1. Pirtobrutinib
LY3527727
Investigator's Brochure

Confidential Information

Lilly Research Laboratories
Eli Lilly and Company
Indiana polis, Indiana 46285

For questions, please contact Eli Lilly and Company, Indianapolis, IN, USA, Telephone (317) 276-2000.

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Investigator's Brochure for Pirtobrutinib
Includes Data to 27 January 2024

Enclosed is an updated investigator's brochure (IB) for pirtobrutinib.

This updated IB is considered a substantial update because:

- it is likely to have a significant impact on safety or physical or mental integrity of the subjects.

If the investigator chooses *not* to retain a superseded version of the IB, it should be destroyed in a confidential manner.

The updated version of the IB must not be implemented until all required regulatory authority and ethics review board notifications/approvals per local regulations have been submitted/obtained.

Record of IB Reviews and Updates

The changes from previous IB version (g) dated 17 April 2023 include the following:

Section	Description of Change
Header	• Lettered version indicator added to the header.
Throughout	• Minor editorial updates and deleted information related to MS as sponsor decided to no longer pursue this indication. .
Section 1. Pirtobrutinib LY3527727 Investigator's Brochure	• The reason for substantiality has been added.
Section 2. Introduction	• Updated the approved indications (MCL and CLL/SLL) for pirtobrutinib. • Added a note on removal of information pertaining to MS.
Section 3. Physical, Chemical and Pharmaceutical Properties and Formulation	**Section 3.2.1.** • Removed all the references to T3 tablets, which was the formulation designed for MS indication. • Minimized the information related to T1 tablets.
Section 4. Nonclinical Studies	Updated template language. **Section 4.1.1** • Removed information on mouse EAE model for MS. **Section 4.2.2** • Added information from 6-month rat toxicology study, 9-month dog toxicology study, and fertility studies in male and female rats. **Section 4.3** • Added toxicity details from 6-month rat toxicity study and 9-month dog toxicity study and information from fertility studies in male and female rats.

Section 5. Effects in Humans	**Section 5.1.1** • Updated population PK analysis for Study LOXO-BTK-18001 and Table 5.4. **Section 5.1.3** • Updated drug distribution details for Study LOXO-BTK-18001. **Section 5.1.5** • An introduction was added to the section. • A note on a clinical pharmacology study evaluating the effect of pH was added. **Section 5.1.6** • An introduction was added to the section. • Minimized the information in in vitro studies and clinical pharmacology studies. **Section 5.1.7.1** • Updated PK data for patients with renal impairment in study LOXO-BTK-20013 and LOXO-BTK-18001. • Added Figure 5.3, which illustrates the effect of renal impairment on apparent oral clearance in BTK-18001 population. **Section 5.1.7.2** • Updated PK data for patients with hepatic impairment in Study LOXO-BTK-20012 and Study LOXO-BTK-18001. **Section 5.1.7.3** • Added details on effect of Asian origin on PK of pirtobrutinib. **Section 5.2.1** • Updated section summary highlighting the study safety data that were presented in the IB. **Section 5.2.1.1** • Summarized clinical safety data from patients across 2 studies, Study LOXO-BTK-18001 (J2N-OX-JZNA) and Study J2N-MC-JZNJ. • Deleted the information on demographics and baseline characteristics to align with template instructions. • Updated data on expanded access protocols.

	• Added rationale for selection of RP2D in hematologic malignancy indications (200 mg QD). **Section 5.2.1.2 and** Table 5.9 Updated per template. **Section 5.2.2** • Updated efficacy data for Study LOXO-BTK-18001. **Section 5.3** • Added marketing experience details.
Section 6. Summary of Data and Guidance for Investigator	**Section 6.1** • Statement about increase in risk of bleeding in patients receiving antiplatelet and anticoagulant agents was added. **Section 6.2.2.1.1** • Added MCL/CLL to development indications as studies are ongoing to evaluate the indication can be broadened. **Section 6.2.2.1.2** • CLL/SLL indication statement is added as approved indication. **Section 6.2.2.2.2** • Added approved indication CLL/SLL and made reference to check individual study protocol for trial-specific guidelines on dose adjustments to manage AEs. **Section 6.2.2.3** • Added results from male and female fertility studies in rats. **Section 6.2.2.5.2** • Statement about increase in risk of bleeding in patients receiving antiplatelet and anticoagulant agents was added. **Section 6.2.2.6.** • The effect of pirtobrutinib on male and female fertility in animals was added. **Section 6.2.2.7** • Updated Table 6.2. Two new ADRs added, hematuria and peripheral edema. **Section 6.2.2.8** DDI information has been updated with details on CYP3A inducers, BCRP substrates, CYP2C19 substrates, and CYP3A substrates. **Section 6.2.2.9**

	• This section was updated with pirtobrutinib overdose information. **Section 6.2.2.12.1** • Updated absorption and hepatic impairment details
Section 7. Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions	• Updated with the template language. • Table 7.1 was revised and updated with the current data; no new RSI events added.
Section 8. References	• This section was updated as per the current content

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2. Introduction

Pirtobrutinib (LOXO-305; also known as LY3527727) is a selective BTK inhibitor that is currently being developed in hematologic malignancies. Pirtobrutinib is a small molecule designed to competitively block the ATP-binding site of BTK. Pirtobrutinib is distinct from the other approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) in several important ways including on the basis of its selectivity, favorable absorption, distribution, metabolism, and excretion (ADME) properties, and noncovalent binding mode (Brandhuber et al. 2018). Pirtobrutinib is a highly selective molecule that is at least 300-fold more selective for BTK than 98% of 370 other kinases tested, thus, limiting the potential for off-target mediated toxicities. These features enable pirtobrutinib to achieve mean trough pharmacokinetic (PK) exposures that exceed the concentration required for IC_{96} and to deliver extensive and sustained BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. Moreover, the noncovalent binding mode of pirtobrutinib is unaffected by BTK C481 substitutions, a common mechanism of drug resistance described for covalent inhibitors (Byrd et al. 2013; Chiron et al. 2014; Woyach et al. 2017; Xu et al. 2017; Woyach et al. 2019). Collectively, these unique properties of pirtobrutinib are expected to deliver more potent, continuous, and selective inhibition of BTK in a variety of settings, potentially resulting in increased efficacy. Of note, the activity of pirtobrutinib in diverse preclinical model systems supports this underlying hypothesis (Brandhuber et al. 2018).

Due to these features, pirtobrutinib represents a potential best-in-class BTK inhibitor for patients with hematological malignancies, compared to currently available covalent BTK inhibitors.

Pirtobrutinib is approved for the treatment of MCL and CLL/SLL and is currently under clinical development for the treatment of other B-cell NHL. Lilly made a business decision to halt the development for multiple sclerosis (MS) indication and no patients were enrolled for the treatment of this indication.

3. Physical, Chemical, and Pharmaceutical Properties and Formulation

3.1. Drug Substance

3.1.1. Nomenclature

- Nonproprietary name: Pirtobrutinib

  CAS: 2101700-15-4
- Lilly compound number: LY3527727
- Chemical name

  CAS: 1H-Pyrazole-4-carboxamide, 5-amino-3-[4-[[(5-fluoro-2-methoxybenzoyl)amino]methyl]phenyl]-1-[(1S)-2,2,2-trifluoro-1-methylethyl]-

  IUPAC: 5-amino-3-{4-[(5-fluoro-2-methoxybenzamido)methyl]phenyl}-1-[(2S)-1,1,1-trifluoropropan-2-yl]-1H-pyrazole-4-carboxamide

  Other: (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazole-4-carboxamide

  (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide

3.1.2. Chemical Structure

Figure 3.1 shows the chemical structure of pirtobrutinib.

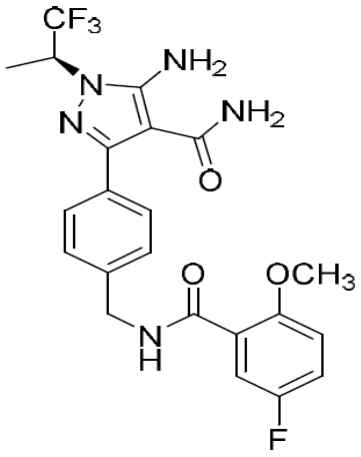


Figure 3.1. Structure of LY3527727.

3.1.3. Physical and Chemical Characteristics

Molecular weight:	479.44 g/mol
Molecular/Empirical formula:	$C_{22}H_{21}F_4N_5O_3$
Description:	White to practically white to yellow to light brown powder
pKa:	Less than or equal to 2
Specific Rotation, $[\alpha]^{20}_D$:	-15.03° (at 589 nm and 25°C)
Stability:	Pirtobrutinib drug substance is stable when stored at room temperature
Solubility:	See Table 3.1. for solvent and solubility data

Table 3.1. Pirtobrutinib Solubility (24 hours at 25°C)

Solvent	Solubility (mg/mL)	Solubility Description
Water	0.013	Practically insoluble, or insoluble
Ethanol	51.000	Soluble

3.2. Drug Product

Pirtobrutinib is supplied as immediate-release film-coated tablets.

3.2.1. Drug Product Name, Formulation, and Strength(s)

Throughout the pirtobrutinib oncology clinical development program, the investigational product was available as 2 different tablet formulations (referred to as T1 tablet and T2 tablet).

The initial tablet (T1 tablet) was a formulation consisting of pirtobrutinib and the following inactive ingredients:

- hydroxypropyl methylcellulose acetate succinate
- microcrystalline cellulose
- mannitol
- sodium starch glycolate, and
- magnesium stearate.

The T2 composition includes pirtobrutinib and the following inactive ingredients:

- hydroxypropyl methylcellulose acetate succinate
- microcrystalline cellulose
- lactose monohydrate
- croscarmellose sodium
- silicon dioxide, and
- magnesium stearate.

T2 tablets are coated with a blue coating mixture comprising hypromellose, titanium dioxide, triacetin, and FD&C Blue #2 - Aluminum Lake (Indigo Carmine).

Hematologic malignances

Pirtobrutinib is supplied as an immediate-release tablet containing 25, 50, or 100 mg of drug substance.

3.2.2. Storage Conditions

Pirtobrutinib tablets are to be stored at room temperature.

4. Nonclinical Studies

The pharmacology, PK, ADME, and toxicology programs described in this section characterized the nonclinical efficacy, disposition, and safety of pirtobrutinib.

Pirtobrutinib was tested for its ability to inhibit both wild-type and mutant BTK in vitro using enzyme and cell-based assay systems. In vivo pharmacological effects of pirtobrutinib were evaluated in immunodeficient mice implanted with human B-cell lymphoma cell lines. In these mice, tumor growth was assessed, and tolerability monitored following oral dosing of pirtobrutinib. Additionally, the potential for off-target pharmacological activity was evaluated in kinase, enzyme, transporter, ion channel, and receptor assays.

These studies used liquid chromatography-mass spectrometry (LC-MS) assays for quantification of pirtobrutinib. The LC-MS methods used for good laboratory practice (GLP) toxicity studies in rats and dogs were validated according to regulatory guidance. Doses and plasma concentrations are expressed as free base equivalents.

Nonclinical safety was evaluated in in vitro, rat, and dog studies. The toxicology, toxicokinetic (TK), and safety pharmacology studies supporting pirtobrutinib were performed in accordance with the GLP regulations and were conducted in countries that are signatories to the Organization for Economic Cooperation and Development mutual acceptance of data agreement and at laboratories that are members of their national GLP compliance program. Other pharmacodynamic (PD) and PK studies do not fall under these regulations. Applicable International Council for Harmonisation (ICH), Committee for Medicinal Products for Human Use, and FDA guidance documents were also referenced during design of the toxicology, TK, and safety pharmacology studies of pirtobrutinib.

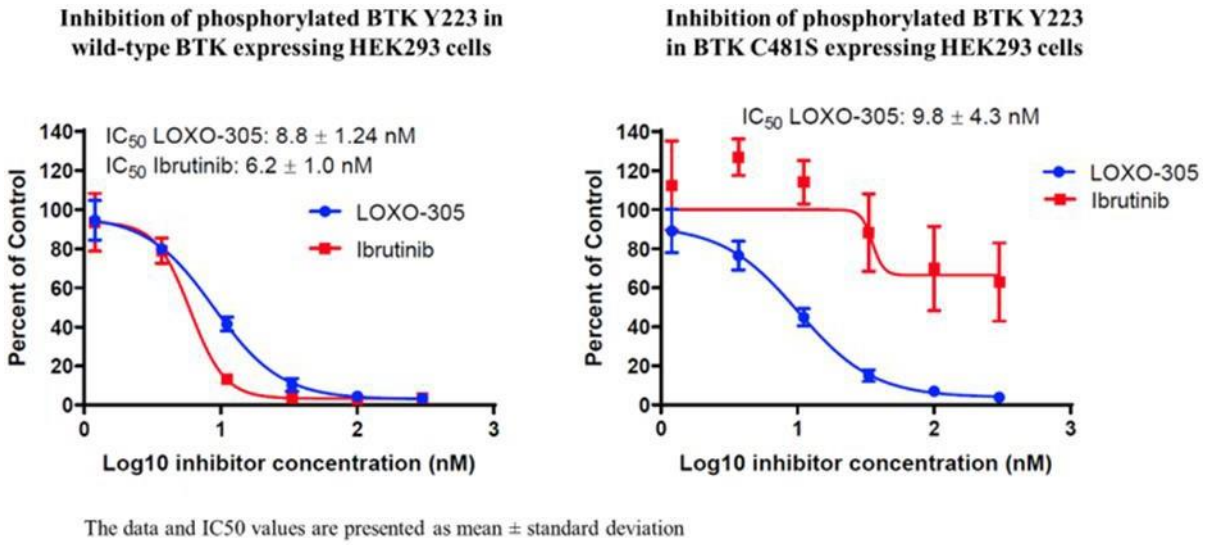
4.1. Nonclinical Pharmacology

The pharmacology studies described in this section were designed to characterize the nonclinical efficacy of pirtobrutinib.

4.1.1. Efficacy Pharmacology

Pirtobrutinib demonstrated potent inhibitory activity against human BTK and BTK C481S, an acquired resistance mutation in oncology, in purified enzyme assays and in cellular assays. Pirtobrutinib inhibited:

- BTK and BTK C481S enzymatic activity
- auto-phosphorylation of cellular BTK and BTK C481S (Figure 4.1)
- BTK-dependent cell proliferation, and
- activation of human B-cells with low nanomolar potency.

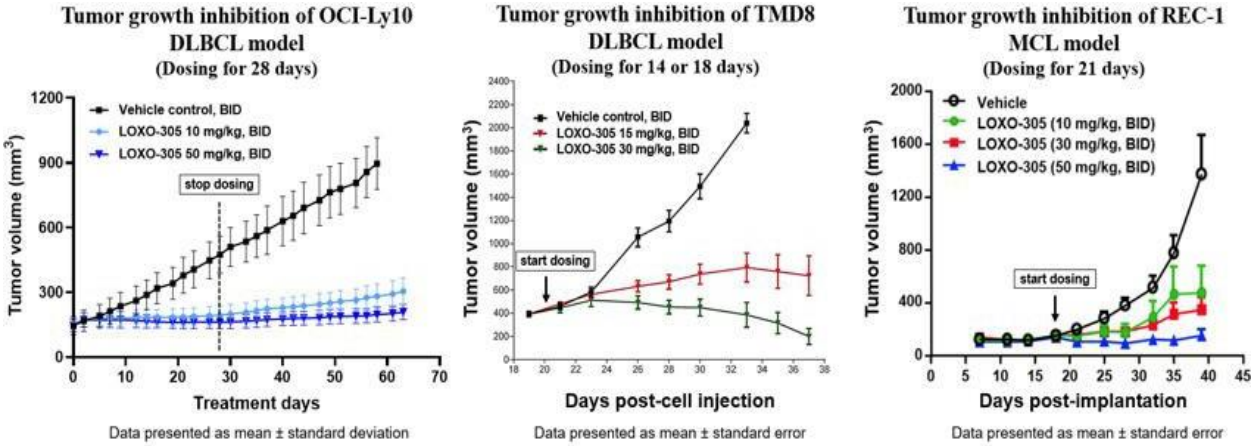


The data and IC50 values are presented as mean ± standard deviation

Abbreviations: BTK = Bruton's tyrosine kinase; HEK = human embryonic kidney; IC_{50} = drug concentration that produces 50% of maximum inhibitory effect.

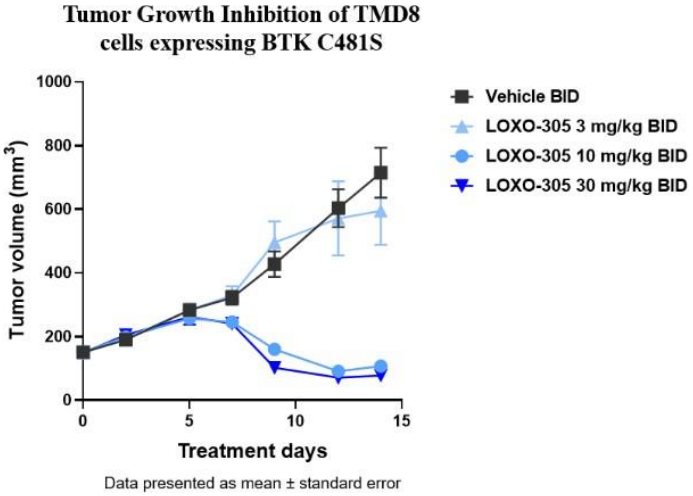
Figure 4.1. Pirtobrutinib and ibrutinib dose-response effects on Y223. Auto-phosphorylation in HEK293 cells stably expressing BTK and BTK C481S.

Pirtobrutinib significantly inhibited the growth of BTK-dependent tumors from human lymphoma lines implanted into immunodeficient mice (Figure 4.2 and Figure 4.3). The tumor growth inhibition by pirtobrutinib was dose dependent. In a tumor xenograft model using a TMD8 cell line engineered to express BTK C481S in addition to BTK, pirtobrutinib demonstrated dose dependent tumor growth inhibition and regression. The combination of pirtobrutinib and venetoclax was also tested in the engineered TMD8 BTK C481S tumor xenograft model. The combination of pirtobrutinib and venetoclax significantly inhibited tumor growth (Figure 4.4), resulting in tumor regressions. Additionally, pirtobrutinib alone and in combination with venetoclax were well tolerated by the mice in the tumor xenograft models, without significant effects on weight.



