CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216059Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA MULTI-DISCIPLINARY REVIEW AND EVALUATION

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original NDA
Application Number(s)	NDA 216059
Priority or Standard	Priority
Submit Date(s)	May 27, 2022
Received Date(s)	May 27, 2022
PDUFA Goal Date	January 27, 2022
Division/Office	Division of Hematologic Malignancies 2
Review Completion Date	January 23, 2023
Established Name	Pirtobrutinib (Loxo-305)
(Proposed) Trade Name	JAYPIRCA
Pharmacologic Class	Kinase inhibitor
Applicant	Loxo Oncology
Formulation(s)	Tablet
Dosing Regimen	200 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with mantle cell lymphoma who have been previously treated with a BTK inhibitor
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a BTK inhibitor

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Denise Felluca, PharmD, MBA
Pharmacology/Toxicology Reviewer(s)	Shwu-Luan Lee, PhD
Pharmacology/Toxicology Team Leader(s)	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewer(s)	Justin Collazo, PharmD, MS Elyes Dahmane, PharmD (Pharmacometrics) Yuching Yang, PhD (PBPK)
Office of Clinical Pharmacology Team Leader(s)	Ruby Leong, PharmD Justin Earp, PharmD (Pharmacometrics) Manuela Grimstein, PhD, MS (PBPK)
Clinical Reviewer	Deepti Telaraja, MD
Clinical Team Leader	Yvette Kasamon, MD
Statistical Reviewer	Kun Wang, PhD
Statistical Analyst	Ping Li, MS
Statistical Team Leader	Lisa Rodriguez, PhD
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Disciplinary Team Leader	Yvette Kasamon, MD
Deputy Division Director (DHOT)	Haleh Saber, PhD
Division Director (OCP)	Brian Booth, PhD
Division Director (OB)	Mark Levenson, PhD
Division Director (OOD)	Nicole Gormley, MD
Office Director (or designated signatory authority)	Marc Theoret, MD

Additional Reviewers of Application

OPQ	Sherita McLamore, PhD (Acting TL) Yang Nan, PhD Kanny Wan, PhD Gerlie Gieser, PhD Qi Zhang, PhD Diane Goll/Bogdan Kurtkya (Facilities/Process) Caryn McNab (ORA) Dahlia Walters, RBPM
Patient Labeling	Laurie Buonaccorsi, PharmD (Patient Labeling)
OPDP	Jennifer Chen, PharmD
OSI	Anthony Orencia, MD Min Lu, MD, MPH (TL)

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OSE/DEPI	Frances Fahnbulleh, PharmD Janet Higgins (TL)
OSE/DMEPA	Nicole Iverson, Pharm D Hina Mehta, PharmD (TL)
OSE/DRISK	Till Olickal, PhD, PharmD Naomi Boston, PharmD (TL)
QT/IRT	Yu-Ting Weng, PhD, MS

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
TL=Team Leader

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEPCS	adverse event of potential clinical significance
AESI	adverse event of special interest
AR	adverse reaction
AUC	area under the concentration versus time curve
$AUC_{0\text{-}24,\ ss}$	area under the concentration-time curve for one dosing interval at steady state
AUC_{tau}	area under the concentration-time curve during one dosing interval
BID	twice daily
BOR	best overall response
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CAR-T	chimeric antigen receptor-modified T cells
CI	confidence interval
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic leukemia
C_{max}	maximum drug concentration
$C_{max,\ ss}$	maximum observed drug concentration during a dosing interval at steady state
$C_{min,\ ss}$	minimum observed drug concentration during a dosing interval at steady state
CNS	central nervous system
COA	clinical outcome assessment
CR	complete response
CSR	clinical study report
DDI	dose-dose interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EFD	embryo-fetal development
eCTD	electronic common technical document
FISH	fluorescence in situ hybridization
HSCT	hematopoietic stem cell transplantation
IC_{50}	50% inhibitory concentration
IRC	Independent Review Committee
K_i	reversible inhibition constant (in units of inhibitor concentration) that defines the affinity of a reversible inhibitor for an enzyme
KM	Kaplan Meier
LDi	longest diameter
LTFU	long-term follow-up
MCL	mantle cell lymphoma

MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MZL	marginal zone lymphoma
NA	not applicable
NE	not evaluated, not evaluable, not estimable
NHL	non-Hodgkin lymphoma
NOAEL	no-observed adverse effect level
NOEL	no-observed effect level
NOS	not otherwise specified
OMTSAS	overall monotherapy safety analysis set
ORR	overall response rate
OS	overall survival
PAS	primary analysis set
PD	progressive disease
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
popPK	population pharmacokinetic
PR	partial remission
PT	preferred term
QD	once daily
R-CHOP	rituximab-cyclophosphamide-hydroxydaunorubicin-oncovin-prednisone
RP2D	recommended Phase 2 dose
R/R	relapsed or refractory
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SCE	Summary of Clinical Efficacy
SCT	stem cell transplantation
SCS	Summary of Clinical Safety
SEER	surveillance epidemiology and end results
sMIPI	Simplified Mantle Cell Lymphoma International Prognostic Index
SMQ	standardized MedDRA query
SPM	second primary malignancy
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TE	treatment emergent
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
TTR	time to response
ULN	upper limit of normal

1.0 Executive Summary

1.1 Product Introduction

Pirtobrutinib is an orally administered, noncovalent Bruton tyrosine kinase (BTK) inhibitor. The FDA review team recommends accelerated approval of pirtobrutinib for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor. The recommended dosage is 200mg orally once daily, continued until disease progression or unacceptable toxicity.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of efficacy of pirtobrutinib in patients with relapsed or refractory MCL is based on overall response rate (ORR) and duration of response (DOR) in the BRUIN trial, a single-arm multicenter trial of pirtobrutinib in patients with hematologic malignancies including MCL. One hundred and twenty MCL patients who had previously received a BTK inhibitor and received pirtobrutinib at the recommended dosage were evaluable for efficacy. In the efficacy population, the median number of prior therapies was 3 (range: 1-9), with 93% receiving 2 or more prior lines of therapy. By independent review committee (IRC) assessment, ORR was 50% (95% CI: 41, 59) and the complete remission (CR) rate was 13% according to Lugano criteria, with a median time to response of 1.8 months. The estimated median DOR was 8.3 months (95% CI: 5.7, NE) and the estimated 6-month DOR rate was 65.3% (95% CI: 49.8, 77.1).

While the data related to durability of response are limited by the degree of early censoring, the ORR, coupled with demonstration of durability of response in those with adequate follow-up, supports the determination that pirtobrutinib has clinically meaningful activity in a highly refractory, BTK inhibitor-pretreated MCL patient population.

Because of the paucity of data in patients with one prior therapy, the recommended indication is restricted to patients with relapsed or refractory mantle cell lymphoma after at least two systemic therapies, including a BTK inhibitor.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Efficacy: The efficacy of pirtobrutinib is based on IRC-assessed ORR and DOR in Study LOXO-BTK-18001, a single-arm study that enrolled patients with relapsed or refractory (R/R) B-cell malignancies, including MCL. In the MCL efficacy population (n=120), the median number of prior systemic therapies was 3 (range: 1-9), with 93% of patients receiving 2 or more prior lines of therapy. All patients received a prior BTK inhibitor; the most common reason for discontinuation of the most recent BTK inhibitor was disease progression (83%), with a minority of patients having discontinued the most recent BTK inhibitor due to intolerance or toxicity (10%) or other causes. ORR per IRC was 50% (95% CI: 41, 59) and CR rate was 13%. With an estimated median follow-up of 7.4 months, the estimated median DOR was 8.3 months (95% CI: 5.7, NE) and the Kaplan-Meier 6-month DOR rate was 65.3% (95% CI: 49.8, 77.1) .

Safety: The safety of pirtobrutinib was evaluated in 128 patients with R/R MCL (including a prior BTK inhibitor) treated with pirtobrutinib 200mg once daily. In patients with MCL, serious adverse events (SAEs) occurred in 38% of patients, most often from infection. Adverse events (AEs) led to treatment discontinuation in 9% of patients, treatment interruption in 32%, and dose reductions in 4.7%; fatal AEs occurred in 7% of patients, driven by infections. Adverse reactions occurring in ≥15% of patients with MCL, excluding laboratory terms, were fatigue, musculoskeletal pain, diarrhea, edema, dyspnea, pneumonia, and bruising. Grade 3 or 4 laboratory abnormalities in ≥10% of patients included decreased neutrophil counts, lymphocyte counts, and platelet counts.

In the pooled safety population of 583 patients with hematologic malignancies treated with pirtobrutinib 200mg daily, adverse reactions of special interest included grade 3 or higher infections (17%, most often pneumonia), including opportunistic infections, bleeding (any grade 14%; major hemorrhage 1.7%), cytopenias including grade 3 or 4 neutropenia (24%; 13% grade 4), anemia (11%), thrombocytopenia (7%), and lymphopenia (10%); second primary malignancies (SPMs; 6%, most often nonmelanoma skin cancer); and atrial fibrillation or flutter (any grade 2.7%; grade 3 or 4, 1.0%).

Overall benefit-risk assessment: Pirtobrutinib has an overall favorable benefit/risk profile in patients with MCL after at least two prior lines of therapy, including a BTK inhibitor. Based on ORR with durability, pirtobrutinib has demonstrated meaningful clinical activity and an advantage over available therapeutic options in this patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MCL is generally incurable and relapse is near universal • Remission duration is generally longest after frontline therapy and successively shortens with subsequent lines	• MCL is a serious and life-threatening condition
Current Treatment Options	• Treatment options for relapsed or refractory MCL include covalent BTK inhibitors (under accelerated approval), chemoimmunotherapy, lenalidomide, bortezomib alone or in combination, and hematopoietic stem cell transplantation (HSCT) in selected patients. Allogeneic HSCT is potentially curative but generally limited to younger, fit patients • BTK inhibitor resistance and intolerance are common and limit the ability to retreat with a second covalent BTK inhibitor.	• There is an unmet need for effective and tolerable treatment options for patients with relapsed or refractory MCL who have received a prior BTK inhibitor
Benefit	• In a single-arm trial of pirtobrutinib monotherapy of 120 BTK inhibitor-pretreated patients with MCL treated with pirtobrutinib 200mg daily, the IRC-assessed ORR was 50% (95% CI: 41, 59) and CR rate was 13% according to Lugano criteria. The estimated median DOR was 8.3 months.	• Based on an evaluation of response rate and durability, pirtobrutinib demonstrates an advantage over available therapies for patients with relapsed or refractory MCL with prior BTK inhibitor exposure
Risk and Risk Management	• In 583 patients with hematologic malignancies in the BRUIN trial, the most common AEs (incidence ≥20%) were neutropenia, anemia, thrombocytopenia, fatigue, musculoskeletal pain, lymphopenia, bruising, and diarrhea. • Events of special interest with pirtobrutinib include serious and opportunistic infections; bleeding; grade 3-4 cytopenias; SPMs; and atrial fibrillation or flutter. • Duration of exposure was limited (median of 7.5 months in the pooled safety population and 3.8 months in the MCL safety population).	• The risks are acceptable in patients with relapsed or refractory mantle cell lymphoma who have an indication for treatment • The USPI includes Warnings and Precautions for include infections, hemorrhage, cytopenias, atrial fibrillation or flutter, and SPMs. • Because of the limited duration of exposure in patients treated in the BRUIN trial, two safety PMRs are warranted: one for characterization of the longer-term

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		safety of pirtobrutinib with at least 2 years of follow up and another for the characterization of the risk of SPMs with at least 5 years of follow up.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply): No patient experience data were submitted.

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study Endpoints]
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X _____

Cross-Disciplinary Team Leader

2.0 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

MCL is a rare subtype of NHL accounting for 3% to 10% of all new NHL cases per year with a typical incidence of approximately 1 to 2/100,000 in the US and Europe (Howlader 2021; ECIS 2021). MCL is more common in men (3:1; male:female) and patients are typically aged 60 to 70 years old at diagnosis which influences treatment selection in frontline and for recurrence (Swerdlow et al. 2016; Cheah et al. 2016). Indolent subtypes of MCL have been characterized; however, the typical presentation of MCL is usually aggressive and incurable requiring treatment at diagnosis for most patients.

Overall survival at the time of MCL diagnosis is estimated at only 3 to 5 years (Dreyling et al. 2018). While initial treatments can be quite effective, cures are rare and relapse is nearly universal (Kumar et al. 2019). After relapse, treatment benefits progressively decrease with each subsequent line of therapy and significant symptom burden becomes more prominent with enlarging lymphadenopathy and systemic symptoms of night sweats, fever, and weight loss, particularly with advanced stages of disease (Kumar et al. 2019). In later stages of the disease, patients become chronically debilitated with increasingly limited options of therapy and ultimately, most succumb to their disease. The MCL patient population previously treated with a BTK inhibitor, which is the subject of this marketing application, has a median survival of only 2.5 months to 8.4 months (Martin et al. 2016; Cheah et al. 2015; Epperla et al. 2017).

The FDA's Assessment:
The FDA agrees with the Applicant's overall assessment of the condition.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Upfront therapy for MCL continues to rely on chemotherapy and anti-CD20 antibody therapy, with fit patients typically receiving autologous stem cell transplant in the first-line setting (NCCN 2022; Flinn et al. 2014; Lenz et al. 2005). PFS in first-line therapy can exceed 4 years, although cure with this approach is rare and relapse almost universal (Dreyling et al. 2017). In relapsed BTK inhibitor-naïve MCL, covalent BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) yield overall response rates of 70% to 84%, a median PFS of 12 months to 22 months, and have become the accepted standard for both fit and unfit patients with R/R MCL, although randomized trial data directly comparing these agents are not available (BRUKINSA® USPI; CALQUENCE® USPI; IMBRUVICA® USPI). The treatment options for relapsed refractory MCL are summarized in Table 1.

Despite the benefit from the BTK inhibitor class of drugs, the vast majority of patients will relapse and options are limited once MCL patients have progressed following both frontline chemoimmunotherapy and a BTK inhibitor for relapsed disease. Remaining available options include the previously established therapies of bortezomib, lenalidomide, or temsirolimus (Goy et al. 2009; Trněný et al. 2016; Hess et al. 2009). Even in the BTK inhibitor-naïve setting, these agents have yielded more modest response rates consistently less than 40%, CRs generally less than 10%, and median PFS consistently less than 9 months (Goy et al. 2009; Trněný et al. 2016; Hess et al. 2009). The sparse data that exist for these agents in the post-BTK inhibitor setting suggest even more limited benefit as a retrospective observational study of patients treated at a single institution with lenalidomide-based therapy following ibrutinib reported an ORR of 29% (Wang et al. 2017).

Consistent with the limited efficacy seen for targeted agents or chemoimmunotherapy following progression on BTK inhibitors, the survival of patients with BTK inhibitor pretreated MCL has been reported to be very poor with median OS ranging from 2.5 months to 8.4 months (Martin et al. 2016; Cheah et al. 2015; Epperla et al. 2017).

The poor outcomes observed in patients previously treated with BTK inhibitors have recently been confirmed by a real-world database study evaluating outcomes in 303 US patients with MCL who received a prior BTK inhibitor. This study found that only 46.9% of US patients received subsequent therapy after BTK inhibitor treatment, with a median time to discontinuation of subsequent therapy or death of 3.8 months and a median OS for all patients of 8.2 months post-BTK inhibitor therapy (Rai et al. 2021). Collectively, the retrospective and real-world data demonstrate that BTK inhibitor pretreated MCL continues to be a population of high unmet need.

Recently, CD19-targeted CAR-T therapy has been granted accelerated approval in the US based on a single arm study in patients with MCL who relapsed on a BTK inhibitor. Despite an impressive ORR of 93% (58/60 patients) with a CR rate of 67%, CAR-T is associated with significant toxicities with Grade ≥ 3 AEs occurring in 99% of patients (TECARTUS® SmPC; Wang et al. 2020). Successful leukapheresis, product manufacture, bridging chemotherapy, and conditioning therapy prior to cell infusion are all required to prescribe CAR-T. In the single arm study leading to approval, 4% of patients could not receive cell infusion due to complications and product manufacture failed in another 4% of patients. Thus, in a community practice environment, where expertise may be lacking, CAR-T therapy may be more challenging than described (Wang et al. 2020; Chomienne et al. 2019). Therefore, while CAR-T therapy has been recently approved, this treatment modality carries significant logistical challenges as well as the potential severe toxicities of the therapy, which limits CAR-T to those who are fit and have slowly progressing disease in order to be able to make it through treatment. It is important to also consider that patients can relapse following CAR-T with no subsequent approved therapy available. It is noted in Study LOXO-BTK-18001 (A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin's Lymphoma (NHL)), 4.4% of the PAS (4/90) patients enrolled following prior CAR-T therapy. Many patients in relapse urgently require an effective and well-tolerated therapy, and this remains a high unmet need given some of the limitations of CAR-T therapy.

