treatment-related events reported at a similar frequency in Arm A (13 participants [6.0%]) and Arm B (11 participants [5.1%]). The most common TEAE of any grade that led to permanent treatment discontinuation in both treatment arms was Pneumonia (3 participants [1.4%] in each treatment arm). The most common treatment-related TEAE that led to permanent treatment discontinuation in Arm A was Pneumonia (2 participants [0.9%]) and in Arm B was Atrial fibrillation (2 participants [0.9%]). Grade 5 TEAEs that led to permanent treatment discontinuation were reported at a similar frequency in Arm A (14 participants [6.4%]) and Arm B (12 participants [5.6%]), with treatment-related Grade 5 events reported in a similar frequency of participants in Arm A (4 participants [1.8%]) and Arm B (4 participants [1.9%]).

Treatment-Emergent Adverse Events Leading to Dose hold

The frequency of participants who experienced any grade and Grade 3 or Grade 4 TEAEs leading to drug hold was similar in the Pirtobrutinib Arm (49.1% and 27.3%, respectively) and the Ibrutinib Arm (51.7% and 27.7%, respectively).

The most common any grade TEAE that led to dose hold of pirtobrutinib or ibrutinib was neutropenia (9.7% and 7.4%, respectively).

Treatment-related TEAEs that led to dose hold were reported at a similar frequency between treatment arms (100 participants [30.3%] Arm A, 106 participants [32.6%] Arm B). The most commonly reported treatment-related TEAE (in ≥5% of participants) that led to dose hold in each treatment arm was Neutropenia (27 participants [8.2%] Arm A, 21 participants [6.5%] Arm B)

In the pretreated safety population, TEAEs of any grade that led to dose hold were reported at a similar frequency in Arm A (107 participants [49.1%]) and Arm B (101 participants [46.8%]). The most commonly reported TEAEs (in ≥5% of participants) that led to dose hold were Neutropenia (25 participants [11.5%]) in Arm A and Neutropenia (18 participants [8.3%]) and Pneumonia (13 participants [6.0%]) in Arm B. Treatment-related TEAEs that led to dose hold were reported at a similar frequency in each treatment arm (69 participants [31.7%] Arm A, 66 participants [30.6%] Arm B). The most commonly reported treatment-related TEAE (in ≥5% of participants) that led to dose hold in each treatment arm was Neutropenia (20 participants [9.2%] Arm A, 15 participants [6.9%] Arm B).

Treatment-Emergent Adverse Events Leading to Dose Reduction

The frequency of participants who experienced any grade TEAEs leading to dose reduction was lower in the Pirtobrutinib Arm (26 participants, 7.9%) compared to the Ibrutinib Arm (58 participants, 17.8%). The most common TEAE that led to dose reduction in at least 2% of participants was neutropenia (2.7%) in the Pirtobrutinib Arm compared to neutropenia (2.5%) and atrial fibrillation (2.2%) in the Ibrutinib Arm.

In the pretreated Safety population, TEAEs of any grade that led to dose reduction of study drug were reported at a lower frequency in Arm A (20 participants [9.2%]) compared to Arm B (31 participants [14.4%]). Treatment-related TEAEs of any grade that led to dose reduction of study drug were at a lower frequency of participants in Arm A (15 participants [6.9%]) compared to Arm B (29 participants [13.4%]). The most commonly reported TEAE in each treatment arm that led to dose reduction of study drug was Neutropenia (9 participants [4.1%] Arm A, 5 participants [2.3%] Arm B).

Treatment-naïve safety population

Treatment Discontinuation due to TEAEs

Discontinuations due to TEAEs of any grade occurred with a lower frequency in the Pirtobrutinib Arm (6 participants, 5.4%) compared to the Ibrutinib Arm (12 participants, 11%). All TEAEs of any grade leading to treatment discontinuation occurred in 1 participant in both treatment arms, except for atrial fibrillation, which occurred in 3 participants (2.8%) in the Ibrutinib Arm.

Treatment-Emergent Adverse Events Leading to Dose Hold

Dose holds due to TEAEs of any grade occurred with a lower frequency in the Pirtobrutinib Arm (55 participants, 49.1%) compared to the Ibrutinib Arm (67 participants, 61.5%).

TEAEs that led to dose hold of pirtobrutinib reported in at least 5% of participants were COVID 19 and neutropenia.

TEAEs that led to dose hold of ibrutinib reported in at least 5% of participants were COVID-19, pneumonia, neutropenia, and atrial fibrillation.