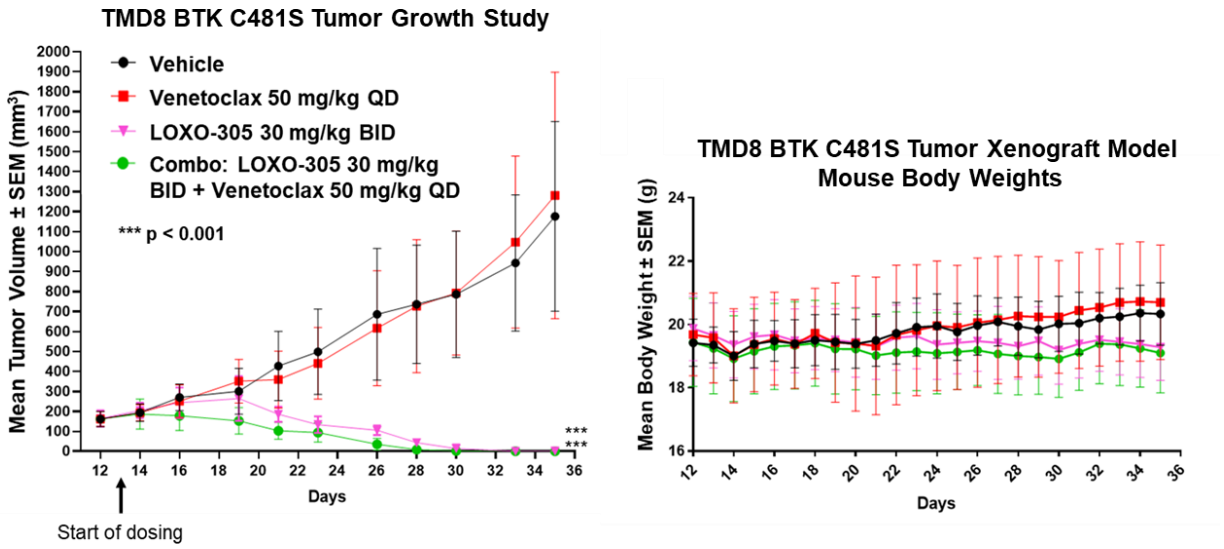
Abbreviations: BID = twice daily; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma.

Figure 4.2. Dose-dependent inhibition of tumor growth in human B-cell lymphoma cell line xenograft tumor models.



Abbreviations: BID = twice daily; BTK = Bruton's tyrosine kinase.

Figure 4.3. Dose-dependent inhibition of tumor growth in a TMD8 BTK C481S human xenograft B-cell lymphoma model.



Abbreviations: BID = twice daily; BTK = Bruton's tyrosine kinase; QD = once daily.

Figure 4.4. **Pirtobrutinib and venetoclax inhibition of tumor growth in engineered TMD8 BTK C481S human diffuse B-cell lymphoma cell line xenograft tumor model.**

4.1.2. Secondary Pharmacology

Pirtobrutinib at concentrations predicted to be achieved in humans is not expected to have a significant effect on a range of non-BTK targets and receptors. Pirtobrutinib was more than 300-fold selective for BTK versus 98% non-BTK kinases tested in a purified enzyme screen. Only 8 kinases other than BTK were inhibited by more than 50% when tested at a concentration of 1-µM pirtobrutinib. Pirtobrutinib was tested against 44 additional transmembrane and soluble receptors, ion channels, monoamine transporters, and enzymes at a concentration of 1 µM, and there was no significant inhibition (at least 50%) of the evaluated targets. The high selectivity of pirtobrutinib for BTK inhibition was maintained in additional cell-based mechanistic assays.

4.2. Nonclinical Absorption, Distribution, Metabolism, and Excretion

4.2.1. Single-Dose Pharmacokinetics

Several single dose studies were conducted to evaluate the absorption and PK of pirtobrutinib and its metabolites. Studies were conducted in male and female Sprague Dawley rats and male and female beagle dogs. Pirtobrutinib has high permeability in vitro but low aqueous solubility. To reduce the variability in oral absorption, a spray-dried dispersion (SDD) tablet formulation was developed that shows consistent oral bioavailability of approximately 50% in rats and 80% in dogs. The bioavailability of the SDD formulation was also not dependent on feeding state in dogs.

The oral exposure, as measured by AUC, of pirtobrutinib was consistently higher (greater than 6-fold) in female rats than in males with the same dose of pirtobrutinib. The sex difference was also apparent after IV administration of pirtobrutinib, which had approximately 6-fold higher clearance in male rats than in females. The lower exposure in males was due to a higher clearance in males and a higher level of circulating plasma metabolites than females. There was no sex difference in the PK of pirtobrutinib in dog, and none is expected in other nonrodent species, including humans. Table 4.1 shows pharmacokinetic properties for radioactivity and pirtobrutinib in male and female rats.

Table 4.1. Pharmacokinetic Parameters for Radioactivity and Pirtobrutinib in Male and Female Rats Following Oral Administration of 35 mg/kg [^{14}C] Pirtobrutinib in Solution (Study LOXO-305-DMPK-035)

	Male			Female		
	^{14}C Plasma	^{14}C Blood	Pirtobrutinib in Plasma	^{14}C Plasma	^{14}C Blood	Pirtobrutinib in Plasma
C_{max} (ng-eq/g or ng/mL)	9860	6920	4130	15700	12100	13900
AUC_{0-t} (ng-eq•hr/g or ng•hr/mL)	130000	86700	15900	135000	108000	106000
AUC_{0-inf} (ng-eq•hr/g or ng•hr/mL)	134000	91300	16100	137000	109000	106000
T_{max} (hr)	1.00	1.00	1.00	2.00	2.00	2.00
$t_{1/2}$ (hr)	16.1	43.3	3.56	9.59	31.6	4.97

Abbreviations: AUC_{0-t} = area under the plasma concentration-time curve from zero to 120 hr; AUC_{0-inf} = area under the plasma concentration-time curve from zero to infinity; C_{max} = maximum observed drug concentration.

4.2.2. Multiple-Dose Toxicokinetics

In the rat 6-month toxicology study, systemic exposure to pirtobrutinib increased less than dose proportionally in males and females. The T_{max} was observed between 1 and 16 hours after first dose in males and between 4 and 24 hours after first dose in females. Exposures were higher in females compared to males on all TK occasions. No substantial accumulation of pirtobrutinib was observed (generally <2-fold) over the course of the 6-month study.

In an enhanced pilot embryofetal development study in female rats, the T_{max} value of pirtobrutinib in plasma was 1 or 4 hours post second dose and exposure increased with increasing dose. Following repeat dosing, no accumulation of pirtobrutinib was observed based on the AUC_{0-24h} value across all dose groups. Exposure in pregnant rats was generally similar to exposure in nonpregnant rats.

In a fertility study in female rats, exposure to both pirtobrutinib and metabolite LSN3828720 increased less than proportionally with dose on Day 0 and Gestation Day 6. There was no evidence of accumulation of pirtobrutinib, but there was accumulation of metabolite over the course of the study. Metabolite AUC exposure was similar to pirtobrutinib exposure on Gestation Day 6. In a fertility study in male rats, exposure to both pirtobrutinib and metabolite LSN3828720 increased less than proportionally with dose on Days 0 and 27. There was no evidence of accumulation of pirtobrutinib but there was accumulation of metabolite over the

course of the study. Metabolite AUC exposure was approximately 3.5-fold higher than pirtobrutinib exposure on Day 27.

In the 9-month dog toxicology study, the T_{max} value was generally observed 1 hour after the first daily dose and the increase in systemic exposure (C_{max} and $AUC_{0\text{-}24h}$) tended to be greater than dose proportional. Following repeated dosing, systemic exposure was similar or increased relative to Day 1 and suggested that steady state in exposure was achieved by Day 90. The accumulation of pirtobrutinib in the 9-month dog study was not considered substantial. No apparent sex difference in exposure was observed.

4.2.3. Distribution

The volume of distribution of pirtobrutinib ranged from approximately 2 L/kg in the dog to 5 L/kg in the male rat, which indicates that pirtobrutinib distributes into tissues. After oral administration of [^{14}C]pirtobrutinib in male rats, pirtobrutinib was widely distributed to tissues. The tissues exposed to the highest calculated radiation absorbed doses following oral administration of [^{14}C]pirtobrutinib, excluding esophagus, gastrointestinal organs, and urinary bladder, were

- epididymis
- liver
- uveal tract
- pigmented skin, and
- testis.

The radioactivity declined over time to below the lower limit of quantitation (less than 178 ng-eq) by 168 hours post dose for all tissues, except uveal tract and liver. The level of radioactivity remaining in the uveal tract and liver at 168 hours was 294 and 262 ng-eq, respectively. Distribution trends in the pigmented uveal tract of the eye suggested that [^{14}C]pirtobrutinib-related radioactivity did associate with melanin-containing ocular tissues. The calculated $t_{1/2}$ for the uveal tract was 66.4 hours with the radioactivity concentrations declining over time and approaching the lower limit of detection at 168 hours post dose. Distribution of [^{14}C]pirtobrutinib-related material to the testis and regions of the brain was rapid with measurable concentrations by 1 hour. Levels in both the testis and the brain then declined to below the lower limit of quantitation by 24 hours.

4.2.4. Protein Binding

In rats and dogs, pirtobrutinib was approximately 87% and 82% bound to plasma proteins, respectively, and did not show concentration-dependent binding. For rats and dogs, the mean blood-to-plasma ratios were 0.84 and 0.88, respectively.

4.2.5. Metabolism

In long-term rat and dog cultured hepatocytes, pirtobrutinib was metabolized by both oxidation and glucuronidation. Inhibition of oxidative metabolism by addition of the P450 inhibitor 1-aminobenzotriazole (ABT) showed that oxidative metabolism is CYP450 dependent. All

metabolites formed by human hepatocytes were also formed in rat and/or dog hepatocytes. In rats, after oral administration of [^{14}C] pirtobrutinib (35 mg/kg), the primary clearance pathways of pirtobrutinib involved

- biliary elimination
- oxidation
- direct glucuronidation
- direct sulfonation, and
- oxidation with glucuronidation.

In time averaged plasma $AUC_{0\text{-}24h}$ pools (Hamilton et al. 1981; Hop et al. 1998) from male rats, a total of 8 metabolites and 1 process impurity (LSN3563791) were quantified and identified. In the $AUC_{0\text{-}24h}$ sample, concentrations of a pyrazole ring opened metabolite with (M1) and without oxidation (M5), were greater than pirtobrutinib, with each individually representing 33.9% (M1), 20.1% (M5), and 17.9% (pirtobrutinib) of TRA. The remaining plasma metabolites were considered minor, each individually representing not more than 3.7% of the TRA. In female rat plasma time averaged $AUC_{0\text{-}24h}$ pool, a total of 3 metabolites and 1 process impurity (LSN3563791) were quantified and identified. In the $AUC_{0\text{-}24h}$ sample, pirtobrutinib was the predominant component representing 74.2% of the TRA, while the remaining metabolites were considered minor, with each individually representing not more than 5.6% of the TRA. The most abundant metabolite circulating in human plasma, M1, was present in rat plasma. After multiple QD doses of pirtobrutinib 200 mg in participants, the M1 represented 10.4% of total daily pirtobrutinib-related exposure (pirtobrutinib + M1) due to the longer half-life of M1 compared with the parent drug. Taken together, these data support the use of rat and dog for nonclinical safety assessment.

4.2.6. Excretion

After oral administration of [^{14}C]pirtobrutinib (35 mg/kg) to male and female rats, intact or BDC, urinary excretion was low (not more than 3%). Pirtobrutinib and 4 trace metabolites were found in urine (each representing not more than 0.6% of dose). In male and female intact rats, the majority of radioactivity was recovered in feces (at least 95%). From BDC rats, the majority of radioactivity was recovered in bile and feces with 52% and 39% of the dose recovered in bile, and 42% and 54% of the dose recovered in feces from male and female rats, respectively. In rat feces from intact male and female rats, pirtobrutinib was the largest component observed (57.7% in male rats and 72.9% in female rats).

A sulfamate M10 (12.3% in male rats, 1.8% in female rats), O-desmethyl pirtobrutinib (M11, 5.7% M, 10.3% F), and process impurity LSN3563791 (3.4% M, 3.9% F) were identified in feces of both males and females, while a direct glucuronide conjugate M14 (5.4% M) was identified only in males.

In BDC rat feces, pirtobrutinib was the major component (34.8% M, 47.3% F), while 2 metabolites M10 (3.5% M, 0.7% F) and M11 (0.9% M, 2.9% F) and process impurity LSN3563791 (1.2% M, 1.5% F) were minor. In bile from the BDC rats, the following were identified:

- pirtobrutinib (14.8% M, 9.7% F)
- N-glucuronide M2 (LSN3829057, 3.8% M, 5.9% F)
- mono-oxy glucuronides M3 (10.5% M, 6.2% F)
- M4 (16.8% M, 11.8% F), and
- O-desmethyl glucuronide M12 (1.3% M, 1.5% F).

Excretion data are not available for other species.

4.3. Nonclinical Safety Pharmacology and Toxicology

The toxicology program for pirtobrutinib was designed to evaluate the toxicity profile of pirtobrutinib and to enable clinical use for the treatment of advanced cancers and other severe or life-threatening diseases. The nonclinical toxicology and safety pharmacology package for pirtobrutinib consists of the following studies:

- repeat-dose studies of up to 6-months duration in rats and up to 9 months duration in dogs, including evaluation of reversibility and cardiovascular, central nervous system, and respiratory safety pharmacology
- in vitro hERG study
- dog cardiovascular safety pharmacology study
- complete battery of genotoxicity studies, including bacterial mutagenicity and in vitro and in vivo micronucleus studies
- male and female fertility studies in rats
- embryofetal development study in rats
- in vitro phototoxicity study
- impurity qualification study in rats, and
- bacterial mutagenicity studies of relevant impurities.

4.3.1. General Toxicity

At tolerated dose levels, pirtobrutinib has a mild toxicity profile in animals, similar to its safety profile in humans. At tolerated dose levels, the primary toxicity in animals was lymphoid organ effects and decreased immune system function, which are likely related to the intended pharmacology of pirtobrutinib as a BTK inhibitor. Minor decreases in red cell mass were consistently observed in rats and dogs. This finding is consistent with the anemia that has been observed in clinical trial participants.

In dogs treated for 3 months with pirtobrutinib, corneal opacities with microscopic erosion, ulceration, single-cell necrosis, fibrosis, and mixed-cell infiltrates were observed in 2 of 8 dogs at the highest dose tested, 5 mg/kg BID. However, no eye effects were observed in dogs treated at the same dose level for 9 months. In rats treated for 6 months with pirtobrutinib, adverse partially reversible vascular and perivascular necrosis and inflammation of pulmonary blood vessels were observed in male rats at clinically relevant exposure levels. No lung effects have been observed in dogs treated for up to 9 months. While there is no definitive method to monitor for this effect, lung effects have not been identified in humans per a thorough analysis of safety data from humans exposed to pirtobrutinib.

Effects observed only at dose levels that exceeded the maximum tolerated dose (MTD) in the 1-month dog study included bone marrow injury, gastrointestinal injury, and lung inflammation. It is common for effects that occur only above the MTD in animals to not translate to a human risk and are considered to be less important to human safety.

4.3.2. Safety Pharmacology

The safety pharmacology package indicates little risk of pirtobrutinib having negative consequences in systems that are vital for life (cardiovascular, central nervous system, and respiratory). While there was a slight increase in QTc interval in the 1-month dog study, this finding was likely spurious because:

- it was not repeated in the dog cardiovascular safety pharmacology study or the 3-month and 9-month dog studies,
- this QTc increase is not consistent with the findings from the in vitro hERG study, and
- QT prolongation has not been identified as a clinical risk.

4.3.3. Genotoxicity Findings

Pirtobrutinib is an aneugenic genotoxicant based on in vitro micronucleus studies. However, based on the unbound C_{max}, human exposure at 200 mg QD, the maximum recommended dose for cancer treatment, is 12-fold lower than the no-effect-level for this genotoxicity in rats.

Pirtobrutinib is not mutagenic.

4.3.3.1. Developmental and Reproductive Effects

Pirtobrutinib is embryotoxic and teratogenic in rats. These effects occurred at clinically relevant exposure levels (Table 4.2). See Section 6.2.2.6 for the implications of these findings.

Pirtobrutinib had no effects on female fertility in rats at 2.8-fold higher exposure than the exposure in humans at 200 mg per day. Pirtobrutinib had no effects on male fertility in rats. However, exposure in male rats as high as human exposure cannot be achieved (see Section 4.3.4).

4.3.3.2. Carcinogenicity

While carcinogenicity has not been assessed in formal carcinogenicity studies, no effects, such as hyperplastic or preneoplastic changes, have been observed in animal studies that would indicate a carcinogenic risk for pirtobrutinib.

4.3.3.3. Other Studies

Pirtobrutinib is not phototoxic.

4.3.3.4. Nonclinical Species Selection

Rats and dogs were chosen as relevant test species for in vivo toxicology studies based on an in vitro and in vivo assessment of pirtobrutinib metabolism, which showed that all relevant metabolites detected in humans were also formed in rat or dog (Section 4.2.5). In addition, rats and dogs express the wild-type BTK target. The BTK protein sequences in rat and dog are more than 98% identical to the human BTK sA equence based on BlastP comparison. Based on the

results from PK studies conducted in rats and dogs (Section 4.1), a BID dosing regimen in these 2 test species was used to ensure that the animals received sustained exposures to pirtobrutinib over a 24-hour period. Due to differences in PK profiles between male and female rats, higher dose levels were evaluated in male rats.

4.3.4. Margin of Safety

As shown in, pirtobrutinib was well tolerated in rats, but not as well tolerated in dogs as in humans. The systemic exposure associated with the nontolerated dose in dogs is lower than the exposure associated with 200 mg QD in humans. The reason for this sensitivity difference is unknown. This is not a significant clinical safety risk, as the general toxicity profile of pirtobrutinib was adequately assessed in dogs in alignment with the recommendations of ICH S9. In addition, female rats tolerated systemic exposure up to 1.9-fold higher than human exposure at 200 mg for 6 months, the longest duration tested. It was not possible to test systemic exposure higher than human exposure in male rats, as pirtobrutinib exposure in male rats was significantly lower than female rat exposure even at the ICH M3(R2) limit dose of 1000 mg/kg per day (500 mg/kg BID). The combination of known information about the nonclinical safety profile of pirtobrutinib and other BTK inhibitors and the clinical safety profile of pirtobrutinib (Section 5.2.1.1) provides reassurance that the safety evaluation of pirtobrutinib has assessed the toxicity risks in humans. Findings at tolerated doses discussed in previous sections were primarily related to the pharmacology of pirtobrutinib and most appear to be clinically monitorable and manageable by supportive care, dose interruptions, or discontinuation.