In conclusion, for patients with MCL who have previously received a BTK inhibitor, treatment options are limited or have been exhausted. Life expectancy is short and there remains an unmet medical need for rapid and tolerable treatment in this aggressive disease setting.

Table 1: Literature Summary for Treatment Options for MCL

Regimen		Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Name of Trial (Reference)
	R/R MCL						
Ibrutinib		Phase 2, single-arm	111	67 (57.1, 75.3)	13 (7.0, 17.5)	22.5 (13.7, NE)	Study 1104 Wang et al. *Blood.* 2015; 126(6):739-745.
Acalabrutinib		Phase 2, single-arm	124	81 (73, 87)	20 (16.5, 27.7)	NR	ACE-LY-004 Wang et al. *Leukemia.* 2019;33(11): 2762-2766.
Zanubrutinib		Phase 2, single-arm	86	84 (74, 91)	22.1 (17.4, NE)	NR	BGB-3111-206 Song et al. *Clin Cancer Res.* 2020;26(16): 4216–4224.

Regimen		Trial Design	Patient number N = Total	ORR (%); (95% CI)	mPFS (months); (95% CI)	mOS (months); (95% CI)	Name of Trial (Reference)
Brexucabtagene autoleucel		Phase 2, single-arm	60	93 (84, 98)	NR (9.2, NE)	NR (24.0, NE)	ZUMA-2 Wang et al. *NEJM.* 2020; 382(14):1331–1342.
Bortezomib		Phase 2, single-arm	155	32 (24, 40)	6.5 (4.0, 7.5)	23.5 (20.3, 27.9)	PINNACLE Goy et al. *Ann Oncol.* 2009; 20(3):520–525.
Lenalidomide		Phase 2, single-arm	134	28 (20, 36)	4 (3.6, 5.6)	19.0 (12.5, 23.9)	MCL-001 EMERGE Goy et al. *J Clin Oncol.* 2013; 31(29):3688-3695.
Lenalidomide/ rituximab		Phase 2, single-arm	52	57	11.1 (8.3, 24.9)	24.3 (19.8, NR)	NCT00294632 Wang et al. *Lancet Oncol.* 2012; 13(7):716-723.

NE = not evaluable; NR = not reached

The FDA's Assessment:

The FDA agrees with the description of current treatment options and that BTK inhibitor pre-treated patients represent a population with high unmet need. The FDA notes that ibrutinib, acalabrutinib, zanubrutinib, and brexucabtagene autoleucel currently have accelerated approval for their respective indications. Thus, for purposes of comparison to available therapies in support of accelerated approval, the options that are considered currently available are bortezomib and lenalidomide. The combination of lenalidomide and rituximab, while used in practice for the treatment of patients with R/R MCL, is not an FDA-approved treatment regimen for MCL.

3.0 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:
To date, pirtobrutinib has not been granted market authorization.

The FDA's Assessment:
The FDA agrees. Pirtobrutinib is a new molecular entity.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2: Pirtobrutinib Key Regulatory Interactions

Key Regulatory Interactions
29 August 2018 – IND 139876 submitted to the Division of Hematologic Malignancies 2 for the evaluation of pirtobrutinib for the treatment of hematologic malignancies. • Included study protocol LOXO-BTK-18001 (Study 18001), entitled "A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin's Lymphoma (NHL)" • Allowed to proceed on 28 September 2018
01 May 2020 – Type B EOP1 meeting to discuss Study 18001 and the pirtobrutinib development program. Agreements/recommendations included: • Primary endpoint of ORR assessed by independent radiologic review was the appropriate endpoint for the LOXO-BTK-18001 single arm Phase 1/2 study • For the primary analysis for an NDA, patients who meet the Phase 2 (dose expansion) eligibility but enroll in the Phase 1 (dose escalation) portion of the study may be included if there is no significant heterogeneity. • Previously treated MCL patients who received a prior BTK inhibitor constitute an unmet need population for whom an accelerated NDA approval could be appropriate • FDA agreed the clinical pharmacology program for pirtobrutinib was sufficient to support an NDA.
28 August 2020 – FDA granted Orphan Drug Designation for pirtobrutinib for MCL (#DRU-2020-7581)
(b) (4)

Key Regulatory Interactions
• [redacted] (b) (4)
04 December 2020 – FDA granted Fast Track Designation for pirtobrutinib "*the treatment of adult patients with relapsed and refractory mantle cell lymphoma (MCL) who have received a prior BTK inhibitor*."
10 December 2020 – Type C guidance meeting to discuss the proposed accelerated approval NDA for pirtobrutinib in previously treated MCL patients who have received a prior BTK inhibitor. Agreements/recommendations included: • Criteria of the primary efficacy population for previously treated MCL patients who have received a prior BTK inhibitor are appropriate • Recommendation for a sample size that is larger than 55 patients in the primary efficacy population • Agreement on total size of safety database of 400-450 patients and to include at least 100 MCL patients with sufficient exposure • Agreement on the filing approach for the interim clinical study report and the Summaries of Clinical Efficacy and Safety • Agreement on the proposed dosing regimen of 200 mg QD
15 April 2021 – Type B EOP1 meeting – chemistry manufacturing controls only. Agreements included: • Starting materials • Drug substance and drug product stability data • Dissolution method
07 May 2021 – FDA agreement on the agreed Initial Pediatric Study Plan/Request for Full Waiver for: • Pirtobrutinib for the treatment of adult patients with relapsed and refractory MCL who have received a prior BTK inhibitor [redacted] (b) (4)
18 October 2021 – Type B pre-NDA meeting to gain alignment on the clinical NDA data package regarding safety and efficacy and the clinical content and format of the planned NDA for pirtobrutinib. Agreements/recommendations included: • Recommendation to provide a proposal for a clinical data package with more than 65 MCL patients and at least 9 months follow-up from beginning of treatment for the primary analysis in relapsed/refractory MCL patients • Recommendation to submit a request for a rolling NDA review for MCL • [redacted] (b) (4)
19 November 2021 – FDA acceptance of NDA Rolling Review Request for MCL • FDA agreed to the request for a rolling NDA review for MCL and to the proposed submission schedule of the NDA, which specified the Sponsor's proposal of the NDA clinical data package with a PAS sample size of 90 patients with at least 9 months of follow-up from response onset in ≥ 90% of patients.

The FDA's Assessment:

The FDA has the following modifications and clarifications to the regulatory interactions described by the Applicant, and otherwise agrees with the Applicant's assessment of the regulatory interactions:

- May 1,2020 Meeting: While the FDA agreed with the proposed clinical pharmacology studies assessing PK and DDI potential of pirtobrutinib, the Agency recommended multiple other studies including food effect studies, PK studies, DDI studies with P-gp substrates, and multiple dose studies in patients rather than in healthy volunteers.
- December 10,2020 Meeting: The FDA stated that the proposed dosing regimen appeared reasonable based on the analyses provided and recommended additional modeling analyses that should be included in the NDA submission.
- October 18,2021 Meeting:
  - The FDA stated that the proposed submission of data from 65 patients with MCL would be insufficient and that responders should have at least 9 months of follow-up for duration of response. The FDA recommended delaying NDA submission until increased sample size and adequate follow-up in the PAS population was achieved.
  - The FDA stated that the proposed safety database may be reasonable, but that adequate exposure duration is necessary to support a comprehensive evaluation of safety and tolerability.

4.0 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

OSI inspected the Applicant for quality of study conduct and oversight, and two clinical sites that were selected by the clinical team due to high accrual (Dr. Michael Wang PI, M.D. Anderson Cancer Center, and Dr. Anthony Mato, Memorial Sloan Kettering Cancer Center). No issues warranting action were identified. The Applicant's site audit included selection, monitoring, and financial disclosures of research staff, study monitoring, safety reporting, data collection and handling, records retention, and electronic records.

4.2 Product Quality

No outstanding issues.

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

Not applicable.

5.0 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Pirtobrutinib (also referred to as LOXO-305 and LY3527727) is a non-covalent BTK inhibitor with activity against the wild-type (WT) and C481 mutants. BTK signaling is involved in activation of pathways necessary for B-cell proliferation, trafficking, and adhesion and thus, is being developed for the treatment of patients with mantle cell lymphoma (MCL).

Pharmacology studies of pirtobrutinib consisted of biochemical assays, and in vitro/cellular and in vivo studies. Pirtobrutinib bound to WT and C481S mutant BTK (a mutant identified in patients with lymphoma as reported in published articles (Buhimschi et al., Biochemistry, 57(26): 3564-3575, 2018; Cheng et al., Leukemia 29: 895, 2015) with comparable affinities and inhibitory effects. Reversibility of binding was demonstrated through estimation of dissociation parameters in a biochemical assay and percent inhibition of B-cell activation in a cellular assay. In vitro studies indicated inhibitory activity of pirtobrutinib against other C481 BTK mutants as well; however, these were not relevant to a lymphoma indication. Pirtobrutinib had anti-tumor activities in vitro against the human lymphoma cell lines tested (Ramos RA1 and TMD8), and in vivo in mouse xenograft models of lymphoma containing WT BTK or C481S mutant BTK.
In secondary pharmacology studies, pirtobrutinib had minimal effects against non-BTK kinases, enzymes, ion channels, and receptors, with the exception of erbB4 with an IC_{50} of 13 nM as compared to 3 nM for BTK inhibition. Safety pharmacology studies did not point to any toxicities of concern in the CNS, respiratory, or cardiovascular systems.

Repeat-dose toxicology studies of up to 3 months were conducted in rats and dogs, using an oral route of administration, consistent with the proposed clinical route. Overall, toxicities were consistent with BTK inhibition and included the following: B-cell suppression, increase in activated T cells, pancreatic findings (e.g., inflammation, hemorrhage, and fibrosis; rats), erythrophagocytosis of lymph nodes, reduced RBCs and lineages (dogs), corneal findings (opacity, single cell necrosis, and fibrosis; dogs), and inflammation. The pancreatic findings in the rat could be species- and strain-specific as observed with the administration of other BTK inhibitors (Erickson et al., J Pharm Exp Ther 360: 226-238, 2017; Bhaskaran et al., Toxicologic Pathology 46(4): 460-472, 2018).

An embryo-fetal development (EFD) toxicity study was conducted in rats at oral doses of 25, 75, 375 and 500 mg/kg twice daily (BID). Adverse EFD effects were observed at ≥375 mg/kg twice daily doses and included decreased fetal body weights, increased incidence of malformations or variations in the urinary tract (dilated ureters; absent or structurally abnormal kidneys), reproductive system (malpositioned ovaries and misshapen uterus), and bone (misshapen sternebrae). These effects occurred in the absence of maternal toxicities. Total resorption was noted at the 500 mg/kg twice daily dose. At 375 mg/kg twice daily in rats, the maternal

systemic exposures (mean AUC of 272 µg/mL*h) were approximately 3-fold the human exposure (mean AUC of 91.3 µg/mL*h) at the recommended dose of 200 mg once daily. A duration of contraception of one week (5 half-lives) after the last dose of the drug is recommended in females. The Applicant provided a justification for not including a duration of contraception in males. We accepted this approach based on an exaggerated estimation (10 x drug accumulation in semen, Klemmt and Scialli; Birth Defects Research 2005, and assumption of complete absorption in female partners) that showed a substantial margin of safety from the no observed adverse effect level (NOAEL) dose in the rat EFD study.

Pirtobrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay but was aneugenic in *in vitro* micronucleus assays using human peripheral blood lymphocytes (at approximately 37-fold the unbound human Cmax (unbound) at the recommended human dose). Pirtobrutinib was not genotoxic in the rat bone marrow micronucleus assay at doses up to 2000 mg/kg. Due to large safety margins, recommendations for the duration of contraception in patients is based on Table 2 of the guidance (Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations) for non-genotoxic drugs.

There are currently no pharmacology/toxicology issues to preclude the approval of pirtobrutinib for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Not applicable.

5.3 Pharmacology

Primary pharmacology

Mechanism of action

Bruton's tyrosine kinase (BTK)-related B-cell lymphomas and acquired resistance to treatment of BTK inhibitors

Approved BTK inhibitors, such as ibrutinib (Imbruvica) and acalabrutinib (Calquence), form covalent bonds. Patients may develop acquired resistance/mutations after treatment with previously approved BTK inhibitors (Woyach et al., J Clin Oncol 35: 1437-1443, 2017).

Pirtobrutinib showed comparable inhibitory activities toward wild-type (WT)- BTK and the mutant BTK C481S, an acquired resistance mutation post-treatment with approved BTK inhibitors, as illustrated in a purified enzyme assay and in cellular assays. In these assays, the B-cell inhibitory effect of pirtobrutinib appears to be reversible.

Inhibitory activity of BTK inhibitors against wild-type and mutant BTKs

The activity of pirtobrutinib against full-length wild type and mutant human BTK enzymes was determined by monitoring the incorporation of [^{33}P]-PO4 from [γ-^{33}P]-ATP into poly-glutamic

acid-tyrosine (poly-EY) peptide substrate. The BTK enzymes and inhibitors were incubated with ATP at either 10 µM or the ATP Km concentration for each respective enzyme. The mutant BTK enzymes included BTK C481S and BTK P190K, a clinically observed lung cancer mutation (Davies et al. Cancer Res 65: 7591-7595, 2005). Pirtobrutinib exhibited comparable inhibitory effects against wild-type BTK and the mutants tested.

Table 3: Inhibition of WT and Mutant BTKs

Kinase	ATP Concentration (µM)	LOXO-305 IC_{50} (Mean ± SD, nM)	n
BTK	$K_m = 50$	3.15 ± 1.32	12
BTK C481S	$K_m = 15/50$*	1.42 ± 0.60	12
BTK E41K	$K_m = 15$	7.85 ± 0.08	2
BTK P190K	$K_m = 15$	2.14 ± 0.09	2

*ATP Km concentration was 15 µM for 10 measurements and 50 µM for 2 measurements due to lot differences in BTK C481S protein.

BTK E41K is a preclinical constitutively active BTK mutant (Fukuda et al. J Biol Chem 271: 30303-06, 1996)
(Table from the Applicant)

The major human metabolite M1 (also known as LOX-00023900-001 and LSN3828720) did not inhibit BTK activity under the conditions tested, as indicated by an IC_{50} greater than 5 µM (data not shown).

Reversible binding of pirtobrutinib toward BTK targets

Binding kinetics of pirtobrutinib toward WT BTK and C481 substitution mutant (resistance mutation) BTKs:

The in vitro equilibrium binding affinities of pirtobrutinib for WT BTK and the resistance mutations, the BTK C481 substitution mutants (i.e., C481S, C481R and C481T), were determined further using a surface plasmon resonance (SPR)-based assay. The data indicate that pirtobrutinib binds WT and C481S mutant BTK with K_D values in the low nM range. Pirtobrutinib demonstrated reversible binding to WT BTK and BTK C481S with off-rates corresponding to a pirtobrutinib dissociation half-life of 1.9 –2.6 hours. While the binding affinities were comparable across the BTK mutants tested, the complex half-lives were higher for the C481R (7.5 h) and C481T (28 h) mutations compared to C481S (1.9 h).

Table 4: Binding Kinetics of Pirtobrutinib with Wild Type and BTK C481 Mutants

Pirtobrutinib		k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)	$t_{1/2}$ (h)	Average K_D (nM)	Average $t_{1/2}$ (h)
BTK (WT)	Run #1	6.0×10^4	5.3×10^{-5}	0.8	3.6		
	Run #2	7.5×10^4	9.7×10^{-5}	1.3	2.0	1.0	2.6
	Run #3	1.1×10^5	8.6×10^{-5}	0.8	2.2		
BTK C481S	Run #1	2.7×10^4	7.2×10^{-5}	2.6	2.6		
	Run #2	1.3×10^5	2.1×10^{-4}	1.5	1.1	1.7	1.9
	Run #3	9.9×10^4	9.6×10^{-5}	1.0	2.0		
BTK C481R	Run #1	5.9×10^4	2.6×10^{-5}	0.4	7.5	N/A	N/A
BTK C481T	Run #1	3.1×10^4	6.8×10^{-6}	0.2	28	N/A	N/A

k_a: association rate constant ($M^{-1}s^{-1}$)
k_d: dissociation rate constant (s^{-1})
K_D: dissociation equilibrium constant (nM) = k_d / k_a
$t_{1/2}$: complex half-life (hours) = ln 2 / k_d
N/A = not applicable
(Table from the Applicant)

The binding reversibility of pirtobrutinib to BTK in studies of purified protein/kinase was supported by data for the inhibition of B-cell activation by pirtobrutinib (LOXO-305-PHARM-016). Pirtobrutinib reversibility was tested in the peripheral blood mononuclear cells (PBMC) B-cell activation assay using a washout method. In the assay, data obtained from the washout and non-washout plates were compared. Less than 10% inhibition of B-cell activation was observed in the washout plate by pirtobrutinib up to the highest concentration of 10 µM, demonstrating the reversibility of pirtobrutinib induced inhibition on CD69+B-cell activation (data not shown).