Treatment-Emergent Adverse Events Leading to Dose Reduction

Dose reductions due to any grade TEAEs occurred with a lower frequency in the Pirtobrutinib Arm (6 participants, 5.4%) compared to the Ibrutinib Arm (27 participants, 24.8%).

TEAEs leading to dose reduction in the Pirtobrutinib Arm were variable and occurred in single participants. In the Ibrutinib Arm, TEAEs led to dose reduction most frequently were atrial fibrillation (4 participants, 3.7%), neutropenia (3 participants, 2.8%), and febrile neutropenia (2 participants, 1.8%).

Integrated safety set

Treatment Discontinuation due to Adverse Events

A total of 127 participants (11%) experienced at least 1 AE leading to study drug discontinuation. Most AEs leading to discontinuation were observed in the SOC of Infections and infestations (41 participants, 3.6%). The most frequently reported event was pneumonia (9 participants, 0.8%).

Treatment-Emergent Adverse Events Leading to Dose Holds

A total of 542 participants (47.0%) experienced at least 1 AE leading to drug hold. Grade 3 or Grade 4 AEs leading to drug hold occurred in 343 participants (29.7%). Most AEs leading to dose holds were observed in the SOC of Infections and infestations (272 participants, 23.6%). The most frequently reported event was COVID-19 (90 participants, 7.8%).

Treatment-Emergent Adverse Events Leading to Dose Reduction

A total of 76 participants (6.6%) experienced at least 1 AE leading to dose reduction. Grade 3 or Grade 4 AEs leading to dose reduction occurred in 44 participants (3.8%). Most AEs leading to dose reduction occurred in the SOC Investigations (21 participants, 1.8%). The most frequently reported event was neutropenia (16 participants, 1.4%).

Adverse Drug Reactions

ADRs were identified for participants treated with pirtobrutinib based on a thorough review of the totality of unblinded safety data for pirtobrutinib based on the integrated safety set in CLL or NHL and are summarised in **Table 43**.

Table 43. Frequencies of Adverse Reactions for Pirtobrutinib Pooled Frequencies from Studies 18001, 20020, 20023, and 20030

System organ class (MedDRA)	ADR	Frequency category (%) (All grades)	Grade ³ 3[c] (%)
Infections and infestations	Pneumonia	Very common (13.9)	8.8
	Upper respiratory tract infection	Very common (13.4)	0.3
	Urinary tract infection	Common (9.2)	1.3
Blood and lymphatic system disorders	Neutropenia[b]	Very common (27.4)	22.8
	Anaemia[b]	Very common (18.4)	9.0
	Thrombocytopenia[b]	Very common (14.7)	7.2
	Lymphocytosis[b]	Common (5.0)	3.2
Nervous system disorders	Headache	Very common (10.7)	0.5
Cardiac disorders	Atrial fibrillation/atrial flutter	Common (3.1)	1.6
Vascular disorders	Haemorrhage[b]	Very common (20.4)	2.9
	Epistaxis	Common (4.2)	0.1

	Haematuria	Common (4.8)	0.2
	Haematoma	Common (2.4)	0.3
	Conjunctival haemorrhage	Common (1.5)	0.1
	Bruising[b]	Very common (17.0)	0.2
	Contusion	Very common (14.2)	0.1
	Petechiae	Common (5.1)	0
Gastrointestinal disorders	Diarrhoea	Very common (19.5)	0.7
	Nausea	Very common (13.0)	0.3
	Abdominal pain	Common (7.4)	0.7
Hepatobiliary disorders	Hepatic enzyme increased	Not known	Not known
Skin and subcutaneous tissue disorders	Rash[b]	Very common (19.2)	1.2
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (12.5)	0.8
General disorders and administration site conditions	Fatigue	Very common (17.9)	1.4
	Oedema peripheral	Common (9.0)	0.3

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in the analysis population; NA = Not applicable.

[a] Very common = ≥10%; Common = ≥1% and <10%; Uncommon = ≥0.1% and <1%.

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

[c] Consolidated term.

Post marketing experience

Pirtobrutinib was first authorised on 27 January 2023 in the US for the treatment of adult patients with R/R MCL after at least 2 lines of systemic therapy, including a BTKi. As of 27 July 2025, pirtobrutinib has been authorised in 43 countries.

Cumulatively, it is estimated that approximately 6200 patients (representing 3700 patient-years of treatment) have received pirtobrutinib worldwide from postmarketing sources. No safety signals arising from postmarketing data have been identified as of the 27 July 2025 Periodic Adverse Drug Experience Report date.