Table 4.2. Exposure Multiples for Oral Administration of Pirtobrutinib

	Dose	Exposure $AUC_{0\text{-}24hr}$ (ng·hr/mL)	Exposure Multiple[a]
Human			
Recommended dose	200 mg QD	90,300[b]	-
Rat			
MTD (M)[c]	500 mg/kg BID	30,600[d]	<1×
NOAEL/MTD (F)[c]	300 mg/kg BID	168,000[d]	1.9×
Pregnant rats			
Fertility effects NOEL (M)[e]	500 mg/kg BID	32,400[f]	<1×
Fertility effects NOEL (F)[e]	500 mg/kg BID	254,000[f]	2.8×
Fetal effects NOEL[g]	75 mg/kg BID	106,000[h]	1.2×
Fetal effects LOEL[g]	375 mg/kg BID	272,000[h]	3.0×
Dog			
NOAEL[i]	10 mg/kg BID	35,200[j]	<1×
Exceeded MTD[k]	30 mg/kg BID	72,500[l]	<1×

Abbreviations: $AUC_{0\text{-}24hr}$ = area under the plasma concentration-time curve from 0 to 24 hr; BID = twice daily; F = female; LOEL = lowest-observed-effect level; M = male; MTD = maximum tolerated dose; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; QD = once daily.

a Exposure multiple is the exposure in animals divided by exposure in humans.

b See Section 5.1.1.

c NOAEL and MTD determined in a 6-month, repeat-dose toxicity study in rats (Study 8003849). Due to lung findings at all dose levels, a NOAEL was not identified in male rats (Section 4.3.1).

d Exposure on Day 182.

e Male and female fertility NOELs determined in fertility studies in rats (Studies 00353680 and 000353681, respectively).

f Exposure on Day 27 in males and Gestational Day 6 in females.

g NOEL and LOEL determined in an embryofetal development study in rats (Report LOXO-305-TOX-019).

h Exposure on Gestational Day 17.

i NOAEL determined in a 9-month repeat-dose toxicity study in dogs (Study 8003850).

j Average of male and female exposure on Day 273.

k In the 28-day dog study (Report LOXO-305-TOX-008), dogs did not tolerate dose levels as low as 30 mg/kg BID.

l Average of male and female exposure on Day 4.

5. Effects in Humans

Clinical trial data represented in this IB were generated in accordance with the principles of Good Clinical Practice (GCP).

5.1. Clinical Pharmacology

Table 5.1 summarizes the completed clinical pharmacology studies and Sections 5.1.1 through 5.1.8 summarize study results.

Table 5.1. Clinical Pharmacology Studies

Study Number	Title	Study Design	Number of Subjects Dosed	Dosing Regimen	Study Population	Duration of Pirtobrutinib Treatment	Status
LOXO-BTK-20014	A Phase 1, Open-Label, Randomized, 2 Way Crossover, 3 Period Study to Evaluate the Effect of Food and a Proton Pump Inhibitor on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects	Single-center, open-label, randomized, 4-treatment, crossover study	10	Single dose of 200-mg pirtobrutinib in each period	Healthy male and female volunteers	Single dose	Completed
LOXO-BTK-20017	A Phase 1, Single-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LOXO-305 in Healthy Adult Subjects	Single-center, parallel single-ascending dose study	Total = 24 300 mg = 6 600 mg = 6 800 mg = 6 900 mg = 6	Single dose of 300-, 600-, 800-, or 900-mg pirtobrutinib	Healthy male and female volunteers	Single dose	Completed
LOXO-BTK-20006	A Phase 1, Open-Label, Two-Part, Fixed-sequence Drug Interaction Study to Investigate the Effect of Strong CYP3A4 Inhibitor (Itraconazole) and CYP3A4 Inducer (Rifampin) on the Pharmacokinetics of LOXO-305 in Healthy Adult Subjects	2-part study at a single-center; each part conducted as an open-label, 2-period, fixed-sequence crossover study	27	Part 1 Period 1: Single dose of 200-mg pirtobrutinib for 1 day Part 1 Period 2: Multiple doses of itraconazole (200 mg BID on first day, QD thereafter, total of 11 days) Part 2 Period 1: Single dose of 200-mg pirtobrutinib on 2 separate days Part 2 Period 2: Single dose of 600-mg rifampin for 16 days	Healthy male and female volunteers	Single dose	Completed

Study Number	Title	Study Design	Number of Subjects Dosed	Dosing Regimen	Study Population	Duration of Pirtobrutinib Treatment	Status
LOXO-BTK-20008	A Phase 1, Open-Label, Fixed-Sequence Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on the Pharmacokinetics of a Single Dose of Intravenous and Oral Midazolam (CYP3A4 Substrate) in Healthy Subjects	Single-center, open-label, 2-period, fixed-sequence crossover study	15	Single dose of 200-mg pirtobrutinib for 13 days in Period 2, Single dose of 500-µg (0.25 mL of 2 mg/mL syrup) midazolam oral once in each period, single dose of 250-µg (0.25 mL of 1 mg/mL solution) midazolam IV once in each period	Healthy male and female volunteers	11 days	Completed
LOXO-BTK-20016	A Phase 1, Open-Label, Fixed-Sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on the Pharmacokinetics of Repaglinide (CYP2C8 Substrate) in Healthy Subjects	Single-center, open-label, 2-period, fixed-sequence crossover study	16	Single dose of 200-mg pirtobrutinib for 11 days in Period 2, single dose of 0.5-mg repaglinide once in each period	Healthy male and female volunteers	11 days (pirtobrutinib given on Days 2 through 11)	Completed
LOXO-BTK-20007	A Phase 1, Open-Label, Two-Part Study of the Absorption, Metabolism, Excretion, and the Absolute Bioavailability of [^{14}C]LOXO-305 in Healthy Male Subjects	Single-center, open-label, parallel 2-part study of [^{14}C]pirtobrutinib	9	Part 1: Single dose of 200 mg [^{14}C]pirtobrutinib (containing approximately 200 µCi), oral Part 2: Single dose of 200-mg pirtobrutinib, oral, followed by single dose of <100 µg of [^{14}C]pirtobrutinib, IV	Healthy male and female volunteers	Single dose	Completed

Study Number	Title	Study Design	Number of Subjects Dosed	Dosing Regimen	Study Population	Duration of Pirtobrutinib Treatment	Status
LOXO-BTK-20009	A Phase 1, Open-Label, Randomized, 2-Way Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of LOXO-305 in Healthy Subjects	Single-center, open-label, 2-period, 2-sequence crossover study	20	Single dose of 200-mg pirtobrutinib in each period	Healthy male and female volunteers	Single dose	Completed
LOXO-BTK-20011	A Phase 1, Single-Dose, Randomized, Partially Double-Blind, Placebo- and Positive-Controlled, 3 Way Crossover Study to Evaluate the Effect of LOXO-305 on QTc Interval in Healthy Subjects	2-center, single-dose, randomized, double-blind (except for the use of moxifloxacin), placebo- and positive-controlled, 3-way crossover study	31	0 (placebo), 900-mg pirtobrutinib and 400-mg moxifloxacin (positive control)	Healthy male and female volunteers	Single dose	Completed
J2N-OX-JZNE (LOXO-BTK-20010)	A Phase 1, Open-Label, Fixed-Sequence, Drug Interaction Study to Investigate the Effect of Multiple Oral Doses of LOXO-305 on CYP1A2, CYP2C9, and CYP2C19 Substrates using a Probe Drug Cocktail in Healthy Subjects	2-center, open-label, 2-period, fixed-sequence crossover study	16	Single dose of 200-mg pirtobrutinib for 14 days in Period 2, Single dose of 200-mg caffeine 40-mg omeprazole and 10-mg warfarin once in each period	Healthy male and female volunteers	14 days	Completed

Study Number	Title	Study Design	Number of Subjects Dosed	Dosing Regimen	Study Population	Duration of Pirtobrutinib Treatment	Status
J2N-OX-JZNT (LOXO-BTK-20021)	A Phase 1, Open-Label, Fixed-Sequence, Drug Interaction Study to Investigate the Effect of Single and Multiple Oral Doses of LOXO-305 on the Pharmacokinetics of Multiple Oral Doses of Digoxin (P Glycoprotein Substrate) in Healthy Subjects	2-center, open-label, 2-period, fixed-sequence crossover study	16	Multiple doses of 200-mg pirtobrutinib for 9 days, BID 0.25-mg digoxin for 1 day, multiple doses of 0.25-mg digoxin for 15 days	Healthy male and female volunteers	9 days	Completed
J2N-OX-JZNF (LOXO-BTK-20012)	An Open-Label, Nonrandomized, Single-Dose, Parallel-Group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-305 Administered to Fasted Hepatically Impaired Male and Female Subjects and Fasted Matched-Control Healthy Subjects	Open-label, nonrandomized, multicenter, single-dose, parallel-group study in hepatically impaired subjects and healthy-matched-control subjects	36 (8 mild, 8 moderate, 6 severe hepatically impaired, 14 healthy matches)	200 mg pirtobrutinib	Male and female healthy volunteers and subjects with hepatic impairment	Single dose	Completed

Study Number	Title	Study Design	Number of Subjects Dosed	Dosing Regimen	Study Population	Duration of Pirtobrutinib Treatment	Status
J2N-OX-JZNG (LOXO-BTK-20013)	An Open-Label, Nonrandomized, Single-Dose, Parallel-Group, Safety, Tolerance, and Pharmacokinetic Study of LOXO-305 Administered to Fasted Renally Impaired Male and Female Subjects and Fasted Matched-Control Healthy Subjects	Open-label, nonrandomized, multicenter, single-dose, parallel-cohort study in subjects with severe renal impairment and healthy-matched-control subjects	16 (8 severe renally impaired and 8 healthy matches)	200-mg pirtobrutinib	Male and female healthy volunteers and subjects with renal impairment	Single dose	Completed
J2N-MC-JZNW	A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single and Multiple Doses of Pirtobrutinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants	Phase 1, fixed-sequence, open-label study in healthy subjects that investigated the effect of single and multiple doses of pirtobrutinib on the PK of rosuvastatin	Total: 32 Male: 27 Female: 5	200-mg pirtobrutinib, administered orally as 2 × 100-mg tablets; 20-mg rosuvastatin, administered orally as 2 × 10-mg tablets	Healthy volunteers	Single dose	Completed
J2N-OX-JZNV (LOXO-BTK-21050)	A Phase I, Open-Label, Randomized, 2-Way Crossover Study to Compare the PK of Pirtobrutinib (LOXO-305) Tablets	Phase 1, open-label, randomized, 2-way crossover study to compare the PK of 2 different lots of pirtobrutinib tablets after a single oral dose in healthy adult subjects	Total=28 Male=25 Female=3	200-mg pirtobrutinib (as 2 × 100 mg) QD	Healthy volunteers	Single dose	Completed

Abbreviations: BID = twice daily; IV = intravenous; PK = pharmacokinetics; QD = once daily.

5.1.1. Pharmacokinetics

The PK of pirtobrutinib has been studied in healthy subjects and in patients with cancer. Figure 5.1 provides the concentration-time profiles of pirtobrutinib after a single dose and multiple QD doses of 25 to 300 mg of pirtobrutinib in patients with cancer in Study LOXO-BTK-18001. Table 5.2 hows steady-state PK parameters of pirtobrutinib in these patients with cancer.

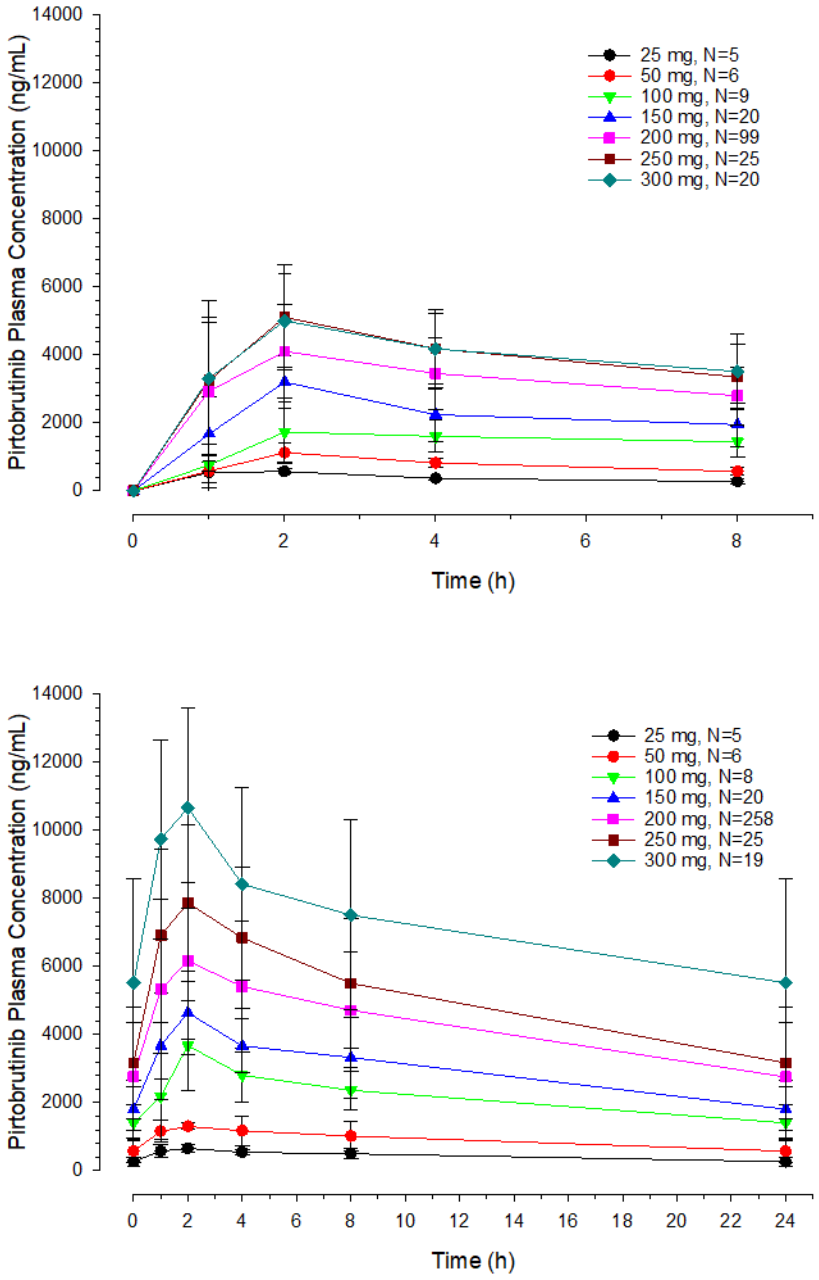
After single and multiple QD pirtobrutinib doses of 25 to 300 mg, the following was observed:

- C_{max} was achieved after approximately 2 hours
- mean CL/F ranged from 0.968 to 2.62 L/hr
- mean elimination $t_{1/2}$ ranged from 17.4 to 30.1 hours
- steady state was achieved after approximately 5 days of QD dosing, and
- AUC and C_{max} increased in a dose-proportional manner (Figure 5.2 and Table 5.3).

In Study LOXO-BTK-20017 in 24 healthy subjects, the AUC of pirtobrutinib after single doses of 300 to 900 mg increased in a dose-proportional manner. C_{max} exhibited dose proportionality over the 300 to 800 mg dose range.

Within the range of clinically relevant doses and exposures, the PK of pirtobrutinib is considered to be dose proportional.

Following administration of the RP2D of 200 mg QD, mean trough plasma levels of pirtobrutinib at steady state exceeded the concentration required for 96% inhibition of BTK in vitro (IC_{50} = 92 ng/mL, IC_{96} = 2200 ng/mL).



Abbreviations: N = number of participants, SD = standard deviation.

Figure 5.1. **Mean (±SD) plasma concentration - time profiles of pirtobrutinib after a single dose (top panel) at steady state (Cycle 1 Day 8) (bottom panel) in patients with cancer (Study LOXO-BTK-18001).**

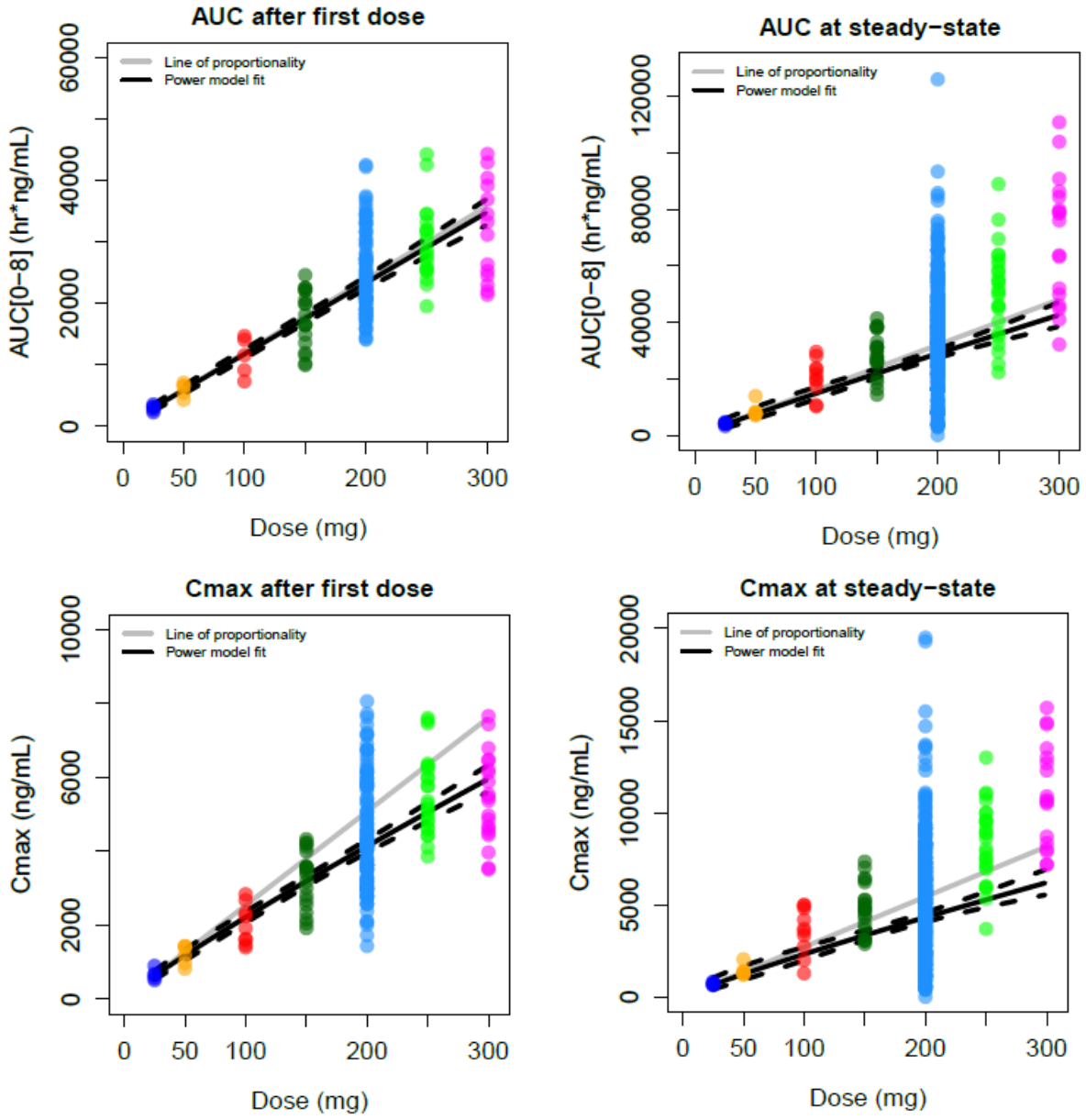
Table 5.2. Pharmacokinetic Parameters of Pirtobrutinib in Patients with Cancer (Study LOXO-BTK-18001) at Steady State (Cycle 1 Day 1 and Cycle 1 Day 8)