Binding kinetics of BTK inhibitors on the targets

The inhibitory effect against BTK C481S, illustrated as binding kinetics in the Proteros Receptor Displacement Assay, was compared among pirtobrutinib, ibrutinib and acalabrutinib.

The table below summarizes the binding kinetics:

- The dissociation kinetic constant (k_{off}) values for pirtobrutinib from BTK and BTK C481S were greater for BTK, indicating a slower rate of dissociation from BTK C481S compared to BTK.
- Pirtobrutinib's residence time (=1/k_{off}) on BTK C481S was 3.8 times longer than ibrutinib's residence time and greater than 14 times longer than acalabrutinib's residence time.
- Pirtobrutinib had similar K_D values for WT and BTK C481S; however, ibrutinib and acalabrutinib showed increased K_D values for BTK C481S, indicating decreased affinities of ibrutinib and acalabrutinib towards C481S mutant BTK.

Table 5: Comparison of BTK Inhibitors on Binding Kinetics to BTK and BTK C481S

Inhibitor	Kinase	K_D [nM]	k_{on} [s^{-1} M^{-1}]	k_{off} [s^{-1}]	Residence Time [min]
LOXO-305	BTK	3.50	3.46×10^{-5}	1.21×10^{-3}	14
LOXO-305	BTK C481S	4.77	1.71×10^{-5}	8.18×10^{-4}	20
Ibrutinib	BTK	3.36	3.45×10^{-5}	1.16×10^{-3}	14
Ibrutinib	BTK C481S	14.3	2.22×10^{-5}	3.17×10^{-3}	5
Acalabrutinib	BTK	8.28	1.92×10^{-4}	1.59×10^{-4}	105
Acalabrutinib	BTK C481S	473	NM	NM	< 1.4*

NM-Not measurable

* Assay limit is 1.4 minutes. Residence times shorter than 1.4 minutes cannot be measured in this assay format.

(Table from the Applicant)

Proposed mechanism of inhibition of BTK and BTK C481S by pirtobrutinib

Kinase activity of pirtobrutinib was determined via Homogeneous Time Resolved Fluorescence (HTRF) KinEASE TK assays in reaction mixtures with various concentrations of pirtobrutinib (0-11 nM) and ATP (1-16 µM) and 250 nM biotin-TK substrate. The study results demonstrated that pirtobrutinib is an ATP-competitive inhibitor of BTK and BTK C481S (data not shown).

Cellular assays

The inhibitory activity of pirtobrutinib and ibrutinib on the BTKs was determined in Human Embryonic Kidney (HEK293) cells stably expressing WT BTK and BTK C481S. BTK phosphorylation activity was assessed by measuring the phosphorylation of tyrosine 223 (Y223), the major autophosphorylation site. In a separate study, the total tyrosine phosphorylation including phosphorylation not associated with BTK-dependent kinase activity was determined. The result is summarized below.

In the cellular assay, while pirtobrutinib inhibited WT and mutant BTKs with similar IC_{50} values, ibrutinib exhibited a much weaker inhibition effect against BTK C481 mutants.

Table 6: Inhibition of BTK and BTK C481 Resistance Mutant Autophosphorylation

Kinase	Pirtobrutinib IC_{50} (Mean ± SD, nM)	n	Ibrutinib IC_{50} (Mean ± SD, nM)	n
BTK	3.9 ± 1.6	3	2.0 ± 0.1	2
BTK C481S	8.1 ± 1.3	2	120.0	1
BTK C481T	7.1 ± 3.3	2	>150.0	2
BTK C481G	13.9 ± 3.8	2	N/D	1
BTK C481R	12.6 ± 5.2	2	N/D	1

N/D, IC_{50} could not be computed; minimal inhibition at highest compound concentration

(Table from the Applicant)

Drug activity related to proposed indication

- In vitro studies

Inhibition of cellular signaling and proliferation in lymphoma cell lines

The anti-tumor activities of pirtobrutinib were assessed in human lymphoma cell lines that exhibit BTK-dependent surviving signaling and proliferation, i.e., Ramos RA1 (B-lymphocyte cell line) and TMD8 (activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL); ABC-DLBCL). Cells incubated with pirtobrutinib were stimulated with crosslinked anti-human IgM (RA1) or sodium orthovanadate (TMD8) and the levels of phospho-BTK Y223 (RA1 and TMD8) and/or phospho-PLCγ2 Y1217 (RA1 only) were determined in the cell lysate. Non-specific toxicity was measured on Jurkat cells, a T-cell line that does not express BTK, as a negative control.

In each of the functional cellular readouts on BTK containing cell lines, pirtobrutinib's IC_{50} was < 10 nM, ranging from 2.33 nM for TMD8 anti-proliferation (data not shown) to 9.1 nM for inhibition of PLCγ2 phospho-Y1217 in Ramos cells. The IC_{50} for inhibition of BTK phospho-Y223 was essentially identical at 3.3 nM in Ramos cells and 3.2 nM in TMD8 cells.

Table 7: Pirtobrutinib Inhibition of BTK Kinase Activity in Lymphoma Cell Lines (Inhibition of Y223 Autophosphorylation)

Cell Line	n	Readout	Pirtobrutinib IC_{50} (Mean ± SD, nM)
TMD8	2	phosphorylated BTK Y223	3.2 ± 3.3
Ramos RA1	3	phosphorylated BTK Y223	3.3 ± 0.8
Ramos RA1	3	phosphorylated PLCγ2 Y1217	9.1 ± 4.1

(Table from the Applicant)

Inhibition of human B-cell activation in peripheral blood mononuclear cells (PBMC) and whole blood

The inhibitory activity of pirtobrutinib (referred as REDX08608 in this study report) on B-cell activation was determined via flow cytometry, based on the percent of CD19+ cells in PBMC or whole blood B cells that were stained for CD69-positive, a B-cell activation marker. The estimated IC_{50} values were 3.6 nM and 30.6 nM for pirtobrutinib induced B-cell inhibition in PBMC and whole blood, respectively.

- In vivo study

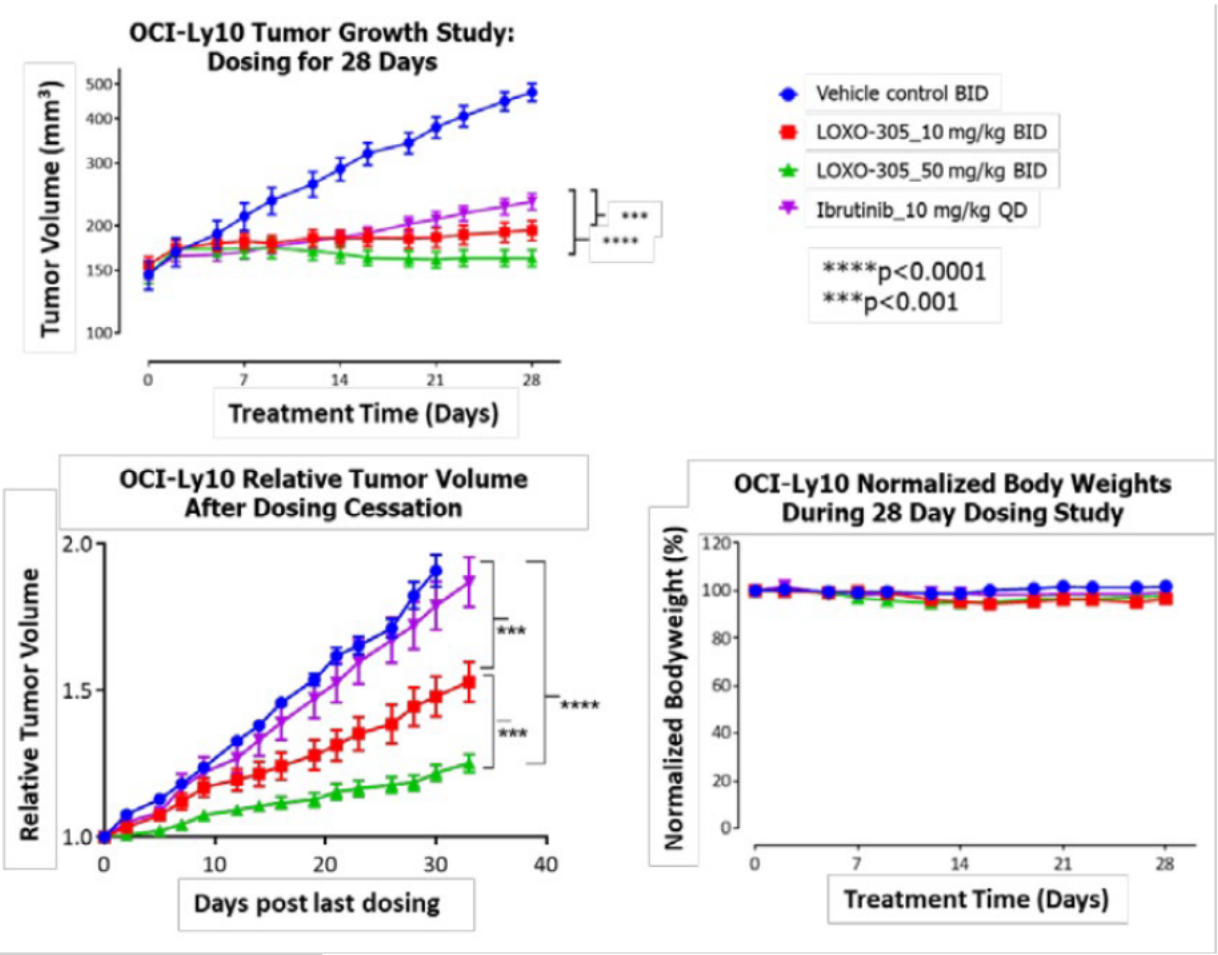
Murine xenograft model

In OCI-Ly10 human B-cell lymphoma cell inoculated severe combined immunodeficiency (SCID)-mice, orally administered pirtobrutinib induced dose-dependent inhibition of tumor growth. The tumor-suppressive effect lasted dose-dependently after dosing cessation. No remarkable toxicities, such as body weight reduction, were noted under the conditions of the study. Pirtobrutinib also induced tumor suppression in the xenograft model harboring TMD8 DLBCL

cells. The antitumor activity of pirtobrutinib was comparable in murine xenograft models bearing wild type or mutant C481S BTK.

In OCI-Ly10 human lymphoma model:

Figure 1: The Anti-Tumor Activity of BTK Inhibitors in OCI-LY10 Xenograft Model



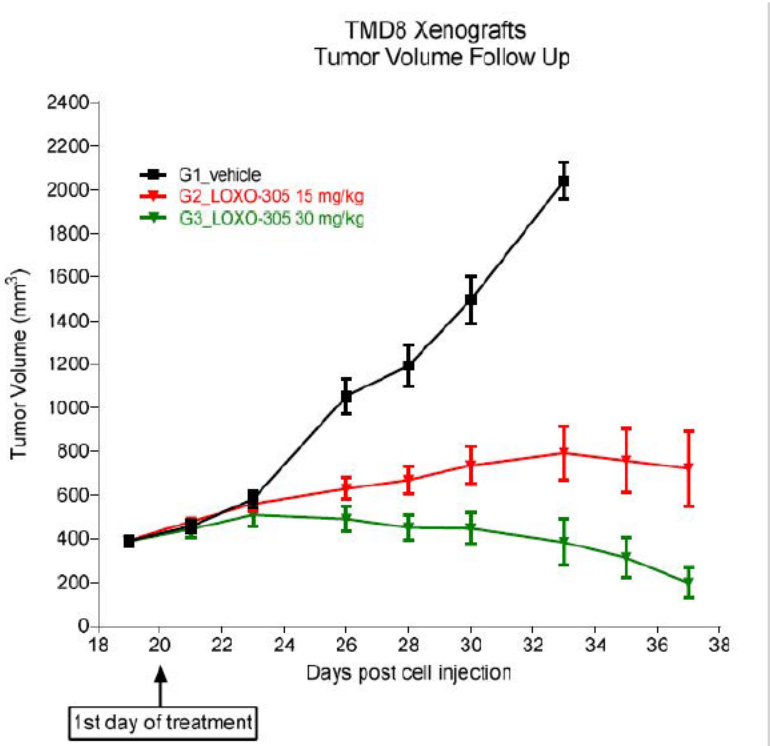
(Figure from the Applicant)

In TMD8 murine xenograft model:

- Wild type: (LOXO-305-PHARM-038)

Pirtobrutinib was evaluated in a human tumor xenograft model of DLBCL with twice-daily dosing at 15 and 30 mg/kg. The daily oral administration of pirtobrutinib was initiated at 20 days post cell injection and continued for 18 days (vehicle treatment for 14 days). Significant tumor growth inhibition (TGI) was observed in the 15 and 30 mg/kg pirtobrutinib treated groups compared to the vehicle treated group with tumor regression observed at 30 mg/kg. The plasma exposure to pirtobrutinib correlated with the observed anti-tumor activity.

Figure 2: The Anti-Tumor Activity of Pirtobrutinib in TMD8 Xenograft Model (Wild Type)



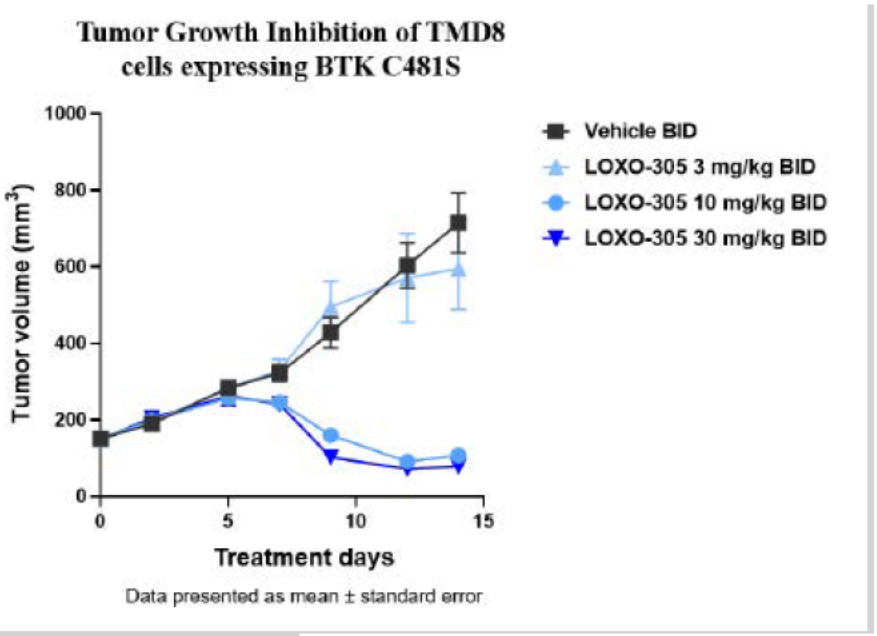
TMD8 xenograft tumor growth profiles (Mean ± SEM) for the three groups of treated SCID mice from day 20 to day 37 post cell injection. Mice were treated with pirtobrutinib at the indicated concentration or with vehicle (10 mL/kg). The experiment was stopped on day 33 for the vehicle treated group and on day 37 for the other groups.

(Figure from the Applicant)

- Mutant C481S: (LOXO-305-PHARM-017)

Mice harboring TMD8 cells expressing BTK C481S were treated orally with pirtobrutinib at 3, 10, or 30 mg/kg BID for 14 days. Pirtobrutinib treatment resulted in a significant dose-dependent tumor growth inhibition at 10 mg/kg and 30 mg/kg BID compared to vehicle treated control animals. Tumor regressions of -29% and -48% were observed at 10 and 30 mg/kg BID, respectively, compared to the tumor volume at the beginning of treatment.