2.5.1. Discussion on clinical safety

The safety profile of pirtobrutinib within the present application was based on data from Studies 20023 and 20030, the treatment-naïve safety population, and the Integrated Safety Set (ISS).

Treatment Exposure, Dose Intensity, and Interpretability of Safety Data

Across the clinical development program, the majority of participants maintained 90–100% the planned dose. This finding is particularly relevant in CLL, where long-term continuous therapy is common and cumulative toxicity can limit treatment sustainability. However, interpretation of exposure-dependent safety outcomes requires caution. In Study 20023, the fixed-duration nature of BendaR compared with continuous pirtobrutinib introduces inherent confounding. Higher crude

incidences of adverse events with pirtobrutinib largely reflect longer exposure rather than greater intrinsic toxicity, highlighting the importance of exposure-adjusted incidence rates (EAIRs). In contrast, Study 20030 offers a more relevant comparison, as both pirtobrutinib and ibrutinib were administered continuously with similar exposure durations, allowing for more credible assessment of relative tolerability between BTK inhibitors.

Dose modifications provide additional insight into manageability. Despite more frequent dose holds with pirtobrutinib, these were often related to participant error rather than toxicity, whereas dose reductions and discontinuations were consistently less frequent than with comparators. This pattern suggests that adverse events associated with pirtobrutinib are generally manageable without permanent treatment compromise, a key consideration for chronic therapy.

Adverse Events burden and serious toxicity

Although any-grade TEAEs were reported more frequently in the pirtobrutinib Arm (93.6%) than in the BendaR Arm (88.6%), this difference reflects substantially longer drug exposure with pirtobrutinib. When adjusting for exposure using EAIRs, TEAEs of any grade were markedly lower with pirtobrutinib (196.7 per 100 patient-years [PY]) compared with BendaR (844.6 per 100 PY). A similar pattern was observed for Grade 3 or Grade 4 TEAEs, with substantially lower EAIRs in the Pirtobrutinib Arm (20.1 per 100 PY) than in the BendaR Arm (245.4 per 100 PY).

TEAEs of any grade that were considered related to study drug by the Investigator were less frequent with pirtobrutinib (83 participants [59.3%]) than with BendaR (113 participants [85.6%]). Grade 3 or 4 TEAEs that were considered related to study drug were less frequent with pirtobrutinib (31 participants [22.1%) than with BendaR (79 participants [59.8%]).

Serious adverse events occurred at a similar crude frequency between treatment arms despite longer exposure to pirtobrutinib (27.9% vs 28.0%). However, EAIRs for serious adverse events were substantially lower with pirtobrutinib (12.4 per 100 PY) than with BendaR (73.8 per 100 PY). Treatment discontinuations due to TEAEs were less frequent in the pirtobrutinib arm, with EAIRs of 1.6 per 100 PY compared with 34.3 per 100 PY in the BendaR arm.

This finding is clinically meaningful, as it indicates a reduced toxicity burden per unit of treatment time despite prolonged exposure.

Deaths within 30 days of the last dose were infrequent in both arms, occurring in one participant (0.7%) in the pirtobrutinib arm and three participants (2.3%) in the BendaR arm. One death in the BendaR arm, due to tumour lysis syndrome, was considered treatment related, whereas the death in the pirtobrutinib arm was not considered treatment related. Although small numbers preclude statistical inference, the numerically lower mortality observed with pirtobrutinib is clinically reassuring, particularly in an elderly and comorbid population.

In Study 20030, where exposure duration was comparable between pirtobrutinib and ibrutinib, overall, TEAE rates were similar (320 participants: 97.0% vs 318 participants: 97.8%). Treatment-related TEAEs occurred less frequently with pirtobrutinib (77.0 vs 83.1%). The incidence of Grade 3–4 TEAEs and SAEs was comparable between arms (49.4 vs 48.6 and 32.4 vs 33.2 respectively). TEAEs leading to permanent treatment discontinuation occurred at similar frequencies overall (9.4% vs 10.8%); however, in the treatment-naïve safety setting, discontinuations due to TEAEs were less frequent with pirtobrutinib than with ibrutinib (5.4 vs 11.0). Deaths within 30 days of last dose were infrequent in the treatment-naïve safety setting, with one non–treatment-related death in the pirtobrutinib arm and two deaths in the comparator arm, including one treatment-related TLS death. Importantly, qualitative differences in causes of death with treatment-related deaths in the pirtobrutinib arm being exclusively infection related, whereas treatment-related deaths in the ibrutinib arm included both infectious and

cardiac causes, is clinically relevant and aligns with the known cardiovascular liability of first-generation BTK inhibitors, although interpretation is limited by small event numbers.