	Formulation: T1							Formulation T2
	25 mg QD	**50 mg QD**	**100 mg QD**	**150 mg QD**	**200 mg QD**	**250 mg QD**	**300 mg QD**	**200 mg QD**
Cycle 1, Day 1	N = 5	N = 6	N = 9	N = 20	N= 89	N = 24	N = 20	N = 12
C_{max} (ng/mL)	655 (21.3)	1180 (23.7)	1950 (26.8)	3140 (25.8)	4240 (34.5)	5450 (18.9)	5300 (22.9)	4440 (23.7)
T_{max}[a] (hr)	1.05 (1.00, 2.07)	1.93 (1.15, 4.10)	2.17 (1.02, 7.65)	2.02 (0.950, 7.50)	2.05 (0.817, 7.67)	2.04 (0.817, 7.53)	2.06 (0.933, 7.62)	2.00 (0.833, 4.15)
AUC_{0-8} (hr*ng/mL)	2930 (17.1)	5910[c] (20.3)	11000[c] (30.1)	16800[d] (29.4)	24300[e] (27.2)	29200[f] (20.1)	30800[g] (26.3)	25000[h] (27.0)
Cycle 1, Day 8	N = 5	N = 6	N = 8	N = 20	N = 100	N = 25	N = 17	N = 373
C_{max} (ng/mL)	734 (11.0)	1420 (19.2)	3700 (33.3)	4680 (29.1)	5940 (48.4)	8100 (28.1)	10700 (26.6)	3670 (89.5)
T_{max}[a] (hr)	1.97 (1.00, 7.52)	1.48 (0.883, 4.02)	1.99 (1.08, 4.08)	2.01 (0.783, 8.00)	2.04 (0.00, 7.82)	2.00 (0.800, 5.77)	1.98 (0.750, 3.83)	0.00 (0.00, 8.17)
AUC_{0-8} (hr*ng/mL)	4240 (12.4)	8650 (24.8)	20500 (32.4)	28000 (29.8)	37900[j] (41.2)	48500 (34.8)	65800 (36.3)	25400 (80.7)
AUC_{0-24} (hr*ng/mL)	9330 (26.9)	20000 (35.1)	48400 (34.9)	62200[i] (38.6)	98700[k] (39.1)	111000 (38.7)	158000 (50.0)	81800[m] (66.6)
CL/F (L/hr)	NC	NC	NC	2.84[c] (65.9)	2.31[l] (36.5)	3.09[o] (35.2)	2.65, 5.70	2.56[n] (32.5)
Half-Life[b] (hr)	NC	NC	NC	9.76[c] (6.89, 11.9)	11.1 (5.74, 13.5)	9.55[o] (6.67, 12.1)	5.54, 12.6	11.0[n] (6.47, 13.8)
AR-AUC_{0-8}	1.45 (22.8)	1.52[c] (30.0)	1.58[o] (34.3)	1.68[d] (18.9)	1.63[p] (26.7)	1.63[f] (26.7)	2.10[q] (20.2)	1.48[h] (30.9)
C_{trough} (ng/mL)	241 (50.1)	510 (53.3)	1310 (50.6)	1550 (69.4)	2550 (61.0)	2700 (69.3)	4430 (98.0)	2270[r] (75.7)

Abbreviations: N = number of participants, AUC_{0-8} = area under the plasma concentration-time curve from 0 to 8 hr; AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hr; C_{max} = maximum observed drug concentration; C_{trough} = predose trough concentration; NC = not calculable; QD = once daily; T1 = Tablet 1; T2 = Tablet 2; T_{max} = time of maximum observed drug concentration, AR_{AUC} = accumulation ratio based on AUC_{tau}.

[a] Median and range.

[b] Geomean and range.
[c] N = 5.
[d] N = 18.
[e] N = 63.
[f] N = 20.
[g] N = 14.
[h] N = 8.
[i] N = 19.
[j] N = 98.
[k] N = 74.
[l] N = 17.
[m] N = 180.
[n] N = 37.
[o] N = 4.
[p] N = 50.
[q] N = 13.
[r] N = 372.



Abbreviations: $AUC_{[0\text{-}8]}$ = area under the plasma concentration-time curve from 0 to 8 hr; C_{max} = maximum observed drug concentration.

Figure 5.2. **Dose linearity assessment for pirtobrutinib after a single dose or after multiple once-daily doses in Study LOXO-BTK-18001.**

Table 5.3. Dose Linearity Assessment for Pirtobrutinib After a Single Dose (Cycle 1 Day 1) or After Multiple Once-Daily Doses (Cycle 1 Day 8) in Study LOXO-BTK-18001

		Cycle 1 Day 1		Cycle 1 Day 8	
Parameter	Dose Ratio (to 25 mg)	Ratio Estimate	Ratio Estimate 90% CI	Ratio Estimate	Ratio Estimate 90% CI
AUC_{0-8} (hr*ng/mL)	2	0.992	(0.945, 1.04)	0.967	(0.864, 1.08)
	4	0.985	(0.892, 1.09)	0.935	(0.747, 1.17)
	6	0.980	(0.863, 1.11)	0.917	(0.686, 1.23)
	8	0.977	(0.843, 1.13)	0.905	(0.646, 1.27)
	10	0.974	(0.828, 1.15)	0.895	(0.616, 1.30)
	12	0.972	(0.815, 1.16)	0.887	(0.593, 1.33)
C_{max} (ng/mL)	2	0.934	(0.886, 0.985)	0.927	(0.819, 1.05)
	4	0.872	(0.785, 0.970)	0.859	(0.670, 1.10)
	6	0.838	(0.731, 0.961)	0.821	(0.596, 1.13)
	8	0.815	(0.695, 0.955)	0.796	(0.549, 1.15)
	10	0.797	(0.668, 0.951)	0.776	(0.515, 1.17)

Abbreviations: $AUC_{[0-8]}$ = area under the plasma concentration-time curve from 0 to 8 hr; CI = confidence interval; C_{max} = maximum observed drug concentration.

Population PK analysis

A population PK analysis was performed based on 668 patients enrolled in Study LOXO-BTK-18001 (database snapshot: 08 February 2023). The pirtobrutinib PK data were best described by a 2-compartment model with transit compartments for absorption. Model fit was significantly improved by inclusion of body weight as an allometric scaling component on clearance and volume. Model parameter estimation was performed with overall high precision and interindividual variability was generally low to moderate. Table 5.4 reports the PK model parameter estimates, including typical population values and interindividual variability.

After single and multiple QD pirtobrutinib doses of 25 to 300 mg, the following was observed:

- C_{max} was achieved after approximately 2 hours
- mean apparent oral clearance was 2.05 L/hour
- mean apparent oral volume of distribution was 52.6 L
- mean elimination $t_{1/2}$ was estimated to be 18.8 hours
- steady state was achieved after approximately 5 days of QD dosing, and
- AUC and C_{max} increased in a dose-proportional manner.

At a dose of 200 mg QD in patients in Phase 2 Study LOXO-BTK-18001, the mean estimated pirtobrutinib $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$ were 6380 ng/mL (26% CV), 2230 ng/mL (62% CV), and 90,300 ng*hr/mL (40% CV), respectively.

Table 5.4. Parameter Estimates for the Population Pharmacokinetic Model for Pirtobrutinib in Patients in Study LOXO-BTK-18001

Parameter	Parameter Estimates (%RSE)		Final Model Bootstrap
	Base Model	Final Model	95% CI
Bioavailability (F, fraction, Θ1)	1 fixed	1 fixed	1 fixed
Mean transit time (MTT, hr, Θ_2)	1.15 (0.0495)	1.07 (3.43)	(1.00, 1.14)
Clearance (CL, L/hr, Θ3)	2.09 (0.0299)	2.05 (1.98)	(1.98, 2.12)
Intercompartmental clearance (Q, L/h, Θ5)	7.90 (0.0206)	7.68 (16.9)	(5.73, 9.81)
Central volume of distribution (Vc, L, Θ4)	34.2 (0.0475)	34.1 (4.57)	(31.3, 36.8)
Peripheral volume of distribution (Vp, L, Θ6)	19.1 (3.48)	18.5 (5.58)	(16.2, 21.0)
Covariate Effects			
Allometry on CL and Q			
Body Weight (kg; Θ9)[a]	0.363 (12.1)	0.348 (28.8)	(0.198, 0.504)
Allometry on Vc and Vp			
Body Weight (kg; Θ10)[b]	0.760 (5.23)	0.806 (6.76)	(0.710, 0.902)
Covariate effects on CL			
eGFR (mL/min/1.73 m^2; Θ12)[c]	NA	0.00366 (21.7)	(0.00211, 0.00530)
Albumin (g/L; Θ11)[d]	NA	-0.647 (17.6)	(-0.876, -0.417)
Covariate effect on Vc			
Albumin (g/L; Θ13)[e]	NA	-0.519 (25.0)	(-0.763, -0.303)
Interindividual variability CV%			
MTT (Ω_2)	26.5 (4.17)	26.2 (13.8)	(17.8, 33.0)
CL (Ω_3)	39.3 (2.35)	37.2 (3.64)	(34.3, 40.3)
Interoccasion variability CV%			
MTT	50.7 (0.228)	49.3 (6.32)	(42.3, 56.7)
Residual variability			
Proportional	0.214 (0.000856)	0.211 (2.32)	(0.202, 0.221)

Abbreviations: ALB = serum albumin; CI = confidence interval; CL = clearance; CV = coefficient of variance; F = relative bioavailability; eGFR = absolute estimated glomerular filtration rate; MTT = mean transit time; NA = not applicable; Q = intercompartmental clearance; RSE = relative standard error; Vc = central volume of distribution; Vp = peripheral volume of distribution; WT = body weight.

[a] CL/F = Population estimate of CL*((WT/70)**Θ9); Q/F = Population estimate of Q*(WT/70)** Θ9).

[b] Vc/F = Population estimate of Vc*((WT/70)**Θ10); Vp/F = Population estimate of Vp*((WT/70)**Θ10).

[c] CL/F = Population estimate of CL*(exp(Θ12*(eGFR-76.8)).

[d] CL/F = Population estimate of CL*((ALB/41)**Θ11).

[e] Vc/F = Population estimate of Vc* ((ALB/41)**Θ13).

5.1.2. Absorption and Bioavailability

In Study 20007, after less than 100 µg (approximately 1 µCi of radioactivity) IV dose of [^{14}C]pirtobrutinib was taken together with a 200-mg oral dose of pirtobrutinib in 5 healthy subjects, the mean (CV) absolute bioavailability of pirtobrutinib was 85.5% (7.2%).

Across the PK studies conducted in healthy subjects and patients, the T_{max} was approximately 2 hours.

5.1.3. Distribution, Metabolism, and Excretion

Distribution

In humans, pirtobrutinib was moderately bound to human plasma proteins and human serum albumin, with a mean bound fraction of approximately 95% and 98%, respectively. Binding to both matrices was independent of the concentration at 0.5, 5, and 50 µM. Pirtobrutinib was less bound to human α_1-acid glycoprotein. Although binding to α_1-acid glycoprotein was independent of pirtobrutinib concentration, the binding was dependent on the concentration of α_1-acid glycoprotein with binding fraction of approximately 50% and 25% at 2 mg/mL and 0.5 mg/mL of α_1-acid glycoprotein, respectively. The blood-to-plasma ratio of pirtobrutinib in humans is approximately 0.79.

In Study LOXO-BTK-20007 (20007), after less than 100 µg (approximately 1 µCi of radioactivity) IV dose of [^{14}C]pirtobrutinib was taken together with a 200-mg oral dose of pirtobrutinib in 5 healthy subjects, the mean (CV) volume of distribution at steady state was 36.3 L (24.2%).

Based on a population PK analysis of 668 patients in Study LOXO-BTK-18001 who received oral doses of pirtobrutinib (Section 5.1.1), the mean V_c/F of pirtobrutinib is 34.1 L and the mean V_p/F of pirtobrutinib is 18.5 L.

Metabolism

In humans, pirtobrutinib is metabolized by oxidation, glucuronidation, and hydrolysis. In plasma, pirtobrutinib is the major circulating entity, accounting for 86.7% of total circulating radioactivity after a 200-mg oral dose of [^{14}C]pirtobrutinib. Three minor metabolites were present in plasma, M1, M2, and M4, each accounting for a mean of 7.8%, 3.3%, and 2.3%, respectively, of circulating radioactivity. M2 was the most abundant metabolite in urine representing approximately 22% of the dose, while M20 was the most abundant metabolite in feces, accounting for 6.5% of the dose.

The metabolic clearance pathways that represented more than 5% of dose were as follows:

- direct glucuronidation of the primary amine on the pyrazole (M2; total 22.8%)
- amide hydrolysis and further oxidative deamination to a carboxylic acid with and without glucuronidation (M18, M16, and M17; total 13.5%)
- mono-oxidation on the methoxyfluorobenzene with and without sulfation (M20 and M15; total 7.3%)

- O-demethylation with and without glucuronidation (M11 and M12; total 5.8%), and
- mono-oxidation on a nitrogen atom without and with glucuronidation (M19, M3, and M4; total 5.0%).

Excretion

After oral administration of [^{14}C]pirtobrutinib, the overall mean recovery of radioactive dose in combined excreta (urine and feces) was 94.3%, with urinary excretion accounting for 57.0% and fecal excretion accounting for 37.3%. Pirtobrutinib was cleared renally with 10% of the dose recovered unchanged in urine and 18.2% of the dose recovered unchanged in feces.

5.1.4. Effect of Food

The effect of food on the PK of pirtobrutinib was evaluated in 2 clinical studies.

In Study LOXO-BTK-20014 (20014), 10 healthy subjects received pirtobrutinib tablets either under fasted conditions or with a standard breakfast (approximately 50% carbohydrates, 30% fat, and 20% protein). The standard breakfast decreased the C_{max} of pirtobrutinib by 20% and delayed T_{max} by 0.5 hours. There was no effect on pirtobrutinib $AUC_{0\text{-inf.}}$

In Study LOXO-BTK-20009, 20 healthy subjects received pirtobrutinib tablets either under fasted conditions or with a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat). The high-fat meal decreased the C_{max} of pirtobrutinib by 23% and delayed T_{max} by 1 hour. There was no effect on pirtobrutinib $AUC_{0\text{-inf.}}$

Although these changes were statistically significant, they are not considered to be clinically relevant. Therefore, pirtobrutinib can be taken with or without food.

5.1.5. Effect of Other Drugs on the PK of Pirtobrutinib

The following section describes in vitro and clinical data evaluating the effect of other drugs on the PK of pirtobrutinib. Please refer to the study protocol for specific recommendations for exclusion criteria, prohibited medications, and any advice for coadministration with pirtobrutinib.

In vitro studies

The potential of CYP450 enzymes to metabolize pirtobrutinib was assessed in vitro using a substrate depletion approach. Depletion of pirtobrutinib by a panel of recombinant human CYP450s (rCYP1A2, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2D6, rCYP2E1, rCYP2J2, rCYP3A4, and rCYP3A5) was evaluated. This study concluded that pirtobrutinib is metabolized by CYP3A4 in vitro.

A panel of 12 recombinant human UGT (UGT1A1, 1A3, 1A4, 1A6, 1A8, 1A9, 1A10, 2B4, 2B7, 2B10, 2B15, and 2B17) were used to determine which UGTs metabolized pirtobrutinib. This study concluded that UGT1A8 and UGT1A9 are the primary UGTs responsible for the glucuronidation of pirtobrutinib.

In vitro, pirtobrutinib is a substrate of P-gp and BCRP. It is not a substrate of the hepatic transporters OCT1, OATP1B1, OATP1B3, or BSEP.

Clinical pharmacology studies

A series of clinical pharmacology studies were conducted to determine the clinical relevance of the above noted interactions. A clinical pharmacology study was also conducted to assess the impact of gastrointestinal pH on PK of pirtobrutinib. The results of these studies are summarized in the following sections.

Effect of H2 antagonists and acid-reducing agents

In Study 20014, the effect of coadministration of a proton pump inhibitor, omeprazole, on the PK of pirtobrutinib (200 mg single dose) was evaluated in 10 healthy subjects. Pirtobrutinib $AUC_{0\text{-inf}}$ was approximately 11% higher when pirtobrutinib was administered with omeprazole compared to pirtobrutinib administered alone. There was no omeprazole-mediated effect on pirtobrutinib C_{max}.

Effect of CYP3A4 inhibitors and inducers and P-gp inhibitors

In Study LOXO-BTK-20006, the effect of itraconazole (strong CYP3A4 inhibitor and P-gp inhibitor) and rifampin (strong CYP3A4 inducer and P-gp inhibitor) on the PK of pirtobrutinib (200 mg QD) was evaluated in 12 healthy subjects. Itraconazole increased $AUC_{0\text{-inf}}$ of a single dose of pirtobrutinib by approximately 49% but had no effect on C_{max}. Rifampicin decreased exposure (C_{max} and $AUC_{0\text{-inf}}$) of pirtobrutinib by 42% and 71%, respectively. Inhibition of P-gp by a single dose of itraconazole or rifampin had no effect on the PK of pirtobrutinib.

5.1.6. Effect of Pirtobrutinib on the PK of Other Drugs

The following section describes in vitro and clinical data evaluating the effect of pirtobrutinib on the PK of other drugs. Please refer to the study protocol for specific recommendations for exclusion criteria, prohibited medications, and any advice for coadministration with pirtobrutinib.

In vitro studies

Pirtobrutinib showed no detectable inhibition (IC_{50} >60 μM) of CYP1A2, CYP2B6, CYP2C19, and CYP2D6 and weak inhibition of CYP2C8, CYP2C9, and CYP3A4 in human liver microsomes, with K_i values ranging from 11.7 to 22.8 μM. Preincubation of pirtobrutinib in liver microsomes suggested potential for time-dependent inhibition of CYP3A4. Further kinetic evaluation confirmed that pirtobrutinib is a time-dependent inhibitor of CYP3A4 with a K_I value of 4.70 ± 1.20 μM and a maximal rate of enzyme inactivation (k_{inact}) of 2.44 ± 0.15 h^{-1}. Concomitant use of pirtobrutinib with sensitive substrates of CYP2C8, CYP3A4, and CYPC19 increased their plasma concentrations to some extent.

In human hepatocytes, pirtobrutinib induced mRNA for CYP3A4, CYP3A5, CYP2B6, and CYP2C19. This in vitro induction potential did not result in clinically meaningful changes in PK

of drugs metabolized by these enzymes. Pirtobrutinib did not induce CYP2D6, CYP2C8, and CYP2C9 mRNA in human hepatocytes.

In vitro, pirtobrutinib inhibited P-gp, BCRP, MATE1, and MATE2K. Pirtobrutinib did not inhibit OAT1, OATP1B1, OATP1B3, OCT1, OCT2, OAT3, and BSEP. Concomitant use of pirtobrutinib with sensitive substrates of P-gp and BCRP increased their plasma concentrations.

Clinical pharmacology studies

A series of clinical pharmacology studies were conducted to determine the clinical relevance of the above noted interactions. The results of these studies are summarized in the following section.