Figure 3: The Anti-Tumor Activity of Pirtobrutinib in TMD8 Xenograft Model (Mutant C481S)



(Figure from the Applicant)

Secondary Pharmacology

The Applicant's Position:

Pirtobrutinib at clinically relevant concentrations had minimal effects on a panel of non-BTK kinases, enzymes, ion channels, transporters, and receptors. Pirtobrutinib was greater than 300-fold selective for BTK versus 98% of 370 non-BTK kinases tested in a purified enzyme screen with only eight kinases other than BTK being inhibited by more than 50% when tested at a concentration of 1 µM. The high selectivity of pirtobrutinib for BTK inhibition was maintained in cell-based kinase assays. When pirtobrutinib was tested against 44 additional targets at a concentration of 1 µM, there was no significant inhibition (≥ 50%) of the receptors, transporters, ion channels, or enzymes evaluated.

The FDA's Assessment:
The FDA generally agrees with the Applicant. See additional information below.

Effect of LOXO-305 on non-BTK kinases
LOXO-305 (0.1 µM and 1 µM) was tested for inhibition of the kinase activity of 371 human wild-type kinases and 208 human mutant kinases using a radiolabeled ATP activity assay. The IC_{50} values and fold enzyme activity (relative to BTK) are presented in the table below.

At a pirtobrutinib concentration of 1 µM, 8 (of 371) kinases showed more than 50% inhibition. These 8 kinases are ERBB4, MEK2, BRK, MEK1, TXK, CSK, YES1 and FYN (see table below), with erbB4 having an IC_{50} of 13 nM as compared to 3 nM for BTK inhibition (a 4-fold difference).

Table 8: Effect of LOXO-305 on BTK and Non-BTK Kinases (POC <50)

Kinase	Km [ATP] (µM)	Percent of control at 1 µM pirtobrutinib		Pirtobrutinib IC_{50}		
		Mean ± SD, %	N	Mean ± SD, nM	N	Fold selectivity vs BTK
BTK	50	1.78 ± 0.40	4	3.15 ± 1.32	12	1
ERBB4/HER4	2.5	2.64 ± 0.66	4	13.25 ± 2.47	2	4.2
BRK	100	10.33 ± 0.37	4	54.25 ± 3.04	2	17.2
MEK2	1	7.60 ± 0.61	4	82.70 ± 5.37	2	26.3
MEK1	2.5	12.19 ± 1.56	4	147.00 ± 5.66	2	46.7
YES/YES1	50	38.57 ± 0.55	4	157.00 ± 4.24	2	49.8
TXK	30	19.58 ± 0.67	4	209.00 ± 12.73	2	66.3
CSK	50	34.25 ± 0.52	4	552.00 ± 49.50	2	175.2
TEC	10	64.56 ± 1.12	4	1234.08 ± 255.66	12	391.8
FYN	30	48.83 ± 1.95	4	1710.00 ± 183.85	2	542.9

(Table from the Applicant)

LOXO-305 was evaluated at a concentration of 1 µM against 44 targets in a radioligand binding assay, which included primary molecular targets, transmembrane and soluble receptors, ion channels, and monoamine transporters. No remarkable inhibition was noted in the study (data not shown).

Safety Pharmacology

The Applicant's Position:

The safety pharmacology package indicates that there is little risk of pirtobrutinib having negative consequences in systems that are vital for life: cardiovascular, CNS, and respiratory. While there was a slight increase in QTc interval in the 1-month dog study, this finding was likely spurious. It was not repeated in the dog cardiovascular safety pharmacology study or the 3-month dog study. In addition, this QTc increase is not consistent with the findings from the GLP in vitro hERG study.

The FDA's Assessment:

The FDA agrees with the Applicant's summary for safety pharmacology. Additional details regarding the safety pharmacology assessments are provided below.

Cardiovascular system
LOXO-305 was tested in a standard GLP-compliant in vitro hERG assay at 3, 10, 30 and 100 µM; Saline (HB-PS) + 0.3% DMSO and terfenadine (60 nM) were used as the vehicle and positive controls, respectively (Study #LOXO-305-TOX-003). LOXO-305 did not significantly inhibit hERG-mediated potassium currents under the conditions tested; the IC_{50} was determined to be 32.1 µM.

Male beagle dogs (n=4) were administered LOXO-305 (0, 5, 20, or 60 mg/kg) orally (5 mL/kg) on test sessions 1-4 with each animal receiving all treatments according to a Latin square design with a ≥7-day washout between treatments. Body temperature, blood pressure (systolic, diastolic, and mean arterial), and ECG were monitored continuously for ≥3 hours prior to dosing and for ≥25 hours postdose (Study #LOXO-305-TOX-002). Under the conditions tested, LOXO-305 had no effect on mortality, clinical signs, body temperature, diastolic and mean arterial blood pressure, heart rate, or the quantitative and qualitative ECG parameters. There were no LOXO-305-related effects on hemodynamic and electrocardiographic parameters in the 28-day repeat-dose toxicology study in dogs (#LOXO-305-TOX-008).

5.4 ADME/PK

The Applicant's Position:

In rats and dogs, pirtobrutinib was readily absorbed after oral administration. In dogs, there was no food effect after administration of a pirtobrutinib (b) (4) In both rats and dogs, exposures (C_{max} and AUC) increased with increasing dose with minimal accumulation. In rats, the females consistently had higher exposure than the males (greater than 6-fold). Male rats had a higher clearance value and greater metabolism than females. In dogs, males and females had similar exposures.

In rats, pirtobrutinib was widely distributed across tissues. In rat and dog plasma, pirtobrutinib is approximately 87% and 82% protein bound, respectively, and the plasma protein binding of pirtobrutinib was not concentration dependent. For rats and dogs, the mean blood-to-plasma ratios were 0.84 and 0.88, respectively.

The primary metabolic pathways involved in the clearance of pirtobrutinib in rat were consistent with oxidation, glucuronidation, and sulfonation. The main circulating metabolite in human (M1) is present in rat, with appropriate steady state coverage in the rat 3-month toxicology study.

The route of excretion in male and female rats (bile duct intact or bile duct cannulated), after administration of [^{14}C]pirtobrutinib, was primarily through the bile and feces. In both male and female rats, less than 4% of the radioactive dose was eliminated in urine.

The FDA's Assessment:

The FDA generally agrees with the Applicant's statement. The absorption, exposure, and oral bioavailability were formulation dependent (b) (4) as evidenced in single-oral dose bioavailability studies in rats and in dogs. (b) (4), was used in nonclinical toxicology studies. The quantitative whole-body autoradiography (QWBA) data indicated that the highest calculated radiation absorbed doses were in the epididymis, liver, uveal tract, pigmented skin, testis, esophagus, gastrointestinal (GI) organs, and urinary bladder. Distribution of [^{14}C]pirtobrutinib-related material to the testis and regions of the brain was rapid with measurable concentrations by 1 hour. The levels in both the testis and the brain then declined to below the lower limit of quantitation by 24 hours. Plasma protein binding was 95% in the human, and ranged from 82% to 92% in the laboratory animals. For the rat and dog, the mean blood-to-plasma ratios were 0.84 and 0.88, while the mean red blood cell-to-plasma ratios were 0.64 and 0.74, respectively.

The in vitro and in vivo metabolism studies indicated the primary clearance pathways of pirtobrutinib in rats involved biliary elimination, oxidation, direct glucuronidation, direct sulfation, and oxidation with glucuronidation. In vitro studies in human hepatocytes indicated that the metabolic pathways were mainly via CYP3A4 and 3A5, and were consistent with hydroxylation, N-glucuronidation, O-demethylation followed by glucuronidation, and hydroxylation followed by glucuronidation. The in vitro human metabolites were detected in the rat and/or dog. The most abundant metabolite circulating in human plasma, M1 (at approximately 87%), is present in rat plasma.

The reviews of the toxicokinetic assessments are included in the respective toxicology studies below. The toxicokinetic parameters determined in the repeat-dose toxicology studies in rats and dogs (b) (4) formulation) generally retained the following characteristics: the exposures to pirtobrutinib (C_{max} and AUC_{0-24h}) increased less than dose-proportional as a function of increasing dose with saturation at higher doses in rats; however, when (b) (4) formulation of pirtobrutinib was administered to dogs, exposure tended to be greater than dose-proportional. There was no noticeable accumulation of pirtobrutinib in plasma following repeated administration in rats and dogs. In rats, females had consistently higher exposure (greater than 6-fold) than males; in contrast, no effect of sex on plasma pirtobrutinib levels was observed in dogs.

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

At tolerated dose levels, pirtobrutinib has a relatively mild toxicity profile in animals, similar to its safety profile in humans. At tolerated dose levels, the primary toxicity in animals was lymphoid organ and immune system effects, 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 may be related to the anemia that has been observed in clinical trial participants. Effects observed only at dose levels that exceeded the MTD in the 1-month dog study included: bone marrow injury, gastrointestinal injury, and lung inflammation. It is common for effects that only occur above the MTD in animals to not translate to a human risk, and they are considered to be less important to human safety.

Additional findings that have not been identified as significant adverse events in humans are the eye effects observed in dogs. Corneal lesions were only observed in 2 dogs treated for 3 months. To date, this has not been identified as a drug class toxicity and has not been identified as a significant safety finding in the human population. There is an incongruent detectability in animals as compared to humans as these findings would be anticipated to be concurrent with other findings (e.g., scleral injection, ocular discharge, ophthalmic pain, etc.) which would prompt timely ophthalmic evaluation in a human population while remaining potentially unrecognized in animals. This is clinically manageable, as it is detectable and monitorable in humans and is likely to reverse with cessation of treatment with pirtobrutinib. A similar nonclinical eye effect was observed in dogs treated with ibrutinib which does not translate to a clinical effect (see FDA pharmacology/toxicology review for ibrutinib).

The FDA's Assessment:
In general, the FDA agrees with the Applicant's assessment. An additional finding of pancreatic toxicity was found in the rat studies but may be species specific. See additional information provided below for the 3-month repeat-dose toxicity studies in rats and dogs.

Study title/Study number: A 3-month toxicity and toxicokinetic study of LY3527727 administered by oral gavage twice daily to rats/LOXO-305-TOX-018 (alternate project code 230-2019)

Key Study Findings

- Oral doses of pirtobrutinib up to 500 mg/kg/dose twice daily (BID; or 1000 mg/kg/day) in males and 300 mg/kg/dose twice daily (BID; or 600 mg/kg/day) in females for 3 months were tolerated.
- The treatment-related findings included the following: lymphoid tissue toxicity (decreased

cellularity in the spleen; increased erythrophagocytosis in the lymph nodes), altered immunophenotyping (suppressed B-lymphocytes and increased T-lymphocytes), suppressed immune response (KLH IgG and IgM response in the TDAR), and pancreatic toxicity (fibrosis, inflammation and pigment deposit in islet of Langerhans).

GLP compliance: yes

<table>
<tr><td colspan="2">Methods</td></tr>
<tr><td>Drug</td><td>LY3527727 (LOXO-305; pirtobrutinib)*, Lot no. 37094-E-19-001, potency: 96.1%
*as suspension in (b) (4)</td></tr>
<tr><td>*Dose and frequency of dosing</td><td>Males and females: 0 (vehicle, Group 1); Males: 100 or 1000 mg/kg/day (as Groups 2 and 5), Females: 120 or 600 mg/kg/day (as Groups 3 and 4), administered twice daily (BID; 12 hours apart) for 3 months (Days 1-105; Day 106 terminal necropsy).

Based on previously conducted studies, the exposures and toxicities of pirtobrutinib were greater in female rats. Thus, dose levels were set separately for males and females.</td></tr>
<tr><td>Route of administration</td><td>Oral gavage (10 mL/kg)</td></tr>
<tr><td>Formulation/Vehicle</td><td>Oral suspension of 0.5% HPMC, aqueous solution containing 0.5% (w/v)</td></tr>
<tr><td>Species/strain</td><td>Rats/Sprague Dawley</td></tr>
<tr><td>Number/Sex/Group</td><td>Main study: 10/sex/group (Control, LD M/F and HD M/F); toxicokinetic study (TK): 3/sex/group; T-cell dependent antibody response (TDAR): 5/sex/group</td></tr>
<tr><td>Age</td><td>7 weeks; 184-340 g</td></tr>
<tr><td>Satellite groups/unique design</td><td>Toxicokinetics assessment and TDAR study.</td></tr>
<tr><td>Deviation from study protocol affecting interpretation of result</td><td>Not remarkable</td></tr>
<tr><td colspan="2">Observation and Results: changes from control</td></tr>
<tr><td>Parameters</td><td>Major findings</td></tr>
<tr><td>Mortality</td><td>No pirtobrutinib-related mortality.</td></tr>
<tr><td>Clinical signs</td><td>No pirtobrutinib-related clinical findings, because of low and/or sporadic incidence, lack of a dose-related pattern and/or similar incidence in control animals.</td></tr>
<tr><td>Body weight</td><td><u>Changes of mean body weights:</u>
Starting on Day 15 and through the dosing period, statistically significant lower mean body weights (↓10.3%-12.7% of the control) were observed in Group 5 (males treated with 1000 mg/kg/day).

<u>Changes in Body weight gain in Group 5 (Males at 1000 mg/kg/day)</u>
<u>Statistically significant reductions in weight gain (g):</u>
<table>
<tr><td>Days</td><td>1→8</td><td>8→15</td><td>22→29</td><td>1→106</td></tr>
<tr><td>Control (g)</td><td>68.8</td><td>70.7</td><td>53.6</td><td>495.5</td></tr>
<tr><td>Group 5 (g)</td><td>54.5; ↓21%</td><td>56.7; ↓20%</td><td>43.1; ↓20%</td><td>412.5; ↓16.8%</td></tr>
</table>
The number in the cell is the group mean of the weekly weight gain (g) and the percent reduction from the control.</td></tr>
</table>

<table>
<tr><td>Food consumption</td><td>Not remarkable.</td></tr>
<tr><td>Ophthalmology</td><td>Not remarkable.</td></tr>
<tr><td>Hematology and coagulation</td><td>Not remarkable.
The changes in the hematology and coagulation parameters were considered not pirtobrutinib-related based on the small magnitude, absence of a dose response, general overlap of individual values with the range of control values, and/or a magnitude of change commonly observed in rats under similar study conditions.</td></tr>
<tr><td>Clinical chemistry</td><td>The findings were observed at ≥ 100 mg/kg/day. The tables below are summaries of % changes from the control.
Summary of clinical chemistry findings (Day 106)
<table>
<tr><td></td><td>Males</td><td></td><td>Females</td><td></td></tr>
<tr><td>Group</td><td>2</td><td>5</td><td>3</td><td>4</td></tr>
<tr><td>Dose mkd</td><td>100</td><td>1000</td><td>120</td><td>600</td></tr>
<tr><td>N</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>AST ↓</td><td>18%</td><td>20%</td><td>42%</td><td>44%</td></tr>
<tr><td>Globulin ↓</td><td>---</td><td>9% (NS)</td><td>27%</td><td>32%</td></tr>
<tr><td>A/G ratio ↑</td><td>---</td><td>---</td><td>37%</td><td>45%</td></tr>
<tr><td>Urea nitrogen↓</td><td>---</td><td>---</td><td>---</td><td>21%</td></tr>
<tr><td>Total bilirubin ↑</td><td>---</td><td>39% (NS)</td><td>---</td><td>64%</td></tr>
<tr><td>Creatine kinase ↓</td><td>38%</td><td>46%</td><td>53%</td><td>60%</td></tr>
<tr><td>Potassium ↓</td><td>9%</td><td>14%</td><td>11%</td><td>16%</td></tr>
</table>
The numbers in the table represent the percent change from the control; mkd: mg/kg/day; --- No remarkable findings; NS: not statistically significant.</td></tr>
<tr><td>Urinalysis</td><td>Not remarkable.</td></tr>
<tr><td>Immune system effects
Blood immunophenotyping:</td><td>On Day 106, blood samples were collected via jugular veins, and portions of the spleen and thymus tissue samples were saved for immunophenotyping. The table below is the summary of the changes in the various cell populations in the blood and spleen. Pirtobrutinib induced a shift in the balance of T- and B-lymphocytes, with decreases in B cells and increases in T cells. In comparison to the control, there were increases of the relative percentages of blood and spleen total T lymphocytes (up to 40%) and helper T lymphocytes (up to 48%) in all pirtobrutinib-treated rats. Increases of the relative percentages in NK cells were also observed (blood: up to 64% in males; spleen: up to 48%/43% in males/females).