The most frequently reported TEAEs (reported by ≥10% of participants) with pirtobrutinib or ibrutinib were neutropenia (22.7% vs 17.8%), upper respiratory tract infection (17.9 vs 19.4), anaemia (15.2% vs 14.2%), pneumonia (13.6% vs 15.1%), diarrhoea (13.3% vs 19.1%), COVID-19 (12.1% vs 10.2%), hypertension (10.6% vs 15.1%), contusion (10.0 vs 9.2), arthralgia (7.9% vs 12.6%), atrial fibrillation (2.4% vs 12.6), urinary tract infection (7.9% vs 12.3%), thrombocytopenia (7.9% vs 11.4%). Grade 3 or 4 TEAEs were reported at a similar frequency with pirtobrutinib (163 participants [49.4%]) and ibrutinib (158 participants [48.6%]). The most common Grade 3 or 4 TEAEs was neutropenia (57 participants [17.3%] with pirtobrutinib, 43 participants [13.2%] with ibrutinib). In the pretreated safety population, the most frequently reported TEAEs of any grade (reported in ≥10% of participants) with pirtobrutinib or ibrutinib were neutropenia (25.7% vs 19.4%), upper respiratory tract infection (18.8% vs 17.1%), pneumonia (16.5% vs 16.7%) , anaemia (14.2% vs 13.4%), diarrhoea (12.4% vs 18.1%), cough (10.6% vs 9.7%), hypertension (8.7% vs 13.4%), thrombocytopenia (8.7% vs 13.4%), urinary tract infection (7.3% vs 11.0%), and Arthralgia (7.8% vs 10.2%);

Deaths occurring on treatment or within 30 days of the last dose were reported at similar frequencies in the pirtobrutinib and ibrutinib arms (5.2% vs 4.0%). In both arms, all such deaths were attributed to adverse events and most commonly were due to Infections and infestations-related AEs (11 participants [3.3%] for pirtobrutinib, 8 participants [2.5%] for ibrutinib).

In the pirtobrutinib arm, 17 deaths occurred, most commonly due to infections and infestations, followed by nervous system, cardiac, and gastrointestinal disorders. Six deaths were considered treatment related, all due to serious infections (including 2 pneumonia, 2 septic shock, 1 pulmonary sepsis, and 1 cryptococcal pneumonia), and all occurred in the pretreated safety population. In the ibrutinib arm, 13 deaths were reported, again predominantly due to infections, followed by cardiac and respiratory disorders; in two cases, the cause of death was not reported. Five deaths were considered treatment related, including 2 cases of cardiac arrhythmias and 3 cases of serious infections.

Pirtobrutinib treatment induced more frequent Grade 3 or Grade 4 neutropenia. In the pre-treated safety population pneumonia was the most common treatment-related TEAE in the pirtobrutinib arm that led to permanent treatment discontinuation. Higher frequency of neutropenia in the pirtobrutinib arm is a concern especially in the elderly CLL/SLL population and the SmPC recommends monitoring of complete blood counts in patients during treatment as medically indicated and the scenarios requiring dose interruption to reduce this risk.

Comparisons with ibrutinib revealed broadly similar overall safety, but with important qualitative differences. While rates of serious adverse events and treatment discontinuations were comparable, pirtobrutinib was associated with fewer treatment-related adverse events and fewer dose reductions. These findings suggest improved tolerability rather than reduced toxicity, enabling patients to remain on therapy without permanent dose modification. Nevertheless, reliance on EAIRs may obscure early-onset toxicities, particularly for time-limited regimens such as BendaR. Additionally, the absence of consistent analysis and stratification of serious adverse events by timing relative to treatment limits causal interpretation and represents a methodological weakness, especially in a pivotal trial setting**.**

Across studies, infections emerged as the predominant contributors to SAEs and mortality. Fatal infections occurred in both pirtobrutinib and comparator arms, predominantly in heavily pretreated populations, underscoring the role of disease-related immunosuppression rather than a clear drug-specific signal. In the Integrated Safety Set, treatment-related fatal events were rare and most

commonly infection related, supporting an overall acceptable safety profile in the context of advanced hematologic malignancy.

Although crude infection rates were often higher with pirtobrutinib, exposure-adjusted analyses consistently demonstrated lower or comparable infection incidence relative to BendaR and broadly similar rates compared with ibrutinib.