CYP2C8 substrates

In Study LOXO-BTK-20016, the effect of multiple doses of pirtobrutinib (200 mg QD) on the PK of CYP2C8 prototype substrate repaglinide was evaluated in 16 healthy subjects. Pirtobrutinib increased the $AUC_{0\text{-}inf}$ and C_{max} of repaglinide by approximately 130% and 98%, respectively. Therefore, at 200 mg QD, pirtobrutinib is a moderate inhibitor of CYP2C8.

CYP3A4 substrates

In Study LOXO-BTK-20008, the effect of multiple doses of pirtobrutinib (200 mg QD) on the PK of a single dose of IV or oral midazolam was evaluated in 15 healthy subjects. Pirtobrutinib had minimal effect on the PK of IV midazolam but increased the $AUC_{0\text{-}inf}$ and C_{max} of oral midazolam by approximately 70% and 58%, respectively. Pirtobrutinib did not alter the PK of metabolite 1-OH midazolam following either IV or oral doses of midazolam. Therefore, pirtobrutinib is a weak inhibitor of CYP3A4 in the clinic. The results of this study indicate that the inhibitory effect of pirtobrutinib on CYP3A4 activity occurred predominantly on intestinal expressed CYP3A4.

CYP1A2, CYP2C9, and CYP2C19 substrates

In Study LOXO-BTK-20010, multiple doses of pirtobrutinib (200 mg QD) were coadministered with a single oral dose of probe drug cocktail consisting of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) in 16 healthy subjects.

Pirtobrutinib did not alter the PK of caffeine or its metabolite paraxanthine, demonstrating no effect on CYP1A2 activity. Pirtobrutinib increased the $AUC_{0\text{-}inf}$ and C_{max} of omeprazole by 56% and 49%, respectively, indicating weak but clinically nonmeaningful inhibition of CYP2C19 activity. Pirtobrutinib increased the $AUC_{0\text{-}inf}$ of S-warfarin by 11%, demonstrating no clinically relevant effect on CYP2C9 activity.

Drug transporter substrates

P-gp substrates

In Study LOXO-BTK-20021, the effect of single and multiple doses of pirtobrutinib (200 mg QD) on the PK of digoxin, a sensitive P-gp substrate, was evaluated in 16 healthy subjects. Single and multiple doses of pirtobrutinib increased the AUC_{tau} of digoxin by 17% and 35%, respectively, and C_{max} by 51% and 55%, respectively. This indicates that pirtobrutinib inhibited P-gp in the intestine and increased the oral bioavailability of digoxin. Multiple doses of pirtobrutinib reduced digoxin renal clearance by 12%, indicating the decreased renal elimination of digoxin via inhibition of P-gp in the renal proximal tubules.

MATE1 substrates

In patients in Study LOXO-BTK-18001, no clinically meaningful effect of pirtobrutinib on serum creatinine, a MATE1 substrate, was observed.

BCRP substrates

Pirtobrutinib (200 mg QD) increased the AUC and C_{max} of rosuvastatin (a sensitive BCRP substrate) by 140% and 146%, respectively.

5.1.7. Specific Populations and Pharmacogenomics

The following section describes clinical data comparing pirtobrutinib PK in patients in specific populations, including the effect of organ impairment and the effect of race and ethnicity. Please refer to the study protocol for specific recommendations for different patient populations including inclusion/exclusion criteria related to organ function.

5.1.7.1. Patients with Renal Impairment

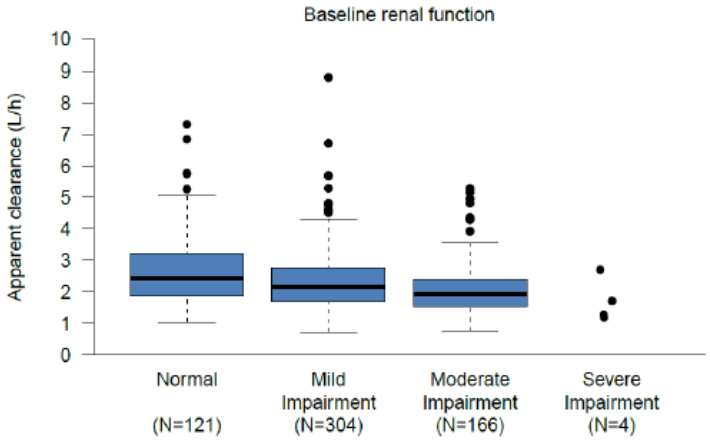
In Study LOXO-BTK-20013 (20013), the effect of renal impairment on the PK of pirtobrutinib (200 mg single dose) was evaluated in 8 subjects with severe renal failure (eGFR less than 30 mL/min/1.73 m^2) and compared to 8 matched healthy subjects with normal renal function (eGFR at least 90 mL/min/1.73 m^2). In subjects with severe renal impairment, pirtobrutinib $AUC_{0\text{-}inf}$ was 36% higher than subjects with normal renal function. However, the largest effect, which was observed in participants with severe renal impairment, is within the normal PK variability of pirtobrutinib in patients with hematological malignancies (that is, 38% interindividual variability CV% for CL based on population PK estimates and geometric CV% of 41% for AUC at steady state for patients with 200 mg QD) and not considered clinically relevant. There was no difference in C_{max}.

Additionally, in the popPK analysis using data from study LOXO-BTK-18001 (data cutoff date: 31 January 2022), eGFR was found to have a statistically significant effect on pirtobrutinib clearance. The assessment included patients with normal renal function (eGFR $\geq$ 90 mL/min/1.73 m^2) (N=121), mild (60 mL/min/1.73 $m^2 \leq$ eGFR $<$ 90 mL/min/1.73 m^2) (N=304), moderate (30 mL/min/1.73 $m^2 \leq$ eGFR $<$ 60 mL/min/1.73 m^2) (N=166), and severe renal impairment (15 mL/min/1.73 $m^2 \leq$ eGFR $<$ 30 mL/min/1.73 m^2) (N=4). The effect of renal impairment in this population on apparent oral clearance is shown in Figure 5.3. This plot

demonstrates the minimal change in apparent clearance between patients with normal renal function and mild or moderate renal impairment.

Nevertheless, exposure-response analyses to evaluate the range of safe and efficacious exposures in patients with MCL identified a wide therapeutic window for pirtobrutinib. Over the range of average concentrations at doses of 25 to 300 mg QD evaluated in Study LOXO-BTK-18001, no change in the safety profile of pirtobrutinib was identified based on exposure-safety analyses. Geometric mean average drug concentration at steady state (C_{av}) up to approximately 2-fold (100%) higher than those at 200 mg is deemed safe. In patients with severe renal impairment, projected C_{av} at steady state is 5090 ng/ml but is still within the 2-fold (100%) safety range.

Therefore, no adjustment of the dose of pirtobrutinib is required for patients with mild-to-severe renal impairment. The effect of dialysis on the PK of pirtobrutinib has not been studied.



Abbreviations: eGFR = estimated glomerular filtration rate; N = number of participants; PK = pharmacokinetic.
Notes: Box plots depict the 25th, 50th, and 75th percentiles.
Whiskers represent 1.5 times the interquartile range.
Normal = eGFR ≥ 90 mL/min/1.73 m^2.
Mild impairment = 60 mL/min/1.73 m^2 ≤ eGFR <90 mL/min/1.73 m^2.
Moderate impairment = 30 mL/min/1.73 m^2 ≤ eGFR < 60 mL/min/1.73 m^2.
Severe impairment = 15 mL/min/1.73 m^2 ≤ eGFR < 30 mL/min/1.73 m^2.

Figure 5.3. Population PK model-estimated apparent clearance stratified by baseline renal function.

5.1.7.2. Patients with Hepatic Impairment

The effect of mild, moderate, and severe hepatic impairment based on CP criteria was evaluated in a clinical pharmacology study (Study LOXO-BTK-20012). Based on analysis of covariance (ANCOVA), the following results were observed:

- Mild hepatic impairment reduced exposure (AUC_{0-t} and AUC_{0-inf}) of pirtobrutinib by 10% compared to participants with normal hepatic function but had no effect on C_{max}.

- Moderate hepatic impairment reduced exposure (AUC_{0-t} and AUC_{0-inf}) of pirtobrutinib by 14% compared to participants with normal hepatic function but had no effect on C_{max}.
- Severe hepatic impairment reduced exposure (AUC_{0-t} and AUC_{0-inf}) of pirtobrutinib by 25% compared to participants with normal hepatic function but had no effect on C_{max}.

The plasma fraction unbound (fu) for pirtobrutinib in participants generally increased as the severity of hepatic impairment increased. Therefore, after correcting pirtobrutinib PK exposure parameters with fu, there was no clinically relevant difference observed in the unbound pirtobrutinib PK exposure parameters ($AUC_{0-t,u}$ and $C_{max,u}$) between participants with any degree of hepatic impairment and normal hepatic function.

In addition, in an updated popPK analysis using data from Study LOXO-BTK-18001 (data cutoff date: 31 January 2022), the effect of hepatic function at baseline on the PK of pirtobrutinib was evaluated using NCI classification criteria. There were 531 patients with normal hepatic function, 116 patients with mild hepatic impairment, 18 patients with moderate hepatic impairment, and 1 patient with severe hepatic impairment. There was no statistically significant effect of hepatic impairment on the PK of pirtobrutinib.

In summary, hepatic impairment had no clinically meaningful effect on pirtobrutinib exposure, and no safety concerns were identified from the administration of single doses of 200 mg pirtobrutinib to patients with mild, moderate, or severe hepatic impairment. Therefore, no adjustment of the dose of pirtobrutinib is required for patients with mild-to-severe hepatic impairment.

5.1.7.3. Asian Patients

A combined population PK analysis of Study JZNJ and Study LOXO-BTK-18001 was conducted to assess the effect of Asian origin on the PK of pirtobrutinib. A total of 83 patients from Study JZNJ (database snapshot: 10 April 2023) and 668 patients from Study LOXO-BTK-18001 (database snapshot: 08 February 2023) were included in the analysis. Of the total 751 patients, 130 (17%) were Asian. Simulations performed for both Asian and non-Asian patients with the median body weight, albumin, and eGFR of their respective populations in Study 18001 and Study JZNJ combined suggested that the median steady-state C_{max} and AUC_{0-24} were 21% and 24% higher in Asian patients with 200 mg QD than in the non-Asian patients, respectively. The higher pirtobrutinib exposures in Asian patients than non-Asian patients were attributed to an effect of Asian race on CL/F, with Asian patients exhibiting a 21% decrease in CL/F compared to non-Asian patients. The difference was not attributed to body weight. However, the range of PK exposures in Study JZNJ was within the range of those achieved in Study LOXO-BTK-18001 after a 200-mg once-daily dose of pirtobrutinib.

Also, there were no meaningful differences in safety or tolerability for cancer patients in Study JZNJ compared to Study LOXO-BTK-18001 (Section 5.2.1.1). This is consistent with the known exposure-response relationships for pirtobrutinib in patients with MCL, which indicates a wide therapeutic window where cancer patients can tolerate changes in exposure up to 2-fold without any expected impact on safety.

No dose adjustment of pirtobrutinib is recommended for Asian patients with cancer.

5.1.8. Pharmacodynamics

Effect of pirtobrutinib on the QT interval

In Study LOXO-BTK-20011 (20011), the effect of a single 900-mg dose of pirtobrutinib on the QTc interval was evaluated in a placebo and positive-controlled study in 30 healthy subjects. The selected dose is equivalent to approximately 2 times higher than the concentrations achieved at steady state at the recommended dosage of 200 mg QD. Pirtobrutinib had no clinically meaningful effect on the change in QTcF interval (that is, >10 ms). No relationship between pirtobrutinib exposure and change in QTc interval was observed.

5.2. Safety and Efficacy

5.2.1. Safety

This IB update summarizes clinical safety data from patients across 2 studies, namely Study LOXO-BTK-18001 (J2N-OX-JZNA) and J2N-MC-JZNJ.

Study LOXO-BTK-18001 is a Phase 1/2 study aimed to assess maximum tolerated dose and RP2D of oral pirtobrutinib as monotherapy and in combination with venetoclax and rituximab in patients with previously treated CLL/SLL, MCL and other types of NHL. Safety data from both mono- and combination therapy are summarized in this IB.

Study J2N-MC-JZNJ is a Phase 2 study aimed to evaluate the safety and efficacy of pirtobrutinib as monotherapy in Chinese population with previously treated CLL/SLL or NHL.

Data from 5 ongoing Phase 3 randomized MCL and CLL/SLL studies is not available at the time of this IB update. However, for these studies, independent review of unblinded safety data was performed by DMC (Data Monitoring Committee) on a periodic basis as specified in the individual study DMC charter. As of the IB finalization date, at least 3 DMC meetings have taken place for four Phase 3 studies and 2 for 1 phase 3 study (LOXO-BTK-20020) with a recommendation to continue the study without any modification. Data for the Phase 3 Study LOXO-BTK-20020 has been unblinded and is being evaluated by the regulatory agencies at the time of this IB update.

Study LOXO-BTK-20020 (J2N-OX-JZNN) is a Phase 3 study comparing pirtobrutinib as continuous monotherapy to investigators choice of either IdelaR or BendaR in BTK inhibitor pretreated CLL/SLL. This study is comprised of 2 arms: Arm A, which received a single dose of pirtobrutinib, and Arm B, which received either IdelaR or BendaR.

5.2.1.1. Summary of Safety Data across Clinical Studies

Study LOXO-BTK-18001 (J2N-OX-JZNA)

As of 27 January 2024, clinical safety data were available from 778 patients on monotherapy and 25 patients receiving combination therapy who received at least 1 dose of pirtobrutinib in the ongoing global Phase 1/2 Study LOXO-BTK-18001 for patients with previously treated

CLL/SLL, MCL, and other types of NHL. Patients have been treated with pirtobrutinib in the Phase 1/2 monotherapy cohorts at doses ranging from 25 to 300 mg QD, and in the Phase 1b combination therapy arms (including 15 patients in Arm A [pirtobrutinib plus venetoclax] and 10 patients in Arm B [pirtobrutinib plus rituximab and venetoclax]). The RP2D of pirtobrutinib of 200 mg QD was administered as a starting dose to 693 of the 778 (89.1%) treated patients in the Phase 1/2 monotherapy cohorts and to all 25 patients treated in Phase1b combination therapy arms.

For the monotherapy cohort, the primary safety analysis set is based on patients who received at least 1 dose of pirtobrutinib as monotherapy, at any dose level irrespective of B-cell malignancy, as of the data cutoff of 27 January 2024 and is referred to as the Overall Monotherapy Safety Analysis Set (OMTSAS; n =778). Additional subsets within OMTSAS population includes patients with MCL, referred to as MCL Safety Analysis Set (MSAS; n=166), and patients with CLL/SLL, referred to as CLL/SLL Safety Analysis Set (CSAS; n=317).

At the time of data cutoff, treatment was continuing in 186 of 778 (23.9%) patients in the Phase 1/2 monotherapy cohorts. Of the 778 patients in the Phase 1/2 monotherapy cohorts, 592 (76.1%) patients discontinued treatment with reasons for discontinuation as follows:

- progressive disease (400 [51.4%])
- AE (78 [10%)
- death (38 [4.9%])
- requirement for alternate treatment (20 [2.6%])
- withdrawal of consent (15 [1.9%])
- intercurrent illness compromising ability to fulfill protocol requirements (10 [1.3%])
- dose delay >28 days without sponsor approval (3 [0.4%]), and
- listed as "other" in 28 (3.6%) patients.

The median duration of treatment in the Phase 1/2 monotherapy cohorts was 11.99 months with maximum treatment duration of 57.8 months.

All the 25 patients in the combination Phase 1b study have discontinued pirtobrutinib.
Ten patients in Arm A and 7 patients in Arm B discontinued pirtobrutinib due to the completion of treatment. Two patients (enrolled to Arm A) discontinued all treatment due to progressive disease. One patient (enrolled to Arm A) discontinued all treatment due to significant protocol noncompliance, and 2 patients (enrolled in Arm B) discontinued all treatment due to AEs. In Arm B, 1 death was reported, and in Arm A, 2 patients discontinued due to other reason.

Determination of recommended Phase 2 dose (RP2D)
Dose escalation for the LOXO-BTK-18001 Phase 1/2 monotherapy cohorts was conducted under a standard 3 + 3 design. The protocol allowed enrollment during Phase 1 to dose levels previously cleared for safety by the Safety Review Committee, also termed "backfill" enrollment. Intrapatient dose escalation was also allowed. In January 2020, based on the cumulative review of safety and PK data of enrolled patients to Phase 1/2 monotherapy cohorts, the Safety Review Committee recommended that additional patients be enrolled at 300 and 200 mg QD dose levels to further evaluate the safety and efficacy. In March 2020, the Sponsor

and Safety Review Committee reviewed the totality of efficacy, clinical PK, and safety data and decided that further dose escalation was not medically justified; therefore, no MTD was established for pirtobrutinib. On 07 May 2020, the RP2D was identified as 200 mg QD. The preliminary population PK and exposure-response analyses to date support the pirtobrutinib RP2D of 200 mg QD. For individual patients with higher or lower concentrations than the average steady-state concentrations in the population (due to natural PK variability and/or dose escalations/reductions), there does not appear to be any meaningful differences in safety or efficacy endpoints within the patients who received pirtobrutinib 200 mg QD in Study LOXO-BTK-18001. In addition, the analysis indicated that pirtobrutinib is safe within at least a 2-fold increase and efficacious within a 3-fold decrease of mean plasma concentrations for a 200-mg QD starting dose within the range of exposures studied in patients thus far. These findings support the use of dose to manage side effects while maintaining treatment benefit.

Dose-limiting toxicities

No dose-limiting toxicities have been reported in the Phase 1 monotherapy population or the Phase 1b combination therapy arms and no MTD was established.

TEAEs

TEAEs are defined as adverse events that started on or after the first day of pirtobrutinib dosing through 30 days (+ 7 days window) after the date of the last dose of pirtobrutinib or the first date starting new anticancer therapy (whichever is earlier). TEAEs were coded according to the Medical Dictionary for Regulatory Activities by PT and SOC. If a patient reported more than 1 TEAE within a single PT, that patient was counted only once in the frequency for that PT (and counted at the highest grade reported for that term).

Phase 1/2 monotherapy cohorts: TEAEs

In the Phase 1/2 monotherapy cohorts, 748 of the 778 (96.1%) patients treated reported a TEAE (regardless of relationship to study drug) of any grade, as listed in Table 5.5. Most frequently reported TEAEs (those in at least 15% of the patients overall) were as follows:

- Fatigue (245 patients [31.5%])
- Diarrhoea (207 patients [26.6%])
- COVID-19 (173 patients [22.2%])
- Contusion (165 patients [21.2%])
- Cough (156 patients [20.1%])
- Anaemia (145 patients [18.6%])
- Nausea (144 patients [18.5%])
- Dyspnoea (144 patients [18.5%])
- Arthralgia (131 patients [16.8%])
- Neutrophil count decreased (125 patients [16.1%]), and
- Constipation (118 patients [15.2%]).