Blood
<table>
<tr><th colspan="2" rowspan="2">Cell Population of Interest</th><th colspan="2">Males</th><th colspan="2">Females</th></tr>
<tr><th>50 mg/kg BID</th><th>500 mg/kg BID</th><th>60 mg/kg BID</th><th>300 mg/kg BID</th></tr>
<tr><td>Total Lymphocyte Counts</td><td>Abs</td><td>-23</td><td>-26</td><td>27</td><td>0</td></tr>
<tr><td rowspan="2">Total T lymphocytes</td><td>Abs</td><td>-</td><td>-</td><td>56b</td><td>28</td></tr>
<tr><td>%</td><td>18</td><td>29b</td><td>25b</td><td>27b</td></tr>
<tr><td rowspan="2">Helper T lymphocytes</td><td>Abs</td><td>-</td><td>-</td><td>62b</td><td>42a</td></tr>
<tr><td>%</td><td>27a</td><td>40b</td><td>29b</td><td>42b</td></tr>
<tr><td rowspan="2">Cytotoxic T lymphocytes</td><td>Abs</td><td>-21</td><td>-25</td><td>36</td><td>-</td></tr>
<tr><td>%</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td rowspan="2">B lymphocytes</td><td>Abs</td><td>-46</td><td>-52b</td><td>-</td><td>-39a</td></tr>
<tr><td>%</td><td>-27b</td><td>-35b</td><td>-31b</td><td>-39b</td></tr>
<tr><td rowspan="2">NK cells</td><td>Abs</td><td>-</td><td>25</td><td>22</td><td>-</td></tr>
<tr><td>%</td><td>59a</td><td>64b</td><td>-</td><td>-</td></tr>
<tr><td colspan="2">Helper T : Cytotoxic T Ratio</td><td>27</td><td>44</td><td>21</td><td>61b</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>Spleen
<table>
<tr><th rowspan="2" colspan="2">Cell Population of Interest</th><th colspan="2">Males</th><th colspan="2">Females</th></tr>
<tr><th>50 mg/kg BID</th><th>500 mg/kg BID</th><th>60 mg/kg BID</th><th>300 mg/kg BID</th></tr>
<tr><td>Total Lymphocyte Counts</td><td>Abs</td><td>-50</td><td>-62b</td><td>-18</td><td>-29</td></tr>
<tr><td rowspan="2">Total T lymphocytes</td><td>Abs</td><td>-35</td><td>-47a</td><td>-</td><td>-</td></tr>
<tr><td>%</td><td>26b</td><td>39b</td><td>40b</td><td>39b</td></tr>
<tr><td rowspan="2">Helper T lymphocytes</td><td>Abs</td><td>-35</td><td>-43</td><td>27</td><td>-</td></tr>
<tr><td>%</td><td>26b</td><td>44b</td><td>47b</td><td>48b</td></tr>
<tr><td rowspan="2">Cytotoxic T lymphocytes</td><td>Abs</td><td>-43</td><td>-56a</td><td>-</td><td>-</td></tr>
<tr><td>%</td><td>-</td><td>-</td><td>27b</td><td>-</td></tr>
<tr><td rowspan="2">B lymphocytes</td><td>Abs</td><td>-66a</td><td>-76b</td><td>-44a</td><td>-56b</td></tr>
<tr><td>%</td><td>-29b</td><td>-36b</td><td>-31b</td><td>-37b</td></tr>
<tr><td rowspan="2">NK cells</td><td>Abs</td><td>-30</td><td>-41a</td><td>-</td><td>-</td></tr>
<tr><td>%</td><td>35a</td><td>48b</td><td>19</td><td>43b</td></tr>
<tr><td colspan="2">Helper T : Cytotoxic T Ratio</td><td>-</td><td>20</td><td>-</td><td>27a</td></tr>
</table>
Numbers in the table represent % difference from the vehicle control: -: reduced, Ab: absolute counts. %: relative counts
a, b: Statistically significant changes
(Table from the Applicant)</td></tr>
<tr><td>T-cell dependent antibody response (TDAR) analyses</td><td>Animals were immunized with keyhole limpet hemocyanin (KLH; first KLH injection on Day 26 and the second injection on Day 92) followed by the treatment of pirtobrutinib. Pirtobrutinib treatments resulted in a decrease in the primary and secondary TDAR responses in all treated rats, with more prominent effects following the first KLH injection. Pirtobrutinib-induced decreases of TDAR responses in males at 1000 mg/kg/day were adverse, based on the number of animals for which no detectable primary and secondary anti-KLH antibodies were measured (i.e., 5 out of 5 animals and 3 out of 5 animals, respectively, in both the IgG and IgM settings).

Maximum statistically significant (% reduction compared to the control) changes:
<table>
<tr><th></th><th>Males (100-1000 mg/kg/day)</th><th>Females (120-600 mg/kg/day)</th></tr>
<tr><td>IgG Primary KLH response</td><td>-95%</td><td>-98%</td></tr>
<tr><td>Secondary KLH response</td><td>-100%</td><td>-99%</td></tr>
<tr><td>IgM Primary KLH response</td><td>-86%</td><td>-54% (not significant)</td></tr>
<tr><td>Secondary KLH response</td><td>-99%</td><td>-92%</td></tr>
</table>
Primary KLH response: % changes during Day 26-Day 47; Secondary KLH response: % changes during Day 92-Day 106</td></tr>
<tr><td>Gross anatomy</td><td>Not remarkable, except for small spleen noted in one Group 5 rat.</td></tr>
<tr><td>Organ weights</td><td>Spleen weights were decreased at all doses without dose dependence in the magnitude of reduction.</td></tr>
<tr><td>Histopathology</td><td>Pirtobrutinib target organs included the spleen, pancreas and lymph nodes
• Decreased lymphoid cellularity (minimal to moderate) occurred in the spleen at all dose levels. The finding correlated with decreases in spleen weights.
• Increased incidence and/or severity of fibrosis, inflammation, and pigment deposit mostly centered around the islet of Langerhans was observed in the pancreas.
• Increased incidence and/or severity of erythrophagocytosis was observed in the mandibular, mesenteric, and other lymph nodes.
See Table below for data.</td></tr>
<tr><td>Toxicokinetics</td><td>• The systemic exposures to pirtobrutinib increased with increasing doses, following a generally less than dose-proportional pattern.
• There was no apparent accumulation (R_{AUC} up to 2-fold) with repeated administration. An apparent sex difference in exposures was observed with ~6-fold higher AUC values in females.

See Table below.</td></tr>
</table>

Table 9: Histopathological Findings (3-Month Study in Rats)

	Males			Females		
Group	**1**	**2**	**5**	**1**	**3**	**4**
Dose (mg/kg BID)	**0**	**50**	**500**	**0**	**60**	**300**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Examined)	10	10	10	10	10	10
Decreased cellularity; marginal zone; periarteriolar lymphoid sheath	(0)[a]	(9)	(10)	(0)	(9)	(9)
Minimal	-	9	3	-	3	3
Mild	-	0	5	-	6	6
Moderate	-	0	2	-	0	0
Pancreas (No. Examined)	10	10	10	10	10	10
Fibrosis; islet of Langerhans	(2)	(10)	(10)	(0)	(6)	(6)
Minimal	2	2	2	-	1	1
Mild	0	7	7	-	5	5
Moderate	0	1	1	-	0	0
Inflammation; acinar and/or islet of Langerhans	(0)	(6)	(5)	(0)	(1)	(6)
Minimal	0	3	4	-	1	2
Mild	0	3	1	-	0	4
Pigment; islet of Langerhans	(4)	(10)	(10)	(0)	(5)	(7)
Minimal	4	6	8	-	4	6
Mild	0	4	2	-	1	1
Atrophy; acinar	(2)	(4)	(6)	(1)	(1)	(3)
Minimal	1	1	5	0	1	2
Mild	1	3	1	1	0	1
Hemorrhage; islet of Langerhans	(0)	(1)	(0)	(0)	(2)	(2)
Minimal	-	1	0	-	2	1
Mild	-	0	0	-	0	1
Hemorrhage; acinar	(0)	(0)	(0)	(0)	(0)	(2)
Minimal	-	-	-	-	-	2
Inflammation, mixed cell; acinar	(0)	(0)	(0)	(0)	(1)	(1)
Minimal	-	-	-	-	1	1
Inflammation, vascular/perivascular	(0)	(0)	(1)	(0)	(0)	(0)
Minimal	-	-	1	-	-	-
Lymph node, mandibular (No. Examined)	10	10	10	10	10	10
Erythrophagocytosis	(2)	(0)	(5)	(1)	(4)	(5)
Minimal	2	-	2	1	3	5
Mild	0	-	3	0	0	0
Moderate	0	-	0	0	1	0
Lymph node, mesenteric (No. Examined)	10	10	10	10	10	10
Erythrophagocytosis	(0)	(6)	(5)	(0)	(4)	(5)
Minimal	-	4	5	-	3	5
Mild	-	2	0	-	1	0
Lymph node, (submitted for gross lesions) (No. Examined)	1	6	7	1	4	6
Erythrophagocytosis	(1)	(6)	(7)	(1)	(4)	(6)
Minimal	0	3	3	1	1	1
Mild	1	3	2	0	1	2
Moderate	0	0	2	0	2	3

[a] Numbers in parentheses represent the number of animals with the finding.

(Table from the Applicant)

Table 10: Mean Plasma Pirtobrutinib Toxicokinetic Parameters (3-Month Study in Rats)

Day 1

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
100*	863	8.63	9650	96.5	13					
120						4.5	0.0375	63.4	0.528	13
600						12.8	0.0213	220	0.367	13
1000	3170	3.17	37100	37.1	13					

Day 28

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
100*	701	7.01	9850	98.5	13					
120						5940	49.5	82800	690	13
600						15900	26.5	291000	485	16
1000	2900	2.9	38000	38	4					

Day 105

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
100*	1380	13.8	19100	191	13					
120						7980	66.5	126000	1050	13
600						20800	34.7	369000	615	1
1000	4990	4.99	63000	63	4					

*Dose: mg/kg/day; Cmax: ng/mL; $AUC_{0\text{-}24h}$: ng*h/mL; Tmax: hr

Study title/Study number: A 3-month toxicity and toxicokinetic study of LY3527727/ (b) (4) administered by twice daily oral gavage to dogs/LOXO-305-TOX-017 (alternate project code 230-2079)

Key Study Findings

- Oral doses of pirtobrutinib up to 5 mg/kg/dose twice daily (BID; or 10 mg/kg/day) for 3 months were tolerated.
- The treatment-related findings included the following: hematological effects (suppression of erythroid mass), lymphoid tissue toxicity (decreased cellularity in GLAT and lymph node), altered blood immunophenotyping (suppressed B-lymphocytes and activated T-lymphocytes), a suppressed immune response (KLH IgM response in the TDAR), and bilateral cornea opacity in two male dogs.
- The target organs of toxicity for pirtobrutinib in dogs included the bone marrow, lymphoid tissues, and eyes (cornea).

GLP compliance: yes

Methods	
Drug	LY3527727 (LOXO-305; pirtobrutinib)*, Lot no. BREC-2129-072, potency: 48.6%; (b) (4) * (b) (4)
*Dose and frequency of dosing	0 (vehicle), 1, 5 or 10 mg/kg/day, twice daily (BID; 12 hours apart) for 3 months (Days 1-105; Day 106 terminal necropsy). The selection of the high dose of 10 mg/kg/day was based on the expected exposure, which was below the exposure levels not tolerated in previous studies (e.g., the GLP 28-day study) but was likely to be near the limit of tolerability. Of note, due to exposure variability observed in dogs with the (b) (4) form of pirtobrutinib in the 28-day dog study, a (b) (4) was used in this 3-month dog study. The change in form resulted in a change in the dose-exposure relationship; thus, dose levels were used that targeted specific exposure (AUC) levels.
Route of administration	Oral gavage (5 mL/kg)
Formulation/Vehicle	Oral suspension of 50/50 pirtobrutinib/HPMC- (b) (4), aqueous solution containing 0.5% (w/v).
Species/strain	Dogs/beagle
Number/Sex/Group	Main study: 4/sex/group (Control, LD, MD and HD)
Age	6-7 months; 5.7-8.8 kg
Satellite groups/unique design	Toxicokinetics assessment: animals in the main study participated.
Deviation from study protocol affecting interpretation of result	Not remarkable
Observation and Results: changes from control	
Parameters	Major findings
Mortality	None
Clinical signs	No pirtobrutinib-related clinical findings, because of low and/or sporadic incidence, lack of a dose-related pattern and/or similar incidence in control animals.
Body weight	Slight changes in mean group body weight and body weight gain: Starting Day 77, lower mean body weights were observed in males at 10 mg/kg/day (↓7.4%-9% of the control).
Food consumption	Not remarkable, fluctuated food intake was observed in the individuals, but the finding was not dose-dependent
ECG and hemodynamics	Not remarkable.
Ophthalmology	Bilateral corneal opacities occurred mainly in two males at the high dose of 10 mg/kg/day. The opacity was superficial and most of the incidences were faint opacities; however, there were focal or multifocal smaller and denser (more opaque) opacities that were described as subepithelial or anterior stromal. These changes did not cause noticeable vision impairment in dogs.
Hematology and coagulation	The main findings were reduced erythroid (red cell mass) parameters (red blood cells [RBC], hemoglobin [HGB], hematocrit [Hct]) in females at ≥ 1 mg/kg/day. The changes were

<table>
<tr><td></td><td>statistically significant compared to the concurrent controls.

<table>
<tr><td></td><td colspan="3">Week 6</td><td>Week 15</td></tr>
<tr><td>Dose mkd</td><td>1</td><td>5</td><td>10</td><td>10</td></tr>
<tr><td>N</td><td>4</td><td>4</td><td>4</td><td>4</td></tr>
<tr><td>RBC ↓</td><td>8.6% NS</td><td>12.4%</td><td>15.6%</td><td>8.6% NS</td></tr>
<tr><td>HGB ↓</td><td>9.1%</td><td>14.5%</td><td>15.1%</td><td>9.0% NS</td></tr>
<tr><td>Hct ↓</td><td>10.3%</td><td>16.0%</td><td>17.2%</td><td>10.3% NS</td></tr>
</table>
Number indicates % change from the control; NS: not statistically significant</td></tr>
<tr><td>Clinical chemistry</td><td>The findings were mainly observed at ≥ 5 mg/kg/day. The table below is a summary of the % changes from the pretest values.

<table>
<tr><td></td><td colspan="3">Males</td><td>Females</td></tr>
<tr><td>Dose mkd</td><td>1</td><td>5</td><td>10</td><td>10</td></tr>
<tr><td>N</td><td>4</td><td>4</td><td>4</td><td>4</td></tr>
<tr><td>Week 6</td><td colspan="4"></td></tr>
<tr><td>Total protein ↓</td><td>---</td><td>---</td><td>---</td><td>9%</td></tr>
<tr><td>Albumin ↓</td><td>---</td><td>---</td><td>---</td><td>8%</td></tr>
<tr><td>Phosphorus ↓</td><td>10%</td><td>6%</td><td>8%</td><td>---</td></tr>
<tr><td>Week 15</td><td colspan="4"></td></tr>
<tr><td>Phosphorus ↓</td><td>22%</td><td>11%</td><td>20%</td><td>---</td></tr>
</table>
--- No remarkable findings; bolded values indicate statistically significant changes from the control.</td></tr>
<tr><td>Urinalysis</td><td>Not remarkable.</td></tr>
<tr><td>Immune system effects
Blood immunophenotyping:</td><td>Blood samples were collected on Weeks -2 and -1 (pretest), Week 6 and Week 15 via jugular veins. Pirtobrutinib induced an increase in T lymphocytes and a reduction in B cells.

Pirtobrutinib treatment resulted in a dose-dependent decrease in B lymphocytes:
<table>
<tr><td></td><td>Males</td><td>Females</td></tr>
<tr><td>Absolute counts ↓</td><td>33-77%</td><td>19-54%</td></tr>
<tr><td>Relative percentage ↓</td><td>31-76%</td><td>16-59%</td></tr>
</table>
See Table below for additional data.</td></tr>
<tr><td>T-cell dependent antibody response (TDAR) analyses</td><td>Animals were immunized with keyhole limpet hemocyanin (KLH; first KLH injection on Day 26 and the second injection on Day 92) followed by the treatment of pirtobrutinib. Pirtobrutinib treatments resulted in a decrease in the primary and secondary anti-KLH IgM response at all dose levels (up to 97% reduction compared to the control), with no apparent dose-dependence and a more pronounced reduction in females.