Cytopenias, particularly neutropenia, represent a key component of the pirtobrutinib safety profile. Compared with BendaR, pirtobrutinib showed a markedly more favourable hematologic profile, with substantially lower rates of any-grade and severe neutropenia, reflecting the absence of cytotoxic chemotherapy effects. In contrast, comparisons with ibrutinib revealed higher rates of neutropenia and severe anaemia with pirtobrutinib, although serious and fatal events were uncommon.

Laboratory shift analyses support the clinical findings, demonstrating that hematologic abnormalities were generally transient and reversible, with most participants recovering to baseline or improved grades by last assessment. The absence of cumulative marrow toxicity and the low incidence of serious cytopenia related complications suggest that these events are manageable with routine monitoring and supportive care. Nonetheless, the frequency of transient high-grade neutropenia reinforces the need for regular hematologic surveillance, particularly in heavily pretreated or treatment-naïve patients with limited bone marrow progenitors.

One of the most clinically meaningful differentiators between pirtobrutinib and first-generation BTK inhibitors is cardiovascular safety. Across studies, atrial fibrillation and other atrial arrhythmias occurred substantially less frequently with pirtobrutinib than with ibrutinib, including severe and serious events. This lower frequency translated into fewer dose reductions and discontinuations, addressing a major limitation of earlier BTK inhibitors in clinical practice.

Bleeding events followed a different pattern. Compared with BendaR, bleeding adverse events were more frequent with pirtobrutinib, consistent with BTK inhibitor class effects. However, most events were low grade, and severe or fatal bleeding was rare. Comparisons with ibrutinib showed broadly similar bleeding risk, with fatal events occurring infrequently in both arms and largely in the context of significant comorbidities and concomitant anticoagulation.

Second primary malignancies, particularly non-melanoma skin cancers, occurred more frequently as crude proportions with pirtobrutinib (8 participants (5.7%) in the pirtobrutinib arm vs 2 participants (1.5%) in the BendaR arm in study 20023 and 8 participants (7.1%) in the Pirtobrutinib vs 3 participants (2.8%) in the ibrutinib Arm in study 20030) but showed similar or lower exposure-adjusted incidence rates compared with comparators. Events were predominantly low grade and rarely led to treatment modification. A long-term follow-up analysis of such events from ongoing studies with pirtobrutinib is expected to be submitted by 2028 to further characterise this risk.

2.5.2. Conclusions on clinical safety

The cumulative safety evidence from randomised studies 20023 and 20030, supported by the Integrated Safety Set indicates that pirtobrutinib has an expected and manageable safety profile in CLL patients. Across the studies, adverse events were consistent with the known pharmacological class and the known safety profile of pirtobrutinib.

Infections and hematologic adverse events, particularly neutropenia, constitute the principal identified risks. These events were generally manageable with standard supportive measures and rarely resulted in fatal outcomes.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

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

Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 – Required additional pharmacovigilance activities				
-LOXO-BTK-18001 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 second primary malignancies for a 5-year follow-up	- second primary malignancies other than non-melanoma skin cancer - second primary non-melanoma skin cancer	An interim analysis was submitted to EMA prior 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				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or 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 Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-314) **Status:** ongoing				

Risk minimisation measures

Safety Concern	Risk Minimisation Measures
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. • 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

Safety Concern	Risk Minimisation Measures
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
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. • 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
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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8, 5.1, and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH and was found acceptable for the following reasons:

The aim of the current procedure is to extend the existing CLL indication to allow use of Jaypirca independent of line of therapy/prior therapeutic agents. The proposed text modifications to the package leaflet resulting from the modification of the indication do not have a significant impact on the design and readability of the package leaflet and do not include text that is significantly different from that already user tested. Overall, the structure and design of the revised package leaflet have not changed due to the new information and the revisions do not significantly affect the overall readability.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The sought indication with this application for pirtobrutinib as monotherapy is for treatment of adult patients with chronic lymphocytic leukaemia.

3.1.2. Available therapies and unmet medical need

Available treatment options in first line patients with CLL and no evidence of del(17p) include: cBTKi, BCL2i, chemotherapy, and chemoimmunotherapy (CIT). The selection of 1 treatment strategy over another is highly influenced by patient age, comorbid illness, patient preference and molecular prognostic factors.

The available therapy options in the EU for the treatment of R/R CLL overlap with those used in frontline CLL but also include PI3Ki. The treatment option selected in R/R CLL is similarly influenced by patient and disease characteristics considered in frontline, but also by the choice of frontline therapy as well as the fitness of the patient. Since many patients will have historically received CIT in frontline therapy, there is a large proportion of patients with R/R CLL that are cBTKi naive.