TEAEs considered related to study drug were reported in 507 of 778 (65.2%) patients. The most frequently reported drug-related TEAEs (those in more than 5% of patients overall) were as follows:

- Contusion (111 patients [14.3%])
- Diarrhoea (77 patients [9.9%])
- Fatigue (76 patients [9.8%])
- Neutrophil count decreased (70 patients [9.0%])
- Neutropenia (61 patients [7.8%])
- Anaemia (46 patients [5.9%])
- Platelet count decreased (44 patients [5.7%]), and
- Nausea (40 patients [5.1%]).

TEAEs in the Phase 1/2 monotherapy cohorts were Grade 3 or 4 in severity in 434 (55.8%) patients. The most frequently reported Grade 3 or 4 TEAEs (those in at least 5% of patients overall) were as follows:

- Neutrophil count decreased (103 patients [13.2%])
- Neutropenia (79 patients [10.2%])
- Anaemia (79 patients [10.2%])
- Platelet count decreased (56 patients [7.2%]), and
- Pneumonia (51 patients [6.6%]).

Grade 3 or 4 TEAEs reported as related to study drug were observed in 186 (23.9%) patients. The most frequently reported related Grade 3 or 4 TEAEs (those in at least 1% of patients overall) were as follows:

- Neutrophil count decreased (56 patients [7.2%])
- Neutropenia (49 patients [6.3%])
- Anaemia (19 patients [2.4%])
- Febrile neutropenia (12 patients [1.5%])
- Platelet count decreased (12 patients [1.5%]), and
- Pneumonia (9 patients each [1.2%]).

The frequency of Grade 3 or 4 TEAEs was higher in CSAS (195 [61.5%] patients) compared to MSAS (77 [46.4%] patients), while the frequency of TEAEs considered related to the study drug was comparable between both the subsets (CSAS: 81 [25.6%] patients and MSAS: 39 [23.5%] patients).

Table 5.5. TEAEs (All Grades) by Frequency in 10% or More Patients Treated with Pirtobrutinib Monotherapy[a], the Corresponding Related Events, and Events of Severity Grade 3 or 4: Study LOXO-BTK-18001

MedDRA Preferred Term n (%)	All Patients Treated with Pirtobrutinib Monotherapy (N=778)			
	TEAEs by Frequency (≥10%)	Drug-Related TEAEs	TEAEs of Severity Grade 3 or 4	Drug-Related TEAEs of Severity Grade 3 or 4
Patients with any TEAEs	748 (96.1)	507 (65.2)	434 (55.8)	186 (23.9)
Fatigue	245 (31.5)	76 (9.8)	17 (2.2)	6 (0.8)
Diarrhoea	207 (26.6)	77 (9.9)	9 (1.2)	3(0.4)
Contusion	165 (21.2)	111 (14.3)	1 (0.1)	0
Cough	156 (20.1)	22 (2.8)	1 (0.1)	0
COVID-19	173 (22.2)	13 (1.7)	21 (2.7)	0
Nausea	144 (18.5)	40 (5.1)	2 (0.3)	1 (0.1)
Dyspnoea	144 (18.5)	25 (3.2)	12 (1.5)	2 (0.3)
Anaemia	145 (18.6)	46 (5.9)	79 (10.2)	19 (2.4)
Arthralgia	131 (16.8)	31 (4.0)	7 (0.9)	0
Neutrophil count decreased	125 (16.1)	70 (9.0)	103 (13.2)	56 (7.2)
Pyrexia	116 (14.9)	20 (2.6)	10 (1.3)	0
Constipation	118 (15.2)	19 (2.4)	2 (0.3)	0
Headache	115 (14.8)	34 (4.4)	6 (0.8)	3 (0.4)
Abdominal pain	108 (13.9)	12 (1.5)	9 (1.2)	1 (0.1)
Back pain	109 (14)	5 (0.6)	6 (0.8)	0
Platelet count decreased	113 (14.5)	44 (5.7)	56 (7.2)	12 (1.5)
Oedema peripheral	96 (12.3)	10 (1.3)	3 (0.4)	0
Upper respiratory tract infection	100 (12.9)	30 (3.9)	1 (0.1)	0
Pneumonia	96 (12.3)	21 (2.7)	51 (6.6)	9 (1.2)
Neutropenia	91 (11.7)	61 (7.8)	79 (10.2)	49 (6.3)
Dizziness	94 (12.1)	16 (2.1)	1 (0.1)	0
Urinary tract infection	87 (11.2)	13 (1.7)	16 (2.1)	0
Hypertension	80 (10.3)	26 (3.3)	25 (3.2)	5 (0.6)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; CTCAE = common terminology criteria for adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients in the specified category; RP2D = recommended phase 2 dose; TEAE = treatment-emergent adverse event; QD = once daily.

[a] The monotherapy comprises Phase 1 dose escalation and dose expansion, as well as Phase 2 RP2D of 200 mg QD. The pirtobrutinib dose in Phase 1 was between 25 and 300 mg QD.

Notes: TEAEs are defined as adverse events that started on or after the first day of pirtobrutinib dosing through 30 days (+ 7 days window) after the date of the last dose of pirtobrutinib or the first date starting new anticancer therapy (whichever is earlier).

If a patient experienced more than 1 adverse event within a preferred term, the patient is counted once in that preferred term**.**

The reported AE term is coded using version 26.0 of the MedDRA.

Severity grade assignment based on CTCAE (v5.0): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal).

Drug-related TEAEs are based upon investigator assessment of causality.
Data cutoff date: 27 January 2024

SAEs

Table 5.6 summarizes treatment-emergent SAEs and the corresponding events considered drug-related by the investigators for patients treated in the Phase 1/2 monotherapy cohorts.

Treatment-emergent SAEs were reported in 365 of the 778 (46.9%) patients treated with pirtobrutinib monotherapy. The most frequently reported SAEs occurring in at least 1% (or at least 7) of patients were as follows:

- Pneumonia (52 patients [6.7%])
- COVID-19 pneumonia (48 patients [6.2%])
- COVID-19 (27 patients [3.5%])
- Sepsis (19 patients [2.4%])
- Anemia (19 patients [2.4%])
- Febrile neutropenia (17 patients [2.2%]
- Pyrexia (17 patients [2.2%])
- Acute kidney injury (13 patients [1.7%])
- Urinary tract infection (12 patients [1.5%])
- Atrial fibrillation (10 patients [1.3%])
- Dyspnoea (8 patients [1.0%])
- Respiratory failure (9 patients [1.2%]), and
- Bacteraemia (7 patients [0.9%]).

Of the 778 treated patients comprising the pirtobrutinib Phase 1/2 monotherapy cohorts, 54 (6.9%) patients reported SAEs assessed as related to study drug. The treatment-related SAEs with the highest incidences were Febrile neutropenia (11 [1.4%]) and Pneumonia (8 [1.0%]); all other SAEs had incidences of less than 1%.

The frequency and nature of SAEs were similar between the MSAS and OMTSAS and between the CSAS and OMTSAS. The SOC in which SAEs were most common was Infections and infestations (199 [25.6%] patients). Despite the overall differences in incidences of infectious all-grade AEs between the safety analysis sets (reported to be higher in CLL/SLL patients compared to MCL), the difference in incidences of infectious SAEs was less pronounced across analysis sets (MSAS: 30 [18.1%] patients; CSAS: 107 [33.8%] patients; OMTSAS: 199 [25.6%] patients), indicating a similar vulnerability to severity of infection.

Table 5.6. Treatment-Emergent SAEs in at Least 1% of Patients Treated with Pirtobrutinib Monotherapy Overall and the Corresponding Drug-Related Events: Study LOXO-BTK-18001

MedDRA Preferred Term	All Patients Treated with Pirtobrutinib Monotherapy (N=778)	
	Treatment-Emergent SAEs (≥1%)	Drug-Related Treatment-Emergent SAEs
Patients with any SAEs, n (%)	365 (46.9)	54 (6.9)
Pneumonia	52 (6.7)	8 (1.0)
COVID-19 pneumonia	48 (6.2)	3 (0.4)
COVID-19	27 (3.5)	-
Sepsis	19 (2.4)	2 (0.3)
Febrile neutropenia	17 (2.2)	11 (1.4)
Anaemia	19 (2.4)	3 (0.4)
Pyrexia	17 (2.2)	1 (0.1)
Acute kidney injury	13 (1.7)	-
Urinary tract infection	12 (1.5)	-
Atrial fibrillation	10 (1.3)	3 (0.4)
Dyspnoea	8 (1.0)	-
Respiratory failure	9 (1.2)	2 (0.3)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients in the specified category; N = number of participants; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Notes: The reported AE term is coded using version 26.0 of the MedDRA.

At each level of subject summarization, a subject is counted only once if the subject reported 1 or more events. The results are presented in the descending order of incidence.

Data cutoff date: 27 Jan 2024

Deaths

In the Phase 1/2 monotherapy cohorts, 293 (37.7%) deaths have been reported in the 778 patients receiving pirtobrutinib.

Of the 293 patient deaths in the pirtobrutinib Phase 1/2 monotherapy cohorts, 101 (13.0%) occurred within 28 days of the last dose of study drug across dosing cohorts. Of these 101 deaths, 48 (6.2%) were attributed to disease progression, and 53 (6.8%) were attributed to AE.

In the OMTSAS, 60 (7.7%) patients experienced fatal AEs including 6 (0.8%) with fatal AEs that were assessed as being related to study treatment, which are described later in this section. Fatal SAEs that occurred in more than 1 patient included:

- COVID-19 pneumonia (13 [1.7%] patients)
- COVID-19 (7 [0.9%] patients)
- Respiratory failure (6 [0.8%] patients)
- Pneumonia and septic shock (4 [0.5%] patients each), and
- Sepsis, cardiac arrest, and multiple organ dysfunction syndrome (2 [0.3%] patients each).

Notably, 39 of the 60 (65%) fatal AEs were in the SOC Infections and infestations and approximately half (20 of 39 [33%]) of these were related to COVID-19.

Six fatal AEs that were assessed as being related to study treatment occurred in the context of infectious condition and included COVID-19 pneumonia (2 patients), Pneumonia necrotizing (1 patient), Respiratory failure (2 patients), and *Enterococcus faecium*-related Septic shock (1 patient each).

TEAEs leading to study drug discontinuation

Seventy-seven patients (9.9%) enrolled in the Phase 1/2 monotherapy cohorts discontinued pirtobrutinib because of TEAEs. Of the TEAEs that led to permanent treatment discontinuation, the following events occurred in more than 1 patient:

- COVID-19 pneumonia (7 patients [0.9%])
- Pneumonia (5 patients [0.6%])
- Anaemia and Myelodysplastic syndrome (4 patients [0.5%] each)
- COVID-19, Neutropenia, Platelet count decreased, and Sepsis (3 patients [0.4%] each), and
- Fatigue, Neutrophil count decreased, and Septic shock (2 patients [0.3%] each).

Majority of TEAEs leading to treatment discontinuation represented events of infectious nature and second primary malignancy.

The rates of treatment discontinuation due to TEAEs were similar between both the subsets, with 35 (11%) patients in the CSAS and 18 (10.8%) patients in the MSAS.

Table 5.7 summarizes treatment-related AEs (in at least 2 patients) leading to study drug discontinuation.

Table 5.7. Treatment-Related AEs (at Least 2 Patients) Leading to Study Drug Discontinuation: Study LOXO-BTK-18001

	OMTSAS (N=778)	
PT, n (%)	**All**	**Related**
Any AE leading to discontinuation of study treatment	77 (9.9)	22 (2.8)
COVID-19 pneumonia	7 (0.9)	1 (0.1)
Pneumonia	5 (0.6)	-
Anaemia	4 (0.5)	1 (0.1)
COVID-19	3 (0.4)	-
Myelodysplastic syndrome	4 (0.5)	1 (0.1)
Platelet count decreased	3 (0.4)	2 (0.3)
Sepsis	3 (0.4)	-
Septic shock	2 (0.3)	1 (0.1)
Fatigue	2 (0.3)	1 (0.1)
Neutropenia	3 (0.4)	3 (0.4)
Neutrophil count decreased	2 (0.3)	1 (0.1)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; n = number of patients in the specified category; N = number of participants; OMTSAS = Overall Monotherapy Safety Analysis Set; PT = preferred term.

Phase 1b combination therapy arms

TEAEs

In the Phase 1b combination therapy arms, TEAEs were reported for a study drug alone or in combination and were considered related to the study drugs if consistent with known toxicity profile of pirtobrutinib, venetoclax, or rituximab. A "related" event indicates an investigator attribution of a TEAE relationship to a single drug or any of the study drugs in the combination.

Subjects in Arm A received pirtobrutinib plus venetoclax and Arm B received pirtobrutinib plus rituximab and venetoclax. All 25 subjects in the combination therapy reported at least 1 TEAE, of whom 24 were assessed related by the investigator and 15 were of Grade 3/4 severity (Table 5.8). The 5 most frequently reported TEAEs in combination Arm A were:

- Nausea (9 patients [60%])
- Fatigue (8 patients [53.3%])
- Neutrophil count decreased (7 patients [46.7%])
- Diarrhoea (7 patients [46.7%]), and
- Upper respiratory tract infection (6 [40.0%] patients).

The most frequently reported TEAEs in combination Arm B were

- Neutrophil count decreased (7 patients [70%])
- Diarrhoea (6 patients [60%])

- Fatigue (5 patients [50%]), and
- Nausea, Infusion-related reaction, Arthralgia, and Constipation (4 patients [40%] each).

TEAEs considered related to any study drug were reported in 14 of the 15 (93.3%) patients treated in combination Arm A and in 10 of the 10 (100%) patients treated in combination Arm B. The most frequently reported treatment-related TEAEs (those with at least 3 patients in each arm) in combination Arm A related to pirtobrutinib were Neutrophil count decreased (7 patients [46.7%]), Nausea (7 patients [46.7%]), Fatigue (5 patients [33.3%]), Diarrhoea (4 patients [26.7%]), Platelet count decreased (4 patients [26.7%]), Contusion (3 patients [20%]), and Constipation (3 patients [20.0%]). While in combination Arm B, most frequent drug-related TEAEs with pirtobrutinib were Neutrophil count decreased (7 patients [70.0%]), Diarrhoea (6 patients [60.0%]), Nausea (4 patients [40.0%]), and Infusion-related reaction (4 patients [40%]).

Table 5.8. TEAEs (All Grades) by Frequency in More Than 3 Patients Treated in Either Combination Therapy Arm, the Corresponding Related to Pirtobrutinib Events, and Events of Severity Grade 3 or 4: Study LOXO-BTK-18001

MedDRA Preferred Term n (%)	Combination Arm A (N=15)				Combination Arm B (N=10)			
	TEAEs	Pirtobrutinib-Related TEAEs	TEAEs of Severity Grade 3 or 4	Pirtobrutinib-Related TEAEs of Severity Grade 3 or 4	TEAEs	Pirtobrutinib-Related TEAEs	TEAEs of Severity Grade 3 or 4	Pirtobrutinib-Related TEAEs of Severity Grade 3 or 4
Patients with any TEAEs	15 (100.0)	14 (93.3)	8 (53.3)	8 (53.3)	10 (100)	10 (100.0)	7 (70%)	8 (80)
Nausea	9 (60.0)	7 (46.7)	0	0	4 (40.0)	4 (40.0)	0	0
Fatigue	8 (53.3)	5 (33.3)	0	0	5 (50)	2 (20.0)	1 (10.0)	0
Neutrophil count decreased	7 (46.7)	7 (46.7)	7 (46.7)	7 (46.7)	7(70.0)	7 (70.0)	6 (60.0)	6 (60.0)
Diarrhoea	7 (46.7)	4 (26.7)	2 (13.3)	2 (13.3)	6 (60.0)	6 (60.0)	0	0
Upper respiratory tract infection	6 (40.0)	2 (13.3)	0	0	1 (10.0)	0	0	0
Infusion-related reaction	1 (6.7)	0	0	0	4 (40.0)	4 (40.0)	2 (20.0)	2 (20.0)
Hypophosphataemia	5 (33.3)	2 (13.3)	0	0	0	0	0	0
Arthralgia	4 (26.7)	2 (13.3)	0	0	4 (40.0)	1 (10.0)	0	0
Constipation	4 (26.7)	3 (20.0)	0	0	4 (40.0)	1 (10.0)	0	0
Cough	4 (26.7)	1 (6.7)	0	0	3 (30.0)	0	0	0

MedDRA Preferred Term n (%)	Combination Arm A (N=15)				Combination Arm B (N=10)			
	TEAEs	Pirtobrutinib-Related TEAEs	TEAEs of Severity Grade 3 or 4	Pirtobrutinib-Related TEAEs of Severity Grade 3 or 4	TEAEs	Pirtobrutinib-Related TEAEs	TEAEs of Severity Grade 3 or 4	Pirtobrutinib-Related TEAEs of Severity Grade 3 or 4
Vomiting	4 (26.7)	2 (13.3)	0	0	0	0	0	0
Platelet count decreased	4 (26.7)	4 (26.7)	1 (6.7)	1 (6.7)	2 (20.0)	2 (20.0)	1 (10.0)	1 (10.0)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients in the specified category; N = number of participants; TEAE = treatment-emergent adverse event.

Notes: All AEs reported during the treatment-emergent period are considered TEAEs.

The reported AE term is coded using version 26.0 of the MedDRA.

At each level of subject summarization, a subject is counted only once if the subject reported 1 or more events. The results are presented in the descending order of incidence.

Data cutoff date: 27 January 2024

A total of 14 (56%) patients reported 1 or more SAEs (7 SAEs in Arm A and 7 SAEs in Arm B). SAEs occurring in more than one patient were as follows:

- Infusion-related reaction
- Pneumonia
- COVID-19 pneumonia
- Pyrexia, and
- Urinary tract infection.

Infusion-related reaction was seen only in Arm B, Anemia and Pneumonia only in Arm A, and COVID-19 pneumonia and Pyrexia were reported in both arms. Six (24%) patients experienced SAEs considered related to pirtobrutinib by the investigator. Related SAEs in Arm A were as follows:

- Pneumonia
- COVID-19 pneumonia
- Pyrexia
- Sepsis, and
- Anaemia.

Related SAEs in Arm B were as follows:

- Cerebral haemorrhage, and
- Urinary tract infection.

In the combination study, 2 AEs led to permanent discontinuation (Neutrophil count decreased and Urinary tract infection). The events of Neutrophil count decreased and Urinary tract infection were related to both pirtobrutinib and venetoclax.

No event of death has been reported in combination Arm A, while 2 deaths have been reported in combination Arm B. The fatal events reported were COVID-19 pneumonia and Cardiac failure, both assessed as not related to study drug by study Investigator.

Study JZNJ

JZNJ is a Phase 2 study of oral pirtobrutinib in patients with previously treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL) conducted in centers in China. Eighty-seven patients were enrolled, and all were treated with 200 mg QD dose. Presented below is a summary of key safety data.