In contrast, pirtobrutinib treatments induced no effect on the anti-KLH IgG response. The overall profiles of the primary and secondary response were similar in all groups and in animals of both sexes. Dosing with pirtobrutinib caused a decrease in anti-KLH IgG levels at the onset of the primary response (Day 33) only.</td></tr>
<tr><td>Gross anatomy</td><td>Not remarkable.</td></tr>
<tr><td>Organ weights</td><td>Not remarkable.</td></tr>
<tr><td>Histopathology</td><td>The findings were mainly observed at 10 mg/kg/day and included decreased cellularity in the lymphoid tissues and findings in the eyes (2 dogs; bilateral; corneal epithelial mitoses, single cell necrosis, erosion, fibrosis, etc).
See Table 12 below for additional data.</td></tr>
</table>

Toxicokinetics LLOQ:	• The systemic exposures to pirtobrutinib increased with increasing doses, following a generally greater than dose-proportional pattern. • There was no apparent accumulation (R_{AUC} up to 2-fold) with repeated administration or sex difference in exposures. See Table below.

Table 11: Blood Immunophenotyping (3-Month Study in Dogs)

Absolute count changes

Cell Population of Interest		Males			Females		
		0.5 mg/kg BID	2.5 mg/kg BID	5 mg/kg BID	0.5 mg/kg BID	2.5 mg/kg BID	5 mg/kg BID
B lymphocytes	Week 6	-	-27	-30	-41	-33	-47
	Week 15	-31	-41a	-54b	-36	-44	-77b
Total Lymphocyte Counts	Week 6	-	-	-	-	-	-
	Week 15	-	-	-	-	-	-
Total T lymphocytes	Week 6	-	-	22	-	18	-
	Week 15	20	17	35	22	35	27
Helper T lymphocytes	Week 6	21	19	30	-	30	-
	Week 15	32	29	43	24	37	16
Cytotoxic T lymphocytes	Week 6	-	-	-	-	-	-
	Week 15	-	-	37	33	38	41
Helper T : Cytotoxic T Ratio	Week 6	-	-	-	-	-	-
	Week 15	-	-	-	-	-	-

[a] Statistically significant at $P \leq 0.05$ by Dunnet or Dunn
[b] Statistically significant at $P \leq 0.01$ by Dunnet or Dunn

(Table from the Applicant)

Table 12: Histopathological Findings (3-Month Study in Dogs)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg BID)	**0**	**0.5**	**2.5**	**5**	**0**	**0.5**	**2.5**	**5**
Dose (mg/kg/day)	**0**	**1**	**5**	**10**	**0**	**1**	**5**	**10**
No. Animals per Group	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Galt (No. Examined)	4	4	4	4	4	4	4	4
Cellularity, decreased; lymphoid; germinal center	(0)[a]	(1)	(4)	(4)	(0)	(2)	(3)	(4)
Minimal	0	1	2	0	0	2	1	0
Mild	0	0	2	1	0	0	2	2
Moderate	0	0	0	3	0	0	0	2
Lymph node, mesenteric (No. Examined)	4	4	4	4	4	4	4	4
Cellularity, decreased; lymphoid; germinal center	(0)	(0)	(0)	(3)	(0)	(0)	(2)	(4)
Minimal	0	0	0	1	0	0	2	1
Mild	0	0	0	2	0	0	0	3

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg BID)	**0**	**0.5**	**2.5**	**5**	**0**	**0.5**	**2.5**	**5**
Dose (mg/kg/day)	**0**	**1**	**5**	**10**	**0**	**1**	**5**	**10**
No. Animals per Group	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Eye, left (No. Examined)	4	4	4	4	4	4	4	4
Mitoses, increased; epithelial; cornea	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
Minimal	0	0	0	1	0	0	0	0
Mild	0	0	0	1	0	0	0	0
Hyperplasia; epithelial; cornea	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
Mild	0	0	0	2	0	0	0	0
Single cell necrosis; epithelial; cornea	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Minimal	0	0	0	1	0	0	0	0
Fibrosis; stromal; cornea	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
Mild	0	0	0	2	0	0	0	0
Infiltration, mixed cell; stromal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Minimal	0	0	0	1	0	0	0	0

(Table from the Applicant)

Table 13: Mean Plasma Pirtobrutinib Toxicokinetic Parameters (3-Month Study in Dogs)

Day 1

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
1*	0.171	0.171	1.44	1.44	7.25	0.159	0.159	1.29	1.29	4.25
5	1.13	0.226	8.36	1.672	1	1.11	0.222	7.95	1.59	1
10	2.96	0.296	22.2	2.22	1	3.07	0.307	20.6	2.06	1

Day 28

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
1*	0.226	0.226	2.18	2.18	1	0.257	0.257	2.21	2.21	1
5	1.48	0.296	11.1	2.22	1	1.59	0.318	14.4	2.88	4.25
10	4.51	0.451	37.5	3.75	1	5.12	0.512	45.3	4.53	4

Day 105

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
1*	0.258	0.258	2.27	2.27	1	0.273	0.273	2.4	2.4	1
5	1.4	0.28	13.8	2.76	1	2.06	0.412	17.3	3.46	1
10	3.95	0.395	32.2	3.22	1	3.9	0.39	44.9	4.49	1

*Dose: mg/kg/day; Cmax: µg/mL; $AUC_{0\text{-}24h}$: µg*h/mL; Tmax: hr

Study title/Study number: A 28-Day Toxicity and Toxicokinetic Study of LOXO-305 in Sprague-Dawley Rats with a 28 Day Recovery Phase /LOXO-305-TOX007

Oral doses of pirtobrutinib (males: 50, 150 or 500 mg/kg/dose BID; females: 20, 60 or 175 mg/kg/dose BID) administered via gavage for 4 weeks were tolerated up to 1000 mg/kg/day

(males) and 120 mg/kg/day (females). Findings in the high dose groups included mean group weight and weight gain reductions (≥ 10% in males), decreased circulating white blood cells (total and differential counts), and lymphoid depletion in the spleen and mesenteric lymph node. The findings were partially recovered. Three unscheduled deaths occurred in females treated with 350 mg/kg/day. Although evidence of gavage errors and related stress were noted and attributable to the mortality of these rats, the characteristic lymphoid effects of pirtobrutinib (inflammation in multiple organs and related changes of clinical pathological parameters) found in these rats cannot be discounted. Histopathological findings in the pancreas were mainly associated with the islet of Langerhans (inflammation, fibrosis, hemorrhage and pigment deposit) and acinus (atrophy) in all pirtobrutinib treated rats with no apparent dose dependence. The pancreatic findings were not accompanied by elevated serum lipase and/or amylase and were recoverable.

Study title/Study number: A 28-Day Twice Daily Oral Gavage Toxicity and Toxicokinetic Study of LOXO-305 in Beagle Dogs with a 28 Day Recovery Phase /LOXO-305-TOX008

Oral doses of pirtobrutinib resulted in adverse effects in dogs at the high (180 mg/kg/day then 120 mg/kg/day; as twice daily administration) and mid (60 mg/kg/day then 20 mg/kg/day) doses, and in some dogs at the low dose (20 mg/kg/day then 10 mg/kg/day). Pirtobrutinib was not tolerated at 60 mg/kg/day and 180 mg/kg/day. Dose reduction, dosing holidays and veterinary care did not prevent the sacrifice of all dogs at the high dose on Day 13 due to moribund conditions. The main findings were GI related clinical signs, reduced food intake, decreased erythrocyte, platelet, WBC, neutrophil and lymphocyte counts, and increased fibrinogen. These findings were consistent with inflammation in the lungs/large intestines, lymphoid depletion, and hypocellularity in the bone marrow. The target tissues of pirtobrutinib included the bone marrow, lymphoid organs, lung and large intestines.

5.5.2 Genetic Toxicology

The Applicant's Position:

Pirtobrutinib is an aneugenic genotoxicant; however, human exposure at 200 mg QD is 12-fold lower than the no effect level for this genotoxicity in rats. Thus, this is not a significant risk for cancer patients. Pirtobrutinib is not mutagenic.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment, except for the estimation of the exposure margin. Additional details regarding the genetic toxicology studies are provided in the review below.

In vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/number: Bacterial reverse mutation assay/LOXO-305-TOX-009 (GLP compliant)

Key findings:

- Pirtobrutinib at concentrations up to 5000 □g/plate did not increase the number of variant colonies in any of the test strains with or without S9 activation.

To test for mutagenicity, histidine-requiring strains (*Salmonella typhimurium* TA98, TA1535, and TA1537, and *E. coli* WP2*uvr*A) were incubated with pirtobrutinib in the presence and absence of metabolic activation (rat live S9 fraction), and the resultant number of variant colonies were determined. Appropriate conventionally used positive controls or the negative control (DMSO) were used in the study. No evidence of toxicity was observed up to 5000 □g/plate, while precipitation was observed at 5000 µg/plate in all strains in the absence and presence of S9.

In vitro Assays in Mammalian Cells
In vitro micronucleus test
Study title/number: REDX08608: In vitro microwell micronucleus screening assay in Chinese hamster ovary cells/LOXO-305-TOX-013 (non-GLP)

Key findings:

- In cultured Chinese hamster ovary cells, pirtobrutinib did not induce increases in the number of micronucleated (MN) cells in the presence or absence of metabolic activation.

Pirtobrutinib induced roughly concentration-dependent increases in the frequency of bi-nucleated cells with micronuclei (MN-BN) under most of the treatment conditions, but the increase was not significant, except for a statistically significant increase under non-activated 24-hour treatment at 5 µg/mL. However, the increase was within the range of the historical negative control data (0.72% to 2.05%). The table below is the summary of micronuclei induction in the respective condition:

Treatment condition	Treatment time	Pirtobrutinib □□g/mL)	Percent increased of micronucleus	Positive control
Non-activated	3 hours	30, 70, 130	1%, 1.21%, 1.3%	MMC 0.3 µg/mL, +26.66%
	24 hours	0.5, 1, 2, 5	1.39%, 1.06%, 1.23%, 2.01%*	MMC 0.1 µg/mL, +23.2%
S9-activated	3 hours	20, 30, 50, 100, 130	1.07%, 1.23%, 1.34%, 1.5%, 1.54%	CP 5 µg/mL, +17.4%

MMC: Mitomycin C; CP: cyclophosphamide monohydrate
* Statistically significant
cytotoxicity (> 50% cytotoxicity relative to the vehicle control) was observed at concentrations > 130 µg/mL in both the S9-non-activated and activated 3-hour exposure conditions and at concentrations > 5 µg/mL in the non-activated 24-hour exposure condition; Precipitation was observed at 350 µg/mL

Study title/study number: In vitro micronucleus assay in human peripheral blood lymphocytes (HPBL)/LOXO-305-TOX-010 (GLP compliant)

Key findings:

- Under the study conditions, pirtobrutinib was positive for the induction of micronuclei in cultured human peripheral blood lymphocytes with or without S9 activation.

Human lymphocyte cells were prepared from the pooled blood of a healthy nonsmoking female donor. Lymphocytes were mitogen stimulated by phytohemagglutinin (PHA), and the following treatments were employed 48 hours later. Cytotoxicity (≥45% cytokinesis-blocked proliferation index (CBPI) relative to the vehicle control) and precipitation were used as the limit for the concentration selected. Cytotoxicity: 14.4- 479 µg/mL, precipitation: 479 µg/mL

Pirtobrutinib induced statistically significant and concentration-dependent increases in micronuclei induction in the following conditions:

Treatment condition	Treatment time	Pirtobrutinib (µg/mL)	Percent increased of micronucleus	Positive control
Non-activated	4 hours	50, 120, 150	0.85%, 1.25%, 3.5%	None*
	24 hours	5, 12, 16	1.45%, 3.95%, 3.68%	VB: 10 ng/mL, +3.8%
S9-activated	4 hours	50, 100, 225	NS, 1.2%, 3.3%	CP 5 µg/mL, +1.6%

*Mitomycin C (MMC 0.4 and 0.5 µg/mL) was listed in the protocol; however, it states that if +S9 and-S9 are tested concurrently, the positive control without S9 for the 4-hour exposure will be eliminated.
The percent increases in the table were statistically significant, unless indicted, i.e., NS (not statistically significant); VB: vinblastine; CP: cyclophosphamide monohydrate

Study title/study number: In Vitro human lymphocyte micronucleus assay with mechanistic fluorescent in situ hybridization (FISH) Analysis of Micronuclei/LOXO-305-TOX-014 (GLP compliant)

Key findings:

- Pirtobrutinib induced increases in the number of micronucleated (MN) cells at concentrations of 12 and 16 µg/mL without S9 activation following the exposure to pirtobrutinib for 24 hours.
- The use of FISH with pan-centromeric DNA probes demonstrated that micronuclei were generated via a predominantly aneugenic mechanism at 12 and 16 µg/mL.

Test system: Human lymphocyte cells; pre-treatment with phytohemagglutinin (PHA) for mitogen stimulation 48 hours prior to pirtobrutinib treatment; exposure to pirtobrutinib of 24 hours without S9 activation; fluorescence in situ hybridization (FISH) with pan-centromeric DNA probes

Study Design and Study Result

Pirtobrutinib Conc (µg/mL)	Cytotoxicity[a] (%)	MNBN Cell Freq (%)	Centromere+[b] (%)
0 (control)	--	0.40	NC
1.25	0	0.35	NC
2.5	3	0.65	NC
5	5	0.40	NC
12	29	4.7*	67
16	54	10*	79

Abbreviations: Conc = concentration, DMSO = dimethylsulfoxide, Freq = frequency, HPBL = human peripheral blood lymphocytes, MN-BN = bi-nucleated cells with micronuclei, NC=not calculated

*Fisher's Exact test: $p \leq 0.001$

[a] Based on replication index relative to DMSO vehicle control

[b] Percentage of cells that were centromere positive

(Table from the Applicant)

Historical vehicle control range for frequency of micronucleated binucleates (MNBN) cells/cells scored (%): 0.1%-1.4%

Based on the positive response at 12 and 16 µg/mL, which showed a statistically significant linear trend, FISH analysis was performed to ascertain the predominant mechanism of action of micronucleus induction. In the FISH analysis, mitomycin C (MMC) and noscapine (NOS) were employed as clastogenic and aneugenic positive control chemicals, respectively.

Summary of FISH Analysis

	LOXO-305 12 mg/mL	LOXO-305 16 mg/mL	MMC 0.2 mg/mL	NOS 30 mg/mL
C-MN	33%	21%	85%	27%
C+MN	67%	79%	15%	73%
MN mechanism	Predominantly aneugenic mechanism	Predominantly aneugenic mechanism	Predominantly clastogenic mechanism	Predominantly aneugenic mechanism

Analysis was conducted in 100 micronucleated (MN) cells; C+MN=% of cells that were centromere positive; C-MN=% of cells that were centromere negative (100%=C+MN plus C-MN).

In vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/study number: In vivo mammalian erythrocyte micronucleus assay in rats/LOXO-305-TOX-016 (GLP compliant)

Key findings:

- Under the conditions of the assay described in this report, pirtobrutinib was negative for the induction of micronucleated polychromatic erythrocytes (MnPCEs).
- The Cmax at the no-observed-effect-level (NOEL) of 2000 mg/kg was 3620 ng/mL for males and 25900 ng/mL for females. At the Cmax, the unbound (free) plasma concentration was 3300 ng/mL (3.3 µg/mL).

GLP compliance: Yes.

Test system: Sprague Dawley rats (Crl:CD(SD)) were administered a single dose of pirtobrutinib (LOXO-305, potency 98.8%) ranging between 250-2000 mg/kg via oral gavage (dosing volume 20 mL/kg); the rats were euthanized and bone marrow was collected at 24 and/or 48 hours post treatment. The highest dose in the dose range finding study was 2000 mg/kg, the recommended limit dose in a guidance. The sampling time was as follows: 0 (vehicle; 24 and 48 hr sampling), 250 (24 hr sampling), 500 (24 hr sampling), 1000 (24 hr sampling), or 2000 (24 and 48 hr sampling) mg/kg/day.

Study is valid: Yes.

Genotoxicity Assessment for Impurities

Key finding:
No outstanding issues.

Genotoxicity potential assessments for impurities in the drug substance (DS)
Bacterial reverse mutation (Ames) test (GLP compliant studies):

- Tester strains: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvr*A
- The concentration of the test article was up to 5000 µg/plate.
- Vehicle control: DMSO

- The impurities tested: (b) (4)

Results:
Under the conditions of the study, all the tested impurities were negative in the Ames test with or without S9 activation.