Despite multiple options, none of these can cure CLL, and CLL remains a life limiting disease. While some patients may initially follow an indolent course after diagnosis of CLL, with a 5-year relative survival of 89.3%, the trajectory can be aggressive once the disease progresses, particularly in cases where patients present with advanced disease at diagnosis or exhibit poor prognostic markers.

Furthermore, although they have substantially improved outcomes, existing targeted agents have limitations, including tolerability considerations, resistance mechanisms, and practical constraints that influence patient management. Hence, there remains a medical need for a tolerable and effective treatment option that can be utilized across different lines of therapy and treatment sequences. Additional therapeutic options can be considered in the context of the existing treatment landscape.

3.1.3. Main clinical studies

The registration package supporting the proposed indication in CLL includes data from 2 pivotal multicentre, randomised, open-label Phase 3 studies:

- LOXO-BTK-20023 (BRUIN-CLL-313; Study 20023), comparing pirtobrutinib versus bendamustine plus rituximab in untreated patients with CLL/SLL
- LOXO-BTK-20030 (BRUIN-CLL-314; Study 20030): comparing pirtobrutinib versus ibrutinib in patients with BTKi-naive CLL and who were either previously treated or treatment naïve.

3.2. Favourable effects

Treatment-naïve CLL

In Study 20023, conducted in 282 treatment-naïve patients without del(17p), pirtobrutinib demonstrated a statistically significant improvement in IRC-assessed PFS compared with BendaR

(HR=0.199 [0.107, 0.367]). The consistency between IRC- and investigator-assessed PFS supports the robustness of the observed treatment effect. ORR and DOR were numerically in favour of the pirtobrutinib arm (ORR: 94.3% in the pirtobrutinib arm vs 80.9% in the BendaR arm; 12-month DOR rates: 97.7% [93.1, 99.3] in the pirtobrutinib arm vs 88.1 [80.4, 92.9] in the BendaR arm).

Treatment-naïve or previously treated but BTKi naïve CLL

In Study 20030, pirtobrutinib demonstrated significant non-inferiority to ibrutinib in terms of overall response rate (ITT population: 87.0% [82.90, 90.44] in the pirtobrutinib arm and 78.5% [73.73, 82.85] in the ibrutinib arm), confirming comparable antitumour activity in BTK inhibitor-naïve patients, including both treatment-naïve (92.9% [86.41, 96.87] for pirtobrutinib and 85.8% [78.03, 91.68] for ibrutinib) and pretreated populations (84.0% [78.48, 88.61] in the pirtobrutinib arm and 74.8% [68.46, 80.39] in the ibrutinib arm).

PFS results showed a consistent trend favouring pirtobrutinib across populations (in ITT population: HR=0.755 [95% CI: 0.531, 1.075] for IRC-assessed versus 0.569 [0.388, 0.834] investigator-assessed).

3.3. Uncertainties and limitations about favourable effects

Although the submitted package demonstrates antitumour activity of pirtobrutinib in CLL/SLL, several uncertainties limit the strength, precision and generalisability of the favourable effect

In Study 20023, a statistically significant improvement in IRC-assessed PFS versus bendamustine-rituximab was observed. The event-driven primary analysis, while sufficient to demonstrate statistical significance, is based on a limited number of PFS events at the time of analysis. Moreover, OS data remain immature, with median OS not reached in either treatment arm and only a limited number of events observed (3 vs 10 events).

In Study 20030, the primary endpoint was non-inferiority in ORR versus ibrutinib. Although ORR confirms antitumour activity, it does not directly capture duration of disease control or survival benefit.

The Applicant committed to provide extended follow-up data for PFS and OS from studies 20023 and 20030 as a REC.

3.4. Unfavourable effects

In Study 20023, the most common any grade TEAEs reported in pirtobrutinib or BendaR arms were COVID-19 (21.4% vs 9.1%), upper respiratory tract infection (17.9% vs 6.8%), arthralgia (12.1% vs 0.8%), neutropenia (12.1% vs 38.6%), thrombocytopenia (7.9% vs 12.9%), anaemia (9.3% vs 15.9%).

In Study 20030, where exposure duration was comparable between pirtobrutinib and ibrutinib, the most frequently reported TEAEs with pirtobrutinib or ibrutinib were neutropenia (22.7% vs 17.8%), upper respiratory tract infection (17.9 vs 19.4), anaemia (15.2% vs 14.2%), pneumonia (13.6% vs 15.1%). Grade 3 or 4 TEAEs were reported at a similar frequency with pirtobrutinib (163 participants [49.4%]) and Arm ibrutinib (158 participants [48.6%]).