As of 10 April 2023, 86 (98.9%) patients out of 87 patients treated reported a TEAE of any grade. Most frequently reported TEAEs (those in at least 20% of the patients overall) were Anaemia (27 patients [31.0%]), Neutrophil count decreased (26 patients [29.9%]), Blood bilirubin increased (20 patients [23.0%]), Hypokalaemia (20 patients [23.0%]), and White blood cell count decreased (19 patients [21.8%]).

TEAEs considered related to study drug were reported in 79 (90.8%) of 87 patients. The most frequently reported drug-related TEAEs (those in more than 20% of patients overall) were Neutrophil count decreased (23 [26.4%] patients), Anemia (22 [25.3%] patients), and White blood cell count decreased (18 [20.7%] patients).

TEAEs in 57 (65.5%) of 87 patients were Grade 3 or more in severity. The most frequently reported Grade 3 or more TEAEs (those in at least 5% of patients overall) were Neutrophil count decreased (19 patients [21.8%]), White blood cell count decreased (7 patients [8.0%]), Anaemia (7 patients [8.0%]), and Platelet count decreased (6 patients [6.9%]).

Grade 3 or more TEAEs reported as related to study drug were observed in 37 (42.5%) patients. The most frequently reported Grade 3 or more TEAEs (those in at least 5% of patients overall) reported as related to study drug were Neutrophil count decreased (16 patients [18.4%]) and White blood cell count decreased (6 patients [6.9%]).

Treatment-emergent SAEs were reported in 25 (28.7%) of the 87 patients in this study. The most frequently reported SAEs occurring in at least 3 % of patients were COVID-19 (3 patients [3.4%]) and Pneumonia (3 patients [3.4%]).

Of 87 patients in the study, 12 (13.8%) patients reported SAEs assessed as related to study drug. The reported treatment-related SAEs were Acute myocardial infarction, Bronchitis, COVID-19, Gastrointestinal disorder, Haemorrhage, Infection, Neutropenia, Platelet count decreased, Pneumonia, Rash, Thrombocytopenia, Tumor lysis syndrome, Tumor necrosis, Urinary tract infection, and Ventricular extrasystoles each with incidence rate of 1.1%.

In this study, a total of 37 (42.5%) deaths have been reported.

Of the 37 deaths in this study, 12 (13.8%) occurred either on therapy (6 [6.9%]) or within 28 days of study drug discontinuation (6 [6.9%]). Of the 12 deaths, 7 (8%) deaths were attributed to an AE. The fatal AEs that were related to study treatment were 2 (2.3%). The fatal AEs that

resulted in death were COVID-19, Infection, Pulmonary haemorrhage, Shock, and Tumor lysis syndrome, each with incidence rate of 1.1% (1 patient each); death in 2 (2.3%) patients.

A total of 5 (5.7%) patients discontinued pirtobrutinib because of TEAEs in this study. The AEs that led to permanent treatment discontinuation were Ventricular extrasystoles (2 [2.3%] patients), Gastric cancer, Pneumonia viral, and Rash (1 [1.1%] patient each).

Expanded access protocols

As of 27 September 2023, there were 21 expanded access single-patient protocols, 3 ongoing and 18 discontinued. Additionally, Lilly has provided pirtobrutinib through expanded access programs, named patient use programs. Pirtobrutinib was administered at the preferred RP2D dose of 200 mg QD in these patients, except when preexisting toxicities and/or concomitant anticancer therapy required a reduced starting dose. No significant findings from these studies were reported. Efficacy data are not collected on this patient population.

Safety in clinical pharmacology studies

Safety data, as of 29 July 2022, from the 14 completed clinical pharmacology studies (Table 5.1) conducted in participants with nonhematological cancer were assessed. Only Grade 2 or higher AEs, SAEs, and AEs leading to dose interruption, reduction, or discontinuation reported in the clinical pharmacology studies are summarized here.

Two patients with severe renal impairment in Study 20013 experienced Grade 2 (moderate) AEs following the administration of a single dose of pirtobrutinib:

- 2 AEs of Cellulitis and Thrombophlebitis deemed not related to treatment by the investigator, lasting 10 days and 9 days, respectively, and reported in 1 subject with severe renal impairment, and
- 1 study treatment-related AE of Diarrhoea lasting 3 days and 15 hours reported in 1 subject with severe renal impairment (the same subject reported Grade 1 [mild] vomiting).

One patient with severe hepatic impairment in Study 20012 experienced a Grade 2 (moderate) AE of Bacteremia, and 2 patients with normal hepatic function were withdrawn due to AEs of SARS-CoV-2:

- 1 AE of Grade 2 (moderate) Bacteremia lasting at least 28 days, 16 hours, and 47 minutes reported in 1 subject with severe hepatic impairment. The first symptom of this AE (observation of low BP) was observed on Day 1 prior to pirtobrutinib dosing. However, the constellation of symptoms and findings ultimately led to the diagnosis of Bacteremia following the initiation of study drug dosing. Therefore, this event was deemed an AE rather than reported as medical history.
- Two AEs of SARS-CoV-2 deemed not related to treatment lasting 8 days, 7 hours, and 29 minutes, and 12 days and 23 hours was reported in 2 patients with normal hepatic function following a single dose of drug. Both patients were withdrawn from the study.

No other Grade 2 or higher AEs were reported during clinical pharmacology studies.

No SAEs were reported in clinical pharmacology studies. Other than the AEs that lead to study drug discontinuation in Study 20012, 1 other patient who received placebo in Study 20011 discontinued due to Grade 1 increases in alanine aminotransferase and aspartate aminotransferase.

No additional safety concerns or significant safety findings were identified from these clinical pharmacology studies compared with the safety analysis from Study LOXO-BTK-18001.

5.2.1.2. Anticipated Serious Adverse Events (SAE) and Predicted Background Rates in the Study Population

For each relevant study population and/or indication, Table 5.9 presents serious adverse events (SAEs) that are anticipated in the population being studied due to study population, age, comorbid conditions or the disease state, and the predicted background rate (or estimated range of rates) within the population being studied. SAEs of the terms listed in Table 5.9 will be reviewed in aggregate on at least a quarterly basis to evaluate for numerical imbalances between treatment groups in SAEs for reporting to the **FDA in the US.** For adverse events that have been found to have an association with study drug, refer to Sections 6 and 7.

Table 5.9. Anticipated Serious Adverse Events and Predicted Background Rates in the Population Being Studied

Indication or Study Population	MedDRA Search Strategy	Predicted Background Rate (or Estimated Range of Rates) within the Population
Coronary artery disease	Ischemic heart disease (SMQ)	0.5-1.9[a]
Chronic obstructive pulmonary disease	PTs: Chronic obstructive pulmonary disease; Asthma - chronic obstructive pulmonary disease overlap syndrome; - Emphysema; - Bronchitis chronic	0.9-2.8[a]

Abbreviations: CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardised MedDRA Query.

a ClinicalTrials.gov was searched to identify large (N>100), Phase 2/3 studies involving standard of care anticancer therapies for relapsed/refractory CLL/MCL, which are not known to cause the listed events. Estimated ranges of background rates were based on the reported SAE rates in ibrutinib monotherapy arm of 5 trials (3 CLL and 2 MCL).

5.2.2. Efficacy

Based on a data cutoff date of 05 May 2023, efficacy data for the efficacy-evaluable patients treated in the Phase 1/2 monotherapy cohorts of Study LOXO-BTK-18001 were summarized and published. The efficacy-evaluable patient cohort includes

- 282 with CLL/SLL (prior BTKi treated)
- 152 with MCL, and
- 82 with Richter Transformation.

Response as assessed by the independent review committee was based on iwCLL 2018 for CLL/SLL (Hallek et al. 2018), and Lugano 2014 classification (Cheson et al. 2014) for MCL, and for other NHL (MZL, DLBCL, and so on).

In the 282 efficacy-evaluable patients with CLL/SLL (prior BTKi treated), the ORR for all post-cBTKi patients was 72% (95% CI, 66.4-77.1), and ORR including PR-L was 82% (95% CI, 76.5-85.9). Median DoR was 18.4 months (95% CI, 15.3-20.4) for all cBTKi pretreated patients. With a median follow-up of 27.5 months, the median PFS was 19.4 months (95% CI, 16.6-22.1) among all cBTKi pretreated patients. With a median follow-up of 29.3 months, the median OS was not estimable for all cBTKi pretreated patients, BCL2i-naïve, and BCL2i-pretreated; the 24-month OS rates were 73.2% (95% CI, 67.4-78.2), 83.1% (95% CI,75.9-88.2), and 60.6% (50.9-68.9), respectively.

In the 152 efficacy-evaluable patients with MCL, the ORR for cBTKi pretreated patients was 49.3% (95% CI, 41.1-57.6), including 15.8% complete responses (n=24) and 33.6% partial responses (n=51), while cBTKi-naïve patients (n=14) had an ORR of 85.7% (95% CI, 57.2-98.2). The ORR among 128 patients who had discontinued a prior cBTKi due to PD and 21 patients who had discontinued for toxicity/other reasons was 43.0% and 90.5%, respectively. Among the 75 responding cBTKi pretreated patients, the median DoR was 21.6 months (95% CI, 9.2-27.2) at a median follow-up of 24 months. The 18- and 24-month DoR rates were 51.9% (95% CI, 37-64.8) and 38.9% (95% CI, 22.7-54.8), respectively. The 18- and 24-month DoR rates among 12 responding cBTKi-naïve patients were both 90.0% (95% CI, 47.3-98.5). The median PFS and OS for cBTKi pretreated patients was 5.6 months (95% CI, 5.3-9.2) and 23.5 months (95% CI, 17.1-NE), respectively.

In the 82 efficacy-evaluable patients with RT, the ORR by investigator was 50.0% (95% CI, 38.7-61.3) including complete (13.4%, n=11) and partial (36.6%, n=30) responses. For 61 patients who received prior cBTKi therapy, the ORR was 45.9% (95% CI 33.1-59.2). Among 28 patients with an RT-directed cBTKi and 51 patients with prior CLL-directed cBTKi, the ORR was 42.9% (95% CI, 24.5-62.8) and 43.1% (95% CI, 29.3-57.8), respectively. In 50 patients who discontinued prior cBTKi due to disease progression, the ORR was 42.0% (95% CI, 28.2-56.8). At median follow-up time of 9.7 months, the median DoR for all 82 RT patients was 7.4 months (95% CI, 3.1-19.1) and the estimated rate at 12 months was 45.9% (95% CI, 28.3-61.8). The median time on treatment for the 41 patients who responded to treatment was 8.3 months. Eight patients stopped pirtobrutinib to pursue curative-intent allogeneic SCT, and DoR was censored at the last preceding disease assessment. At a median survival follow-up of 18.3 months, the median OS for the entire RT cohort was 12.5 months (95% CI, 6.9-20.5). At 18 months, the OS rate was 44.3% (95% CI, 32.5-55.4).

Based on a data cutoff date of 29 July 2022, efficacy data for 80 efficacy-evaluable Waldenström macroglobulinemia (WM) patients treated in the Phase 1/2 monotherapy cohorts in Study

LOXO-BTK-18001 (Palomba et al. 2022) was summarized. Response as assessed by the investigator was based on IWWM for WM (Owen et al. 2013).

Prior cBTKi-treated WM-evaluable patients included

- 15 patients with very good partial response
- 27 with partial response
- 9 with minor response, and
- 9 with stable disease

cBTKi-naïve WM evaluable patients included

- 5 patients with very good partial response
- 10 with partial response
- 0 with minor response, and
- 2 with stable disease.

Prior cBTKi-treated WM median PFS was 19.4 months (95% CI: 15.1, 22.1); median follow-up for PFS is 14 months.

Efficacy was seen across all dose levels of pirtobrutinib, in patients with B-cell malignancy, and irrespective of prior lines of therapies (including in patients who had been treated with BTK inhibitors and B-cell lymphoma 2 inhibitors).

5.3. Marketing Experience

Pirtobrutinib was first authorized on 27 January 2023 in the US for treatment of adult patients with relapsed/refractory MCL. Subsequent authorization in the US for CLL indication was received on 01 December 2023. Pirtobrutinib has been authorized in 38 countries, including those in the EU, the US, and Switzerland. Refer to the local label for information regarding the precise indications approved in a specific country or region.

The indications currently listed in the company core data sheet are the following:

Mantle cell lymphoma: Pirtobrutinib as a single agent is indicated for the treatment of adult patients with MCL who have been previously treated with a BTK inhibitor.

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): Pirtobrutinib as a single agent is indicated for the treatment of adult patients with CLL/SLL who have been previously treated with a BTK inhibitor.

Cumulative review of marketing experience up to 27 January 2024 has not identified any new safety findings that would warrant changes to the reference safety information.

6. Summary of Data and Guidance for the Investigator

The ADR table in this section (Table 6.1) is NOT to be used for the assessment of suspected serious ADRs for the purposes of suspected unexpected serious adverse reaction (SUSAR) reporting. Refer to Section 7 for Reference Safety Information (RSI).

6.1. Adverse Drug Reactions and Risks Considered to Be Associated with Pirtobrutinib, Summary of Data, and Monitoring Guidance for the Investigator

See Sections 6.2.2.5 and 6.2.2.6 for additional information concerning the risks associated with pirtobrutinib.

Cytopenias

Cytopenias (leukopenia [most commonly neutropenia], erythropenia, and thrombocytopenia) are complications of the diseases enrolled in the clinical studies as well as prior therapy received. Cytopenias are also a recognized drug class effect of BTK inhibitor therapy, and AEs of this nature have been reported in patients receiving pirtobrutinib, most commonly neutropenia followed by anemia and thrombocytopenia. In the clinical studies, all patients undergo standard blood count monitoring at routine intervals to monitor for signs of hematologic toxicity. While high grade (Grade 3 or 4 cytopenia) and serious (for example, neutropenic sepsis) events have been reported, events of this nature are most commonly nonserious and are treated with close monitoring, supportive care, and/or dose modification as clinically indicated. Patients with a finding of neutropenia should be monitored for increased risk of infection as clinically appropriate and managed as outlined in the protocol. Similarly, patients with a finding of thrombocytopenia should be monitored for increased risk of bleeding as clinically indicated.

Lymphocytosis

Pirtobrutinib has been observed to cause an early treatment-induced leukocytosis, particularly lymphocytosis, in patients with CLL and MCL, which is consistent with that reported to occur with other BTK inhibitor therapies. Because this is a recognized on-target effect of BTK inhibitor therapy, occurrence is not always indicative of a safety finding and may represent disease status, including progression of disease. In addition, these reactions are typically not indicative of disease progression if unaccompanied by other evidence of disease progression. However, SAEs of leukocytosis, including events considered related to study drug, have infrequently been reported in patients receiving pirtobrutinib. Patients on clinical studies undergo standard blood count monitoring and should be assessed for occurrence of events of this nature as well as the potential need for procedural intervention, such as leukapheresis, as clinically indicated and as indicated in the protocol.

Second primary malignancies

Development of second primary malignancies (predominantly nonmelanoma skin cancers) is a recognized potential risk of BTK inhibitor therapy. Events of this nature have been reported in

patients receiving pirtobrutinib. This risk is further compounded by the pre-existing risk of developing a second malignancy because of chronic immunosuppression in the oncology patient population treated due to the nature of underlying disease and prior treatment history. As a general precaution, patients should be monitored for skin cancers and advised of sun protection measures.

Tumor lysis syndrome

TLS is a known risk in all patients receiving anticancer therapy, especially in patients with hematologic malignancies and/or large tumor burden. It is not a risk unique to the nature or use of BTK inhibitor therapy specifically. While TLS has been recognized to occur rarely in patients treated with first generation BTK inhibitor therapy, it has not been a recognized drug class risk. Patients should be assessed for possible risk of TLS as clinically indicated.

Bleeding

Bleeding (most predominantly low-grade, nonserious events of bruising and bleeding) is a recognized drug class effect of BTK inhibitor therapy, and events of this nature have been reported with pirtobrutinib. Patients receiving anticoagulant or antiplatelet agents are at increased risk of hemorrhage. Standard coagulation monitoring (prothrombin time, activated partial thromboplastin time, international normalized ratio) is recommended in the setting of increased bruising or signs of bleeding. In the clinical studies, all patients undergo standard blood count monitoring at routine intervals to monitor for signs of hematologic toxicity. Patients should be monitored for signs and symptoms of bleeding. Additionally, study drug hold should be considered for 3 to 5 half-lives in patients undergoing surgical intervention while on study drug.

Atrial fibrillation and atrial flutter

Patients in clinical studies undergo routine, periodic ECG monitoring as well as assessment for symptoms of possible dysrhythmia with reflexive ECG evaluation as clinically indicated and as outlined in the protocol. Cardiac dysrhythmias, particularly atrial fibrillation and atrial flutter, are a recognized drug class risk of BTK inhibitor therapy. Events of this nature, predominantly in patients with a documented history of atrial fibrillation and/or concomitant cardiovascular conditions, have infrequently been reported in patients taking pirtobrutinib.

Infection

The increased occurrence and/or severity of infections is a recognized risk of BTK inhibitor therapy, including life-threatening, opportunistic, and fatal infections (for example, sepsis and septic shock) and events of this nature and severity have been reported in patients receiving pirtobrutinib. This risk is further compounded by the pre-existing risk of infection in this patient population due to advanced age, underlying disease, prior treatment history and comorbidities. The use of prophylactic antimicrobial therapy should be considered when clinically appropriate. Additionally, patients should be monitored throughout the study for signs of infection, particularly in patients with additional concurrent risk factors (for example, patients who have been heavily pretreated, have poor bone marrow function, ongoing neutropenia, diabetes, and so on). Study drug interruption should be considered as clinically appropriate for patients presenting

with fever and/or signs and symptoms of infection, particularly if concurrent risk factors are present that place the patient at increased risk for serious complications.

Recently published data suggest that patients with lymphoid malignancies, including CLL and SLL, often have impaired humoral response to COVID-19 vaccines and this response may be further diminished by concurrent BTK inhibitor and/or anti-CD20 antibody therapy. Given these data, when medically appropriate and feasible, patients receive primary and/or applicable booster SARS-CoV-2 vaccine doses prior to initiating treatment on a pirtobrutinib clinical trial. However, exercise clinical judgment and patient autonomy in guiding these decisions.

As with any acute patient safety event, the use of potentially lifesaving therapy is permitted. This guidance applies to all available oral and IV antiviral therapy, as well as to antibody and immunosuppressive treatments that are part of the outpatient and inpatient management of patients diagnosed with COVID-19. Given the potential increased mortality experienced by patients with lymphoid malignancies who develop COVID-19, consider early use of therapies that have been approved or authorized for use, at the discretion of the treating physician.

Developmental safety

Like other BTK inhibitors, pirtobrutinib is teratogenic. In animal studies of rats, developing embryos showed developmental effects on kidneys, ureters, ovaries, uterus, and skin. Fetal loss was also reported. All patients participating in the clinical study must use contraception as directed in the clinical protocol for the study.

Safety experience with combination molecules

In general, the combination regimens received on Study LOXO-BTK-18001 have not revealed any new or unique safety signals outside of what is anticipated based upon the established safety profiles. Local package inserts should be utilized for further information regarding the safety profile of combination therapies.