Exposure margins and conclusions
Based on the safety margins from an in vitro genotoxicity study showing pirtobrutinib-related aneugenicity (study LOXO-305-TOX-014), as well as margins from the in vivo genotoxicity study showing no genotoxic effects (study LOXO-305-TOX-016), pirtobrutinib will be treated as non-genotoxic for recommendations on the duration of contraception in patients.

Exposure Multiples from the Rat Micronucleus Assay

	Total	Unbound (free)
*Cmax (µg/mL)	6.46	0.323
**Multiple (fold)	25.9/6.46= 4	3.4/0.323= 10.5

*Protein binding in humans is 95% (or free portion as 5%)
** Exposure Multiple: the exposure in rats/the exposure in patients
Based on total and unbound (free) Cmax of 25.9 µg/mL and 3.4 µg/mL, respectively, in female rats at NOEL of 2000 mg/kg (Protein binding 87.1%, or free portion as 13%).

Exposure multiples from the in vitro genotoxicity study (LOXO-305-TOX-014)
Pirtobrutnib concentration resulting in aneugenicity: 12 µg/mL
Cmax in patients at the recommended dose= 6.46 µg/mL (total); 0.323 µg/mL (unbound)
Exposure multiple= 37 (unbound)

5.5.3 Carcinogenicity

The Applicant's Position:

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

The FDA's Assessment:
No carcinogenicity studies have been conducted.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility risks of pirtobrutinib were assessed in repeat-dose toxicity studies. No effects on male or female reproductive organs were observed in any study. Pirtobrutinib caused embryofetal toxicity and malformations in pregnant rats treated during the period of embryogenesis in the absence of significant maternal toxicity. These effects occurred at clinically relevant exposure levels based on human PK. This risk will be managed by appropriate labeling regarding use of contraception.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's assessment. The FDA's review of the embryo-fetal development study in rats is provided below.

Study title/ number An Enhanced Pilot Embryo-fetal Development Study of LY3527727 Administered by Oral Gavage Twice Daily to Rats/#LOXO-305-TOX-019

Key Study Findings

- Orally administered pirtobrutinib during organogenesis induced embryofetal developmental (EFD) toxicities at ≥ 375 mg/kg twice daily doses. EFD findings included decreased fetal body weights, increased incidence of malformations or variations in the urinary tract (dilated ureters; absent or structurally abnormal kidneys), reproductive system (malpositioned ovaries and misshapen uterus), and bone (misshapen sternebrae). There were no maternal toxicities at the highest dose, 500 mg/kg twice daily, used in the study.
- The 500 mg/kg twice daily dose caused total resorption.
- At 375 mg/kg twice daily in rats, the maternal systemic exposures (mean AUC of 272 mcg/mL*h) were approximately 3-fold the recommended human exposure at 200 mg (mean AUC of 91.3 mcg/mL*h).

GLP compliance:	Yes
Methods	
Dose and frequency of dosing: LOXO-305 (pirtobrutinib): potency 96.1%	25, 75, 375 or 500 mg/kg/dose (as LD, MD1, MD2, and HD) twice daily (BID; 50, 150, 750, or 1000 mg/kg/day); twice daily dosing starting on gestation day (GD) 6 through GD 17
Route of administration:	Oral gavage (5 mL/kg)
Formulation/Vehicle:	0.5% (w/v) hydroxypropyl methylcellulose (HPMC) in Ultra-Pure Water
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	10/timed pregnant females/group
Satellite groups:	Toxicokinetics: n=8/group (except for the vehicle control, n=4) with dosing from GD 6 through GD 17. Blood samples

	were obtained at the following time points on GD 6 and GD 17: 0 (predose), 1, 2, 4, 6, 8, and 24 hours postdose (n=3/timepoint).
Study design:	Pregnant female rats (10-11 weeks of age) were administered pirtobrutinib once daily on GD 6-17, scheduled necropsy/cesarean section conducted on GD 20.
Deviation from study protocol affecting interpretation of results:	No

Observations and results

Parameters	Major findings
Mortality (maternal)	No treatment-related mortality. One control female was euthanized moribund for humane reasons.
Clinical signs (maternal)	Discolored teeth in dams at ≥ 150 mg/kg/day, starting on GD 10; a condition not considered adverse.
Body weights (maternal)	There were no statistically significant changes in mean body weight gain at any of the doses tested throughout the treatment period. There were no dose-related or statistically significant changes from the control in gravid uterus weights, mean body weights, or corrected body weight (BW; GD 21). Reductions in corrected body weight gain (GD 6-GD 21) occurred at 750 mg/kg/day and 1000 mg/kg/day (↓10% and ↓13%, respectively). Corrected BW = BW on GD 21 minus gravid uterus weight Corrected BW gain = BW gain from GD 6-21 minus gravid uterus weight
Food consumption	A non-dose-dependent, transient reduction in food consumption was observed between GD 6-7 at 750 mg/kg/day and 1000 mg/kg/day compared to controls (↓24% and ↓15%, respectively). No remarkable changes in the overall food consumption (GD 6-18) were observed in the treated animals.
Necropsy findings Cesarean section uterine data	There were no remarkable gross anatomical findings in the treated dams. One female (#5509) at 1000 mg/kg/day had total resorption. The incidence of dams with total resorption of the litter was 10% in this group (i.e., one out of 10 dams). The incidence was higher than the laboratory's historical control data for this strain of rats (5%); therefore, the finding was treatment-related. The increased numbers of early (1.6) and late (0.3) resorption, and hence higher post-implantation loss (15.1%) for this group of dams were attributable to the total resorption in dam #5509. There were no findings at ≤ 750 mg/kg/day.

Summary of Uterine Examination Data

Endpoints	Dose level (mg/kg/day)				
	0	50	150	750	1000^
# of females mated	10	10	10	10	10
# of pregnant females	10	10	10	10	10
Pregnancy rate (%)	100	100	100	100	100
Unscheduled euthanasia	1	0	0	0	0
# with all dead or resorbed fetuses	0	0	0	0	1
Gravid uterine weight (g)	115.33	112.8	113.31	105.26	112.51
Corpora lutea	14.6	16.7	14.4	15.5	16.5
Implantations	14	15.4	13.6	14.5	15.2
Pre-implantation loss (%)	3.81	7.09	5.27	6.15	7.64

Post-implantation loss (%)		4.86	8.09	2.11	6.34	15.14 (1.6-12.8%)*
Sex ratio (% males)/litter		48.87	49.74	49.55	44.78	56.49
Fetuses	Live	13.3	14.2	13.3	13.6	13.3
	Dead	0	0	0	0	0
Resorptions	Early	0.7	1.2	0.3	0.8	1.6
	Late	0	0	0	0.1	0.3
	Total	0.7	1.2	0.3	0.9	1.9 (0.2-1.8)*

*Numbers represent the historical control range (based on 20-22 fetuses).

Necropsy findings

Offspring

While no treatment-related changes in maternal mean body weights or corrected body weights were observed, fetal weights were statistically significantly lower at ≥ 750 mg/kg/day (approximately 10% and 13% reduction from the control, respectively).

Mean fetal weights (g)

	Dose level (mg/kg/day)				
	0	50	150	750	1000
Males	6.51	6.06	6.43	**5.92***	**5.59****
Females	6.15	5.89	6.11	**5.69***	**5.59****
Total	6.33	5.96	6.28	**5.78****	**5.54****

*P≤0.05, **P≤0.01; Bolded numbers indicting statistically significant changes compared to the control

At ≥750 mg/kg/day, visceral variations and malformations were observed in the kidney, ureter, ovary, and uterus. These malformation findings are not present in the test laboratory's historical control data for Sprague Dawley rats.

There were no malformations noted at the external and visceral examinations in the control or 150 mg/kg/day groups.

Summary of fetal findings: malformations and variations

	Dose level (mg/kg/day)				
	Control	50	150	750	1000
Total No. Litters	120	142	133	136	133
Total No. Fetuses	9	10	10	10	9
Visceral: No. fetuses examined	61	72	68	67	65
Abdomen malformation					
No. fetuses/No. litters	0/0	0/0	0/0	3/3	8/3
% of fetuses with findings*	0	0	0	4.76	11.79
Abdomen variations					
No. fetuses/No. litters	7/2	2/2	1/1	13/5	22/5
% of fetuses with findings*	11.57	2.68	1.43	20.54	30.82
Thoracic malformations					
No. fetuses/No. litters	0/0	1/1	0/0	0/0	0/0
% of fetuses with findings*	0	1.25	0	0	0
Skeletal variations					
Skeletal: No. fetuses examined	59	70	65	69	68
No. fetuses/No. litters	45/9	50/10	41/10	45/10	54/9
% of fetuses with findings*	75.71	69.11	63.38	63.99	79.67

*K values= fetuses with findings/total fetuses examined x 100%; based on Kruskal-Wallis & Dunn

Select fetal visceral observations: malformations

Observations	Dose level (mg/kg/day)		
	0	750	1000
Number of litters examined	9	10	9
Number of visceral examinations	120	136	133
Kidney			
Absent Fetus N/%	0/0.00	0/0.00	**7/10.21***
Litter N/%	0/0.00	0/0.00	3/33.3

Malpositioned Fetus N/%	0/0.00	2/3.1	0/0.00
Litter N/%	0/0.00	2/20.0	0/0.00
Misshapen Fetus N/%	0/0.00	2/3.1	1/1.59
Litter N/%	0/0.00	2/20.0	1/11.1
Small Fetus N/%	0/0.00	2/3.1	1/1.59
Litter N/%	0/0.00	2/20.0	1/11.1
Ovary			
Malpositioned Fetus N/%	0/0.00	0/0.00	4/5.64
Litter N/%	0/0.00	0/0.00	2/22.2
Uterus			
Misshapen Fetus N/%	0/0.00	0/0.00	4/5.64
Litter N/%	0/0.00	0/0.00	2/22.2
Ureter			
Absent Fetus N/%	0/0.00	0/0.00	7/**10.21***
Litter N/%	0/0.00	0/0.00	3/33.3

Bolded numbers represent statistically significant changes compared to the control; *=p≤0.05 (Kruskal-Wallis & Dunn)

Select fetal visceral observations: alterations

Observations	Dose level (mg/kg/day)		
	0	750	1000
Number of litters examined	9	10	9
Number of visceral examinations	120	136	133
Kidney			
Renal papilla, absent Fetus N/%	0/0.00	1/1.67	1/1.59
Litter N/%	0/0.00	1/10.0	1/11.1
Renal papilla, small-moderate Fetus N/%	0/0.00	1/1.67	2/2.78
Litter N/%	0/0.00	1/10.0	1/11.1
Renal papilla, small-severe Fetus N/%	0/0.00	3/4.76	5/7.54
Litter N/%	0/0.00	2/20.0	3/33.3
Ureter			
Dilatation moderate Fetus N/%	2/3.7	3/4.29	7/9.46
Litter N/%	1/11.1	2/20	4/44.4
Dilatation severe Fetus N/%	4/6.48	11/17.68	16/22.75
Litter N/%	2/22.2	4/40	5/55.6

Findings of visceral variations in the liver and renal veins were not dose-dependent and not likely pirtobrutinib-related.

Select fetal skeletal observations (Variations)

Observations	Dose level (mg/kg/day)		
	0	750	1000
Number of litters examined	9	10	9
Number of visceral examinations	120	136	133
Skull			
Interparietal, incomplete ossification Fetus N/%	15/25.26	3/**4.11***	7/12.24
Historical range: 2.27-44.29%			Within range
Litter N/%	7/77.8	2/20.0	5/55.6
Historical range: 9.09-80.95%			Within range
Sternebra			
Sternebra, misshapen Fetus N/%	0/0.00	0/0.00	4/**5.64***
Historical range: 0-1.96%			Greater than range
Litter N/%	0/0.00	0/0.00	4/44.4
Historical range: 0-14.29%			Greater than range
Vertebra			
Lumbar arch, isolated ossification site Fetus N/%	8/14.09	26/37.08	25/**37.37***
Historical range: 0-16.8%			Greater than range

	Litter N/%	4/44.4	8/80.0	8/88.9
	Historical range: 0-62.5%			Greater than range
	Thoracic centrum, incomplete ossification, Fetus N/%	34/55.66	16/**23.39***	15/**22.06****
	Historical range: 0-57.97%			Within range
	Litter, N/%	9/100	9/90.0	7/77.8
	Historical range: 0-100%			Within range

Bolded numbers represent statistically significant changes compared to the control; *P≤ 0.05, **P≤0.01 (Kruskal-Wallis & Dunn)

TK

Mean TK parameters on GD 19/20^

Dose level (mg/kg/dose)	$AUC_{0\text{-}24hr}$ (mg*hr/mL) GD 6	$AUC_{0\text{-}24hr}$ (mg*hr/mL) GD 17	C_{max} (mg/mL) GD 6	C_{max} (mg/mL) GD 17	Tmax (Hours)
25	60.4	40.2	3.87	2.36	13
75	106	106	7.27	7.03	16
375	252	272	16.7	15.9	13-16
500	315	331	19.7	21.6	13-16

There was no apparent accumulation of exposures to pirtobrutinib. The exposure on both days increased in a less than dose proportional manner when the lowest dose (25 mg/kg/dose) was compared to the highest dose (500 mg/kg/dose).

5.5.5 Other Toxicology Studies

The Applicant's Position:

A GLP in vitro neutral red uptake phototoxicity assay was conducted in BALB/c 3T3 mouse fibroblasts with pirtobrutinib. Pirtobrutinib was not found to be phototoxic in this study.

In a GLP impurity qualification study, pirtobrutinib with and without impurities (b) (4) was administered to Sprague Dawley rats for 2 weeks. There was no difference in the toxicity profile between the two lots of pirtobrutinib and there were no new findings compared to previously conducted GLP rat studies.

The FDA's Assessment:
FDA concurs. See additional information below on impurity qualification.

Study title/ number: An Impurity Qualification Study in Rats Administered (b) (4) by Oral Gavage Twice Daily/#LOXO-305-TOX-020 (GLP compliant)

Key findings
To qualify impurities, rats were treated with pirtobrutinib (LOXO-305, (b) (4) or impurity-spiked LOXO-305 at oral doses of 300 mg/kg twice daily (BID, or 600 mg/kg/day) for 2 weeks. The toxicity profiles were comparable for these two groups. Thus, the impurities did not introduce additional toxicities, and the impurities were qualified up (b) (4) for (b) (4) respectively.

X	X
Primary Reviewer	Supervisor

6.0 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The Applicant is seeking accelerated approval of JAYPIRCA (pirtobrutinib) for the treatment of adult patients with mantle cell lymphoma (MCL) who have been previously treated with a Bruton tyrosine kinase (BTK) inhibitor. The proposed dosing regimen is 200 mg daily without regards to food. The primary evidence of efficacy supporting the proposed dosing regimen is overall response rate (complete response + partial response) demonstrated in a Phase 1/2 open-label study (LOXO-BTK-18001) in patients with previously treated CLL/SLL and B-cell NHL. The overall response rate in 120 patients with MCL was 50%. Adverse reactions led to treatment interruptions, dose reductions, and treatment discontinuations in 41 (32%), 6 (4.7%), and 12 (9.4%) of patients, respectively.

The clinical pharmacology section of the NDA is supported by single and multiple dose pharmacokinetic (PK) characterization, an ADME study, a food effect study, an intrinsic factors/special populations (hepatic and renal impairment), drug interaction studies (pirtobrutinib as victim and as perpetrator), a PBPK simulation, a QT/QTc assessment, population PK (popPK) and exposure-response analyses for efficacy, safety, and pharmacodynamics.

The Clinical Pharmacology Review focused on the acceptability of the proposed dosing regimen as well as the drug-drug interaction potential, organ impairment, population PK and exposure-response analyses for safety and efficacy.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 216059. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from the phase 1/2 study LOXO-BTK-18001 in the target population. The overall response rate of 50% was demonstrated in 120 patients with MCL previously treated with a BTK inhibitor.

General dosing instructions	The proposed dosing regimen is 200 mg daily without regards to food. No clinically relevant food effect was observed following co-administration of pirtobrutinib with a standard high-fat meal.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dose modifications are recommended: ▪ **Severe renal impairment:** Reduce the dosage to 100 mg daily if the current dose is 200 mg, otherwise reduce the dose by 50 mg. If the current dosage is 50 mg once daily, discontinue JAYPIRCA. ▪ **Strong CYP3A inducers:** Avoid concomitant use. ▪ **Moderate CYP3A inducers:** Avoid concomitant use. If concomitant use cannot be avoided and the current pirtobrutinib dosage is 200 mg daily, increase the dose to 300 mg, otherwise increase the dose by 50 mg. ▪ **Strong CYP3A inhibitors:** Avoid concomitant use. If concomitant use cannot be avoided, reduce the JAYPIRCA dose by 50 mg.
Labeling	Additions to the Applicant's proposed labeling include dose reduction in patients with severe renal impairment, avoidance or dose increase with concomitant use of moderate CYP3A inducers, avoidance of concomitant use with strong CYP3A inducers, and avoidance or dose reduction with concomitant use of strong CYP3A inhibitors.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

The pharmacokinetics of pirtobrutinib were studied in healthy subjects and in patients with hematological malignancies. Pirtobrutinib exposures (AUC and C_{max}) increased proportionally with increasing dose in the 25 mg to 300 mg QD dose range in patients with cancer and increased proportionally with increasing dose in the 300 mg to 800 mg single dose range in healthy participants. Following oral administration, pirtobrutinib reaches C_{max} approximately 2 hours after dosing. Pirtobrutinib has an estimated mean elimination half-life of 18.8 hours, and steady state is achieved after approximately 5 days of QD dosing. For Phase 2 patients who received the proposed dose of 200 mg QD, popPK model-estimated mean $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$ were 6460 ng/mL (26% CV), 2260 ng/mL (65% CV), and 91300 ng*h/mL (41% CV), respectively.

Absorption

- The absolute bioavailability of pirtobrutinib is 85.5%.
- Maximum concentrations of pirtobrutinib are achieved at approximately 2 hours after dosing.

Distribution

- The mean apparent oral volume of distribution for pirtobrutinib is 52.3 L in patients with cancer.
- Pirtobrutinib is moderately bound to plasma proteins and serum albumin, with a mean bound fraction of approximately 95% and 98%, respectively.

Metabolism

- The primary clearance pathways involved in pirtobrutinib metabolism are oxidative, hydrolytic, and direct glucuronidation.
- The major metabolite M1 represented 10.4% of total daily pirtobrutinib-related exposure (pirtobrutinib + M1). M1 does not inhibit BTK in vitro at clinically relevant concentrations.

Elimination

> Pirtobrutinib is cleared both in the feces and renally with 18.2% and 10% of the radioactive dose recovered as unchanged pirtobrutinib in feces and urine, respectively.
>
> The mean apparent oral clearance of pirtobrutinib is 2.02 L/h, and the mean elimination $t_{1/2}$ is estimated to be 18.8 hours in patients with cancer.

The Applicant's Position:

Overall, the clinical pharmacology profile of pirtobrutinib is considered supportive of the planned commercial dose of 200 mg QD.

The FDA's Assessment:
Pirtobrutinib is extensively protein bound (i.e., fraction unbound < 10%). Otherwise, the general clinical pharmacology profile appropriately characterizes the PK of pirtobrutinib in cancer patients. The Applicant's PopPK model-estimated parameters are similar to those derived based on observed data from patients from Study 18001. See Section 6.2.2 for FDA's assessment of the proposed dosing regimen of pirtobrutinib 200 mg once daily.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

The RP2D of 200 mg QD was established at the end of the Phase 1 portion of Study 18001 based on the PK, safety, and antitumor activity data available at the time. This dose was selected as the starting dose for all patients in Phase 2 and has since proven to provide meaningful benefit in the MCL patient population with a well-tolerated safety profile in patients with hematological malignancies receiving pirtobrutinib monotherapy.

Exposure-response analyses to evaluate the range of safe and efficacious exposures in MCL patients identified a wide therapeutic window for pirtobrutinib (Section 6.3.1)).

The Applicant's Position:

The 200 mg QD dose is both efficacious and safe and allows flexibility to accommodate a wide range of intrinsic/extrinsic patient factors (e.g., renal impairment, CYP3A modulators) with no expected change in safety or treatment benefit, and thus no dose adjustment of pirtobrutinib.

The FDA's Assessment:
Although FDA agrees that pirtobrutinib 200 mg daily appears to be an appropriate dosing

regimen based on the overall benefit-risk profile in patients with MCL, but there are limited data and unknown efficacy and safety profiles at doses below 200 mg (n=6) or above 200 mg (n=7) to determine if 200 mg daily is the optimal dosing regimen.

FDA does not agree with the Applicant's position that (b) (4) . Refer to Section 6.3.2.3 and 6.3.2.4 for specific recommendations for dosage adjustment for severe renal impairment and concomitant use of CYP3A modulators.

6.2.2.2 Therapeutic Individualization

Data:
Please see Section 6.3.1.

The Applicant's Position:

(b) (4) .
Pirtobrutinib can be taken orally with or without food, and administered to patients with mild hepatic impairment, (b) (4)

The FDA's Assessment:
FDA does not agree with the Applicant's position that (b) (4) Refer to Section 6.3.2.3 and 6.3.2.4 for specific recommendations for dosage adjustment for severe renal impairment and concomitant use of CYP3A modulators.

6.2.2.3 Outstanding Issues

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant that there are no outstanding clinical pharmacology issues.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

Pirtobrutinib has been administered at doses ranging from 25 mg to 300 mg QD in patients with cancer as well as at single doses ranging from 200 mg to 900 mg and multiple doses of 200 mg QD in healthy participants. Pirtobrutinib PK is comparable between healthy participants and patients with cancer.

The RP2D of 200 mg QD was established at the end of the Phase 1 portion of Study 18001 based on the PK, safety, and antitumor activity data available at the time. This dose was selected as the starting dose for all patients in Phase 2 and has since proven to provide meaningful benefit in the MCL patient population with a well-tolerated safety profile in patients with hematological malignancies receiving pirtobrutinib monotherapy. At the proposed dose of 200 mg QD, popPK model-estimated mean $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$ were 6460 ng/mL (26% CV), 2260 ng/mL (65% CV), and 91300 ng*h/mL (41% CV), respectively.

Exposure-response analyses to evaluate the range of safe and efficacious exposures in MCL patients identified a wide therapeutic window for pirtobrutinib. At the RP2D of 200 mg QD, 96% of patients are predicted to exceed 90% inhibition of BTK, and 63% of patients are predicted to achieve concentrations which exceed 96% inhibition of BTK across the entire dosing interval. The recommended starting dose of 200 mg QD therefore allows patients to experience extensive and sustained BTK inhibition, which is shown to yield treatment benefit.

Absorption

- The absolute bioavailability of pirtobrutinib is 85.5%.
- Maximum concentrations of pirtobrutinib are achieved at approximately 2 hours after dosing.
- Food does not have a clinically meaningful effect on pirtobrutinib PK.

Distribution

- The mean systemic volume of distribution of pirtobrutinib after an IV dose is 36.3 L in healthy participants.
- The mean apparent oral volume of distribution for pirtobrutinib is 52.3 L in patients with cancer.
- Pirtobrutinib is moderately bound to plasma proteins and serum albumin, with a mean bound fraction of approximately 95% and 98%, respectively.

Metabolism

- The primary clearance pathways involved in pirtobrutinib metabolism are oxidative, hydrolytic, and direct glucuronidation.
- Pirtobrutinib constitutes the majority (73%) of the drug-related exposure in human plasma, with 3 minor metabolites, an oxidative ring opening of the pyrazole ring (M1 or LSN3828720), a direct N glucuronide (M2 or LSN3829057), and a mono-oxy glucuronide (M4), each accounting for a mean of 7.8%, 3.3%, and 2.3%, respectively, in healthy participants after a single 200 mg dose.
- After multiple QD doses of pirtobrutinib 200 mg in patients, the M1 represented 10.4% of total daily pirtobrutinib-related exposure (pirtobrutinib + M1), due to the longer half-life of M1 compared to the parent drug.
- M1 does not inhibit BTK in vitro at clinically relevant concentrations.

Elimination

Following a single oral dose of 200 mg [^{14}C]-pirtobrutinib, approximately 37.3% of the total radioactive dose was recovered in the feces and 57.0% in the urine. Pirtobrutinib is cleared both in the feces and renally with 18.2% and 10% of the radioactive dose recovered as unchanged pirtobrutinib in feces and urine, respectively.

The mean systemic clearance of pirtobrutinib after an IV dose is 1.63 L/h, and the mean $t_{1/2}$ is 17.6 hours in healthy participants.

The mean apparent oral clearance of pirtobrutinib is 2.02 L/h, and the mean elimination $t_{1/2}$ is estimated to be 18.8 hours in patients with cancer.

Effect of Intrinsic Factors on Pirtobrutinib Pharmacokinetics

- Based on a popPK analysis of patients with hematological malignancies, pirtobrutinib disposition is not meaningfully affected by age, sex, body weight, race, serum albumin, (b) (4) mild hepatic impairment (LOXO-305-DMPK-081).

In a clinical pharmacology study (Study LOXO-BTK-20013), (b) (4) .

The effect of mild, moderate, and severe hepatic impairment based on Child-Pugh criteria is currently being evaluated in an ongoing clinical pharmacology study (Study LOXO-BTK-20012).

Effect of Extrinsic Factors on Pirtobrutinib Pharmacokinetics

In vitro, pirtobrutinib is metabolized by CYP3A4, UGT1A8, and UGT1A9. Pirtobrutinib is also a substrate of P-gp and BCRP. Clinically, pirtobrutinib is cleared by CYP3A4 and UGTs; (b) (4)

In a clinical pharmacology study (Study LOXO-BTK-20006), CYP3A modulation by a strong inhibitor (itraconazole) increased pirtobrutinib exposure by 49% and a strong inducer (rifampin) decreased pirtobrutinib exposure by 71%.

Inhibition of P-gp (by itraconazole or single dose rifampin) did not affect the clinical PK of pirtobrutinib.

A proton pump inhibitor, omeprazole, did not have a clinically significant impact on the overall exposure of pirtobrutinib.

Effect of Pirtobrutinib on the Pharmacokinetics of Other Drugs

The ability of pirtobrutinib to inhibit the clearance of other drugs was studied in vitro and in the clinic.

- In vitro, pirtobrutinib showed minimal inhibition (IC_{50} > 60 µM) of CYP1A2, CYP2B6, CYP2C19, and CYP2D6, and inhibition of CYP2C8, CYP2C9, and CYP3A4 with K_i values ranging from 11.7 µM to 25.2 µM in human liver microsomes. Pirtobrutinib also inhibited P-gp and BCRP, but did not inhibit OAT1, OATP1B1, OATP1B3, OCT1, OCT2, OAT3, MATE1, or MATE-2K at clinically relevant concentrations.
  - Pirtobrutinib increased the AUC and C_{max} of repaglinide (CYP2C8 substrate) by approximately 130% and 98%, respectively, demonstrating the inhibitory effect of pirtobrutinib on CYP2C8 activity.
  - Pirtobrutinib increased the AUC_{tau} and C_{max} of digoxin (P-gp substrate) by 35% and 55%, respectively, and reduced digoxin renal clearance by 12%. These results indicate that pirtobrutinib inhibits P-gp in both the intestine and the renal proximal tubules.
  - Pirtobrutinib had no clinically relevant impact on the PK of midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), S-warfarin (CYP2C9 substrate), or omeprazole (CYP2C19 substrate).
  - In patients with cancer, there was no clinically meaningful effect of pirtobrutinib on serum creatinine, a MATE1 substrate.

Exposure-Response Relationships

Exposure-response relationships were evaluated using efficacy and safety data from patients in Study 18001. No statistically significant relationship was identified between pirtobrutinib exposure and safety in the OMTSAS population (TEAEs: Grade ≥ 3 anemia, Grade ≥ 3 neutropenia, Grade ≥ 3 infection/infestation, and any grade hypertension). No statistically significant relationship was identified between pirtobrutinib exposure and efficacy, specifically ORR in the PAS.

By comparing the simulated popPK profiles at the proposed 200 mg QD dose of pirtobrutinib to the protein binding-adjusted IC_{50} for BTK in vitro, it was demonstrated that 96% of patients are

predicted to exceed 90% inhibition of BTK, and 63% of patients are predicted to achieve concentrations which exceed 96% inhibition of BTK across the entire dosing interval.

The Effect of Pirtobrutinib on the Corrected QT Interval

In a clinical pharmacology study (Study LOXO-BTK-20011), pirtobrutinib (900 mg single dose) had no clinically meaningful effect on the change in QTcF interval (for example, > 10 msec) and there was no relationship between pirtobrutinib exposure and change in QTc interval.

The Applicant's Position:

Exposure-response analyses of efficacy and safety data in patients with MCL (Study 18001), pirtobrutinib exhibits a wide therapeutic window. The proposed dose of 200 mg QD pirtobrutinib is both efficacious and safe, and dose reductions for tolerability to a minimum of 50 mg QD are expected to maintain sufficient benefit to warrant continued treatment.

No dose adjustments are recommended based on age, sex, body weight, race, ethnicity, mild hepatic impairment, (b) (4) No dose adjustment of pirtobrutinib is required when administered concomitantly with (b) (4) or inhibitors of intestinal, hepatic, or renal transporters. Pirtobrutinib can be taken orally with or without food.

Pirtobrutinib is a P-gp inhibitor (b) (4) It is advised to follow recommendations for sensitive P-gp or CYP2C8 substrates provided in their approved product labeling. No recommendations are required for coadministration for pirtobrutinib with substrates of CYP1A2, CYP2C9, (b) (4) MATE1, MATE2-K, OATP1B1, or OATP1B3.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the general pharmacology and PK characteristics of pirtobrutinib. FDA agrees that dose reduction in the event of adverse reactions to 50 mg appears acceptable to maintain pharmacological activity based on in vitro data and to allow continued treatment with pirtobrutinib. FDA does not agree that (b) (4)

Additionally, there was limited representation of Black/African American (n=1, 0.8%), Native Hawaiian or Pacific Islander (n=0, 0%), and American Indian or Alaskan Native (n=1, 0.8%) patients in the nonblastoid MCL BTK Treated Cohort of Study 18001. We therefore consider the effect of race/ethnicity, other than White (n= 100, 82%) and Asian (n= 14, 11.5%) on pirtobrutinib PK to be unknown.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

The majority of studies in the clinical pharmacology program were conducted in healthy volunteers. The primary evidence of effectiveness comes from Study 18001 in cancer patients and is discussed in Section 8.0.

The FDA's Assessment:
Study LOXO-BTK-18001 provides adequate evidence of effectiveness in the general population of patients with MCL at the recommended pirtobrutinib dosage of 200 mg once daily.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Please see Section 6.2.2.

The Applicant's Position:

Pirtobrutinib's proposed dosing regimen of 200 mg QD is appropriate for patients with pretreated MCL. Pirtobrutinib exhibits a wide therapeutic window based on exposure-response analyses, with a wide range of exposures which are both efficacious and well-tolerated. At 200 mg QD, 96% of patients are predicted to exceed 90% inhibition of BTK, and 63% of patients are predicted to achieve concentrations which exceed 96% inhibition of BTK across the entire dosing interval (24 hours). The proposed starting dose of 200 mg QD, therefore, allows patients to experience extensive and sustained BTK inhibition, which has been shown to yield treatment benefit in patients with pretreated MCL.

The FDA's Assessment:
Although FDA agrees that pirtobrutinib 200 mg daily appears to be an appropriate dosing regimen based on overall benefit-risk profile in patients with MCL, the Applicant's exposure-response analyses had significant limitations to determine if 200 mg daily is the optimal dosing regimen given that a large majority of patients with MCL received a starting dose of 200 mg. Table 14 shows that 89% (n=109/122) of patients with non-blastoid MCL received a 200 mg starting dose, and a total of 116 out of 122 received a starting dose of 200 mg or higher.

Table 14: Study 18001 Patients Disposition by Phase 2 Cohort

	Nonblastoid MCL (N=122)	Other MCL (N=28)
Starting daily dose of pirtobrutinib, n (%)		
25 mg	3 (2.5)	0
50 mg	0	0
100 mg	2 (1.6)	0
150 mg	1 (0.8)	0
200 mg	109 (89.3)	28 (100.0)
250 mg	2 (1.6)	0
300 mg	5 (4.1)	0

Adapted from Applicant's Table 13 from LOXO-BTK-18001 Study Report

The Applicant's conclusion that there were no apparent relationships between exposure and efficacy and safety was based on limited data at doses other than 200 mg and suggests that there is an unknown potential of a lower efficacious starting dose for the general patient population. Please refer to Section 19.4 for a comprehensive review and analyses of pirtobrutinib dose- and exposure-response relationships.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Please see Section 6.3.1.

The Applicant's Position:

There