Across individual studies and the integrated safety set, pirtobrutinib demonstrated a consistent and predictable safety profile. The nature, frequency, and severity of adverse events were broadly similar across treatment-naïve and previously treated populations, with no emergence of unexpected toxicity

patterns. This consistency across heterogeneous populations and study designs supports a high level of confidence in the overall characterization of pirtobrutinib safety.

Pirtobrutinib was associated with low rates of treatment discontinuation, dose reduction, and permanent interruption due to adverse events. This finding was consistent across treatment-naïve and previously treated populations and reflects good overall tolerability.

Infections represented the most common adverse events. The majority of infections were manageable with standard supportive care measures, and infection-related discontinuations were uncommon. Across studies, infection rates were stable and did not reveal evidence of progressive or cumulative risk within the observed follow-up.

Hematologic adverse events, including neutropenia and anaemia, were common but generally reversible and manageable.

3.5. Uncertainties and limitations about unfavourable effects

A fundamental uncertainty arises from the heterogeneity of treatment exposure across comparators in Study 20023. Pirtobrutinib was administered continuously until progression or intolerance, whereas BendaR was delivered over a short, fixed duration.

In addition, definitions of drug interruption differed between treatment arms, with infusion interruptions included for BendaR and rituximab but not for pirtobrutinib. This lack of harmonisation weakens the interpretability of comparative tolerability based on dose interruptions or modifications.

Second primary malignancies, particularly non-melanoma skin cancers, were observed more frequently as crude proportions with longer pirtobrutinib exposure. Although exposure-adjusted rates were similar to or lower than comparators, uncertainty remains regarding cumulative malignancy risk with prolonged BTK inhibition, given the relatively short follow-up and long latency of many solid tumors. The MAH is conducting an integrated analysis for second primary malignancies with a 5-year follow-up from ongoing studies with pirtobrutinib to address this issue.

3.6. Effects Table

Table 44. Effects Table for Jaypirca for the treatment of untreated adult patients with chronic lymphocytic leukaemia based on study 20023 (data cut-off: 11 July 2025).

Effect	Sort description	Unit	Jaypirca	BR	Uncertainties / Strength of evidence	References
Favourable Effects			**N=141**	**N=141**		
PFS	Time from randomisation until PD by IRC per iwCLL 2018 criteria or death from any cause, whichever occurs first	HR [95% CI]	0.199 [0.107, 0.367]		P-value <0.0001 Results based on limited number of events (13 vs 48).	Study 20023

Effect	Sort description	Unit	Jaypirca	BR	Uncertainties / Strength of evidence	References
Unfavourable Effects			**N=140**	**N=132**		
Infections	Incidence Any grade Grade 3-5	N (%)	80(57.1) 34 (24.3)	44(33.3) 69 (52.3)	Differential exposure across treatment arms	Study 20023
Neutropenia	Incidence any grade		17 (12.1)	51 (38.6)		
Anaemia			13 (9.3)	21 (15.9)		
Thrombocytopenia			11 (7.9)	17 (12.9)		

Abbreviations: BR: bendamustine+ rituximab; PFS: progression free survival PD: progressive disease; IRC: Independent Review Committee; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; HR: hazard ratio; CI: confidence interval

Table 45. Effects Table for Jaypirca for the treatment of treatment-naïve or previously treated but BTKi naïve CLLadult patients with chronic lymphocytic leukaemia based on study 20030 (data cut-off: 11 July 2025).

Effect	Short description	Unit	Jaypirca 200 mg	Ibrutinib 420 mg	Uncertainties / Strength of evidence	References
Favourable Effects			**N=331**	**N=331**		
ORR	Assessed by IRC per iwCLL 2018 criteria in ITT population	% of patients (95% CI)	87.0 (83, 90)	78.5 (74, 83)	Response Rate Ratio (95% CI) 1.11 (1.03, 1.19), p<0.0001 Data from time to event endpoints still immature but positive trend for PFS	Study 20030
DOR	Median	Months (95% CI)	24.67 (24.38, NE)	NE (NE, NE)		

Effect	Short description	Unit	Jaypirca 200 mg	Ibrutinib 420 mg	Uncertainties / Strength of evidence	References
Unfavourable Effects			**N=330**	**N=325**		
Infections	Incidence Any grade Grade 3-5	N (%)	 226 (68.5) 56 (16.9)	 241 (74.2) 54 (16.6)		Study 20030
Neutropenia	Incidence any grade		75 (22.7)	58 (17.8)		
Anaemia			50 (15.2)	46 (14.2)		
Thrombocytopenia			26 (7.9)	37 (11.4)		