Use of live vaccines

Pirtobrutinib has not been studied in combination with live vaccines, and information on safety of this combination is not available. As pirtobrutinib is an immunomodulatory drug, live vaccines should be avoided while taking pirtobrutinib, as well as immediately (approximately 4 weeks) before starting treatment or immediately (approximately 4 weeks) after discontinuing treatment. Individual protocol requirements may vary and should be referred to for study-specific guidance on use of live vaccines.

Findings from other BTK inhibitors

Liver injury has been reported in clinical trials/postmarketing data of other BTK inhibitors (for example, tolebrutinib, fenebrutinib, orelabrutinib, ibrutinib, and zanubrutinib). Clinical trials/postmarketing data of pirtobrutinib has not yet revealed direct causal association with liver injury.

Participants in clinical trials are being monitored for hepatotoxicity.

6.2. Developmental Core Safety Information (DCSI)

6.2.1. International Nonproprietary Name/United States Adopted Names

INN/USAN Name: Pirtobrutinib

6.2.2. Clinical Information

6.2.2.1. Therapeutic Indication(s)

6.2.2.1.1. Development Indications, Formulations, and/or Combinations

Pirtobrutinib as a single agent is under development for the treatment of adult patients with chronic lymphocytic leukemia, small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL) and other non-Hodgkin lymphomas (NHLs).

6.2.2.1.2. Approved Indications, Formulations, and/or Combinations

Mantle cell lymphoma

Pirtobrutinib as a single agent is indicated for the treatment of adult patients with MCL who have been previously treated with a BTK inhibitor.

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Pirtobrutinib as a single agent is indicated for the treatment of adult patients with CLL/SLL who have been previously treated with a BTK inhibitor.

Refer to the local label for information regarding the precise indications approved in a specific country or region.

6.2.2.2. Posology/Dosing and Method of Administration

6.2.2.2.1. Development Indications, Formulations, and/or Combinations

For oncology studies in CLL/SLL, MCL, and other NHLs, the dose under study is 200 mg QD administered orally.

6.2.2.2.2. Approved Indications, Formulations, and/or Combinations

The recommended dose of pirtobrutinib is 200 mg orally, QD for the MCL and CLL/SLL indications.

Treatment should be continued until disease progression or unacceptable toxicity. Pirtobrutinib may be taken with or without food. Patients should take the dose at approximately the same time every day. Instruct patients that if vomiting occurs, do not take an additional dose; continue with the next scheduled dose. If more than 12 hours have passed after a patient has missed a dose, instruct the patient to take the next dose at its scheduled time; an additional dose should not be taken.

Dose adjustments

Table 6.1 outlines general guidelines for dose modification to manage adverse events. Refer to individual study protocols for trial-specific guidance on managing adverse events.

Table 6.1. Recommended Dose Modifications for Adverse Reactions

Adverse Events[a]	Occurrences Requiring Dose Modification	Modification
Grade 3 or 4 non-hematologic toxicity Grade 3 neutropenia with fever and/or infection Grade 4 neutropenia lasting ≥7 days Grade 3 thrombocytopenia with bleeding Grade 4 thrombocytopenia	First	Suspend pirtobrutinib until recovery to Grade 1 or baseline. Resume at original dose of 200 mg once daily.
	Second	Suspend pirtobrutinib until recovery to Grade 1 or baseline. Resume at reduced dose of 100 mg once daily.
	Third	Suspend pirtobrutinib until recovery to Grade 1 or baseline. Resume at reduced dose of 50 mg once daily.
	Fourth	Discontinue pirtobrutinib.

[a] Dose modification is not recommended for asymptomatic lymphocytosis or asymptomatic lipase increase.

6.2.2.3. Nonclinical Toxicology

Carcinogenesis

Carcinogenicity studies have not been conducted with pirtobrutinib.

Mutagenesis

Pirtobrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay. Pirtobrutinib was aneugenic in in vitro micronucleus assays using human peripheral blood lymphocytes. Pirtobrutinib had no effect in an in vivo rat bone marrow micronucleus assay at doses up to 2000 mg/kg, which is approximately 12-fold higher exposure (unbound C_{max}) than human exposure at 200 mg.

Impairment of fertility

Pirtobrutinib had no effects on fertility and male and female fertility studies in rats. In repeat-dose toxicity studies of up to 9 months duration, pirtobrutinib had no effect on male or female reproductive organs.

General toxicity

Repeat-dose studies were conducted in rats and dogs to characterize toxicity. Important effects included decreased size, weight, or cellularity of lymphoid organs and decreases in B lymphocytes and other markers of immune system function. Minimal-to-mild corneal lesions were observed only in dogs, and vascular and perivascular necrosis and inflammation of

pulmonary blood vessels were observed only in rats. These effects occurred at clinically relevant exposure levels.

6.2.2.4. Contraindications

None known.

6.2.2.5. Special Warnings and Special Precautions for Use

6.2.2.5.1. Development Indications, Formulations, and/or Combinations

Refer to Section 6.2.2.5.2.

6.2.2.5.2. Approved Indications, Formulations, and/or Combinations

Infections

Serious infections, including fatal events, have occurred in patients treated with pirtobrutinib. The most frequently reported Grade 3 or higher infections were pneumonia, COVID-19 pneumonia, COVID-19, and sepsis. Consider prophylaxis in patients who are at increased risk for opportunistic infections. Based on the grade of infection and whether it occurs with neutropenia, dose modification may be required.

Hemorrhage

Bleeding events, including fatal events, have occurred in patients treated with pirtobrutinib, with and without thrombocytopenia. Major bleeding events of Grade 3 or higher have been observed, including gastrointestinal and intracranial hemorrhage. Monitor patients for signs and symptoms of bleeding. Patients receiving anticoagulant or antiplatelet agents are at increased risk of hemorrhage. Consider the risks and benefits of anticoagulant or antiplatelet therapy when coadministered with pirtobrutinib. The use of pirtobrutinib has not been studied with warfarin or other vitamin K antagonists. Consider the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and postsurgery depending on the type of surgery and risk of bleeding. Based on the grade of the bleeding event and whether it occurs with thrombocytopenia, dose modification may be required.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia, have occurred in patients treated with pirtobrutinib. Monitor complete blood counts during treatment. Based on the grade of cytopenias, dose modification may be required.

Atrial fibrillation/flutter

Atrial fibrillation and atrial flutter have been observed in patients treated with pirtobrutinib, many who have a history of atrial fibrillation and/or multiple cardiovascular comorbidities. Monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated. Based on the grade of atrial fibrillation or atrial flutter, dose modification may be required.

Second primary malignancies

Second primary malignancies have occurred in patients treated with pirtobrutinib, with the most frequent types being nonmelanoma skin cancers. Monitor patients for the appearance of skin cancers and advise protection from sun exposure.

6.2.2.6. Use during Pregnancy, Lactation, and in Persons of Reproductive Potential

Use during pregnancy

Pirtobrutinib is not recommended during pregnancy. Based on findings from animal studies, pirtobrutinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of pirtobrutinib to pregnant rats during organogenesis resulted in decreased fetal weight, embryo-fetal mortality, and fetal malformations at maternal exposures (AUC) comparable to those in patients with cancer at the recommended dose of 200 mg QD.

Use during lactation

There are no data on the presence of pirtobrutinib in human milk, effects of pirtobrutinib on the breastfed child, or the effects of pirtobrutinib on milk production. Advise a nursing woman to discontinue breastfeeding during treatment with pirtobrutinib and for 1 week after the last dose of pirtobrutinib.

Use in individuals of reproductive potential

Advise women with reproductive potential to use highly effective contraception during treatment and for 1 month after the last dose of pirtobrutinib. Pirtobrutinib is not recommended in women of childbearing potential not using contraception. Pirtobrutinib had no effect on male or female fertility in animal studies.

Individual protocol requirements may vary and should be referred to for study-specific guidance on use of contraception.

6.2.2.7. Undesirable Effects

The purpose of the ADR table in this section of the IB is purely intended as helpful information to the Investigator as to the current safety/ADR profile of pirtobrutinib. Table 6.2 should not be used for the purposes of assessing expectedness for serious suspected ADRs reported on an individual case basis. Only the table of expected serious ADRs listed in Section 7 should be used for the purposes of assessing what needs to be expedited as a SUSAR.

Table 6.2 displays the frequency and severity of ADRs associated with pirtobrutinib used as a single agent for treatment for B-cell malignancies from clinical trial data.

Table 6.2. Adverse Drug Reactions in Patients with B-cell Malignancies Treated with Pirtobrutinib as a Single Agent in Studies LOXO-BTK-18001 and LOXO-BTK-20020

System Organ Class	Event	n/N (%) CIOMS Frequency Category	Occurrence of Fatal SARs n/N (%)	Occurrence of Life-Threatening SARs n/N (%)
Blood and lymphatic system disorders	Neutropenia[a]	245/894 (27.4%) Very common	0	1/894 (0.1)
	Anemia[a]	176/894 (19.7%) Very common	0	2/894 (0.2)
	Thrombocytopenia[a]	149/894 (16.8%) Very common	0	3/894 (0.3)
	Lymphocytosis[a]	56/894 (6.3%) Common	0	0
Gastrointestinal disorders	Diarrhoea	223/894 (24.9%) Very common	0	0
	Nausea	155/894 (17.3%) Very common	0	0
	Abdominal pain	110/894 (12.3%) Very common	0	0
General disorders and administration site disorders	Fatigue	253/894 (28.3%) Very common	0	0
	Pneumonia	114/894 (12.8%) Very common	6/894 (0.7)	3/894 (0.3)
	Upper respiratory tract infection	107/894 (12%) Very common	0	0
	Urinary tract infection	92/894 (10.3%) Very common	0	1/894 (0.1)
	Oedema peripheral	108/894 (12.1%) Very common	0	0
Injury, poisoning, and procedural complications	Contusion	168/894 (18.8%) Very common	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	137/894 (15.3%) Very common	0	0
Nervous system disorders	Headache	126/894 (14.1%) Very common	1/894 (0.1)	0
Renal and urinary disorders	Haematuria	39/894 (4.4%) Common	0	0
Respiratory, thoracic, and mediastinal disorders	Epistaxis	41/894 (4.6%) Common	0	0

Skin and subcutaneous tissue disorders	Rash[a]	172/894 (19.2%) Very common	0	0
	Petechiae	44/894 (4.9%) Common	0	0
Vascular disorders	Haematoma	18/894 (2.0%) Common	0	0

Abbreviations: CIOMS = the Council for International Organizations of Medical Sciences; n = number of patients experiencing the specified event; N = number of patients exposed; PT = preferred term; SAR = serious adverse reaction.

[a] Very common (≥10%); common (≥1% and <10%); uncommon (>1%).

Notes: Neutropenia includes Neutrophil count decreased, Neutropenia, Febrile neutropenia, Neutropenic sepsis, and Neutropenic infection.

Anemia includes Anaemia, Iron deficiency anaemia, Blood loss anaemia, Haemoglobin decreased, Aplastic anaemia, and Microcytic anaemia.

Thrombocytopenia includes Platelet count decreased and Thrombocytopenia.

Lymphocytosis includes Lymphocyte count increased, Leukocytosis, Lymphocytosis, and White blood cell count increased.

Rash includes Rash maculo-papular, Rash, Skin lesion, Erythema, Blister, Rash macular, Rash pruritic, Rash erythematous, Dermatitis, Dermatitis acneiform, Rash pustular, Dermatitis bullous, Pustule, Rash papular, Dermatitis allergic, Erythema multiforme, Dermatitis exfoliative, Drug eruption, Scrotal dermatitis, and Skin reaction.

6.2.2.8. Interactions with Other Medicaments and Other Forms of Interaction

The following section describes clinical studies or model-informed approaches where changes in PK as a result of administration of other drugs with pirtobrutinib were identified. Please refer to the study protocol for specific recommendations for exclusion criteria, prohibited medications, and any advice for coadministration with pirtobrutinib.

Potential for other drugs to affect pirtobrutinib

Moderate and strong CYP3A inducers

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

Potential for pirtobrutinib to affect other drugs

CYP2C8 substrates

Pirtobrutinib increased the AUC and C_{max} of repaglinide (a substrate of CYP2C8) by 130% and 98%, respectively.

BCRP substrates

Pirtobrutinib increased the AUC and C_{max} of rosuvastatin (a sensitive BCRP substrate) by 140% and 146%, respectively.

P-gp substrates

Pirtobrutinib increased the AUC and C_{max} of digoxin (a sensitive P-gp substrate) by 35% and 55%, respectively.

CYP2C19 substrates

Pirtobrutinib increased the AUC and C_{max} of omeprazole (a CYP2C19 substrate) by 56% and 49%, respectively.

CYP3A substrates

Pirtobrutinib increased the AUC and C_{max} of orally administered midazolam (a sensitive CYP3A substrate) by 70% and 58%, respectively. Pirtobrutinib did not have a clinically meaningful effect on the exposure of intravenously administered midazolam.

6.2.2.9. Overdose

One patient experienced Hepatic failure and Grade 4 Neutropenia following intake of significantly higher dose of pirtobrutinib (180 tablets: 18,000 mg equivalent to 90 times the daily dose) along with alcohol for committing suicide. Patient was treated in an intensive care unit with supportive therapies including gastric lavage, activated charcoal, hemodialysis, and plasma exchange and he gradually recovered from the events. In case of overdose, use supportive therapy and monitor liver function test. There is no known antidote for pirtobrutinib overdose.

6.2.2.10. Effects on the Ability to Drive and Use Machines

No studies have been conducted to determine the effects of pirtobrutinib on the ability to drive or use machines.

6.2.2.11. Pharmacological Properties

6.2.2.11.1. Mechanism of Action (D1)

Pirtobrutinib is a small molecule reversible noncovalent inhibitor of BTK. BTK is a signaling protein of the B-cell antigen receptor and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Pirtobrutinib binds to wild-type and BTK C481 mutants, leading to inhibition of BTK kinase activity. In nonclinical studies, pirtobrutinib inhibited BTK-mediated B-cell CD69 expression and inhibited malignant B-cell proliferation. Pirtobrutinib showed dose-dependent tumor growth inhibition and induced tumor regression in BTK wild-type and BTK C481S-mutant mouse xenograft models.

6.2.2.11.2. Pharmacodynamic Properties (D2)

Cardiac electrophysiology

The effect of a single 900-mg dose of pirtobrutinib on the QTc interval was evaluated in a study with placebo and positive controls in 30 healthy subjects. The selected dose is equivalent to approximately 2 times higher than the concentrations achieved at steady state at the recommended dosage of 200 mg QD. Pirtobrutinib had no clinically meaningful effect on the change in QTcF interval (that is, more than 10 ms), and there was no relationship between pirtobrutinib exposure and change in QTc interval.

6.2.2.12. Clinical Pharmacology

6.2.2.12.1. Pharmacokinetic Properties (D3)

Absorption

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

The mean (CV) steady-state AUC and C_{max} were 90,300 hour*ng/mL (40%) and 6380 ng/mL (26%), respectively, at the recommended daily dosage of 200 mg in patients with cancer. In both healthy subjects and patients with cancer, increases in AUC were approximately dose proportional, and steady state was achieved within 5 days of QD dosing. In patients, the mean (CV) accumulation ratio after administration of 200 mg QD was 1.63 (26.7%) based on AUC.

Effect of food

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

Distribution

The mean apparent central volume of distribution of pirtobrutinib is 34.1 L in patients with cancer. The plasma protein binding is 96% and was independent of concentration between 0.5 and 50 µM. In plasma from healthy subjects and subjects with severe renal impairment, the protein binding was 96%. Mean blood-to-plasma ratio is 0.79.

Metabolism

Pirtobrutinib is metabolized to several inactive metabolites by CYP3A4, UGT1A8, and UGT1A9. There was no clinically meaningful impact of CYP3A modulation on pirtobrutinib exposures in healthy subjects.

Elimination

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

Special populations

Based on a population PK analysis in patients with cancer, age (range 27 to 95 years), gender (394 males and 201 females), and body weight (range 35.7 to 152.5 kg) had no clinically meaningful effect on the exposure of pirtobrutinib.

Hepatic impairment

In a hepatic impairment study, there was no clinically meaningful effect of hepatic impairment (Child-Pugh A, B, and C) on the pharmacokinetics of pirtobrutinib compared to normal hepatic function.

Renal impairment

There was no clinically meaningful effect of renal impairment on the PK of pirtobrutinib in otherwise healthy subjects. Patients on dialysis have not been studied.

6.2.2.12.2. Pharmacogenomics (D4)

Not applicable.

6.2.2.13. Other Notable Information

No other notable information available.

7. Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions

This section of the IB is included to comply with regulations of regulatory authorities in Europe in regard to the assessment of serious adverse reactions (SARs). The SARs included in this RSI section are the **only** event terms that can be used by the sponsor to

- assess the expectedness of suspected SARs included in an individual case report submitted by investigators
- determine if reported adverse event terms are SUSARs that qualify for expedited regulatory reporting, and
- determine what events are considered expected in the DSUR.

In light of these considerations, it is acknowledged that the limited nature of the information contained in the RSI in this section does not provide a comprehensive overview of the safety profile of the IMPs pirtobrutinib that would be meaningful or helpful to investigators. Therefore, a safety overview and additional safety information are provided in Section 6.

This section of the IB lists the expected SARs and represents the RSI to be used to assess expectedness of all reported SARs and lists the serious expected ADRs expected in patients with hematological malignancies.

For the purposes of SUSAR reporting, only events that are consistent in the nature and severity of the terms in this section will be considered expected. Fatal and life-threatening events are considered unexpected, and if there is a reasonable causal relationship to the IMP, the case will be submitted as a SUSAR.

The safety profile of pirtobrutinib has not been established in patients below 18 years of age. Therefore, all suspected SARs reported in the pediatric population are considered unexpected.

Table 7.1. Serious Adverse Reactions for Pirtobrutinib Considered Expected for SUSAR Reporting Purposes[a]

		Number of Subjects Exposed N=894		
SOC	**SAR**	**All SARs (Excluding Fatal and Life-Threatening Events)**	**Occurrence of Expected Fatal SARs**	**Occurrence of Expected Life-Threatening SARs**
		n (%) (CIOMS Frequency Category)	**n (%)**	**n (%)**
Blood and Lymphatic system disorders	Anaemia	19 (2.1) Common	Not applicable	Not applicable
	Febrile neutropenia	16 (1.8) Common	Not applicable	Not applicable
	Leukocytosis	6 (0.7) Uncommon	Not applicable	Not applicable
	Thrombocytopenia	3(0.3) Uncommon	Not applicable	Not applicable
Infections and infestations	Pneumonia	61 (6.8) Common	Not applicable	Not applicable

Abbreviations: CIOMS = the Council for International Organizations of Medical Sciences; n = number of patients in the specified category; N = number of participants, SAR = serious adverse reaction; SOC = system organ class; SUSAR = suspected unexpected serious adverse reaction.

[a] Fatal and life-threatening events will be considered unexpected and submitted as SUSARs.

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