Abbreviations: ORR: overall response rate; CI : confidence interval; DOR: duration of response; ITT: intention to treat; NE: not estimable; BTKi: Bruton's tyrosine kinase inhibitor; iwCLL: International Workshop on Chronic Lymphocytic Leukemia

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CLL is a chronic, progressive B-cell malignancy characterised by cumulative morbidity and eventual disease progression requiring repeated lines of therapy. In both first-line and relapsed settings, prolongation of PFS is a clinically meaningful objective, as it reflects sustained disease control, delays the need for subsequent treatment, and may reduce treatment-related morbidity associated with repeated therapeutic exposure.

In this context, the demonstration of a statistically significant and clinically relevant improvement in PFS versus chemoimmunotherapy in previously untreated patients without del(17p) represents an important favourable effect. This finding supports the ability of pirtobrutinib to provide durable disease control in a population where long-term management is central to therapeutic strategy.

In addition, demonstration of non-inferior overall response rate versus ibrutinib confirms that pirtobrutinib achieves substantial antitumour activity comparable to an established BTK inhibitor. Although ORR alone does not capture long-term benefit, high and consistent response rates indicate meaningful biological activity and support the therapeutic relevance of pirtobrutinib within the current treatment landscape. PFS results in study 20030 showed a consistent trend favouring pirtobrutinib vs ibrutinib across populations.

From a safety perspective, infections constitute the most clinically relevant adverse events observed with pirtobrutinib, including occasional fatal cases in heavily pretreated populations. Haematologic toxicities, particularly neutropenia and anaemia, were also common but generally manageable and

reversible with supportive care or temporary treatment modification. Importantly, mortality rates were low overall, and no consistent pattern of treatment-related fatal toxicity emerged.

Overall, no new safety signals arise from the assessment of the data submitted within this application and the safety profile of pirtobrutinib remains unchanged and can be managed with the current warnings and recommendations in the SmPC.

3.7.2. Balance of benefits and risks

The efficacy package helps demonstrate antitumour activity of pirtobrutinib in CLL/SLL across two pivotal studies. In Study 20023, pirtobrutinib showed a statistically significant improvement in IRC-assessed PFS versus bendamustine-rituximab in treatment-naïve patients without del(17p), supporting a clinically meaningful effect on disease control compared with chemoimmunotherapy. In Study 20030, non-inferiority versus ibrutinib was demonstrated for ORR, indicating comparable antitumour activity versus an established BTK inhibitor in BTKi-naïve patients.

Taken together, the efficacy data support that pirtobrutinib provides meaningful antitumour activity and can achieve improved disease control versus chemoimmunotherapy in a defined first-line population. Non-inferiority on ORR versus ibrutinib was demonstrated, indicating comparable antitumour activity to an established BTK inhibitor in BTKi-naïve patients across treatment settings.

Consistent safety findings are provided across randomized controlled studies and integrated analyses. While the available safety data support a well-known and manageable safety profile for pirtobrutinib, residual uncertainties remain regarding long-term safety across studies. These uncertainties do not undermine the overall benefit–risk assessment but highlight areas where additional follow-up, refined analyses, and post-approval evidence are required and will be provided through the final analyses for OS of the pivotal studies and an integrated analysis for second primary malignancies from ongoing studies with pirtobrutinib.

3.8. Conclusions

The overall B/R of Jaypirca is positive in the treatment of adult patients with chronic lymphocytic leukaemia.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include treatment of adult patients with chronic lymphocytic leukaemia (CLL) for JAYPIRCA, based on interim results from studies LOXO-BTK-20023 (BRUIN-CLL-313) and LOXO-BTK-20030 (BRUIN-CLL-314). Study 20023 is a phase 3 open-label, randomised study of pirtobrutinib (LOXO-305) versus bendamustine plus rituximab in untreated patients with CLL/SLL. Study 20030 is a phase 3 open-label, randomised study of pirtobrutinib (LOXO-305) versus ibrutinib in patients with CLL/SLL. As a consequence, sections 4.1, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of pirtobrutinib in the treatment of patients with mantle cell lymphoma (MCL), the clinical study report of the Phase 3 study LOXO-BTK-20019 (BRUIN MCL-321) comparing pirtobrutinib to investigator choice of BTK inhibitor in patients with previously treated BTK inhibitor naïve MCL should be submitted by	31 December 2026

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000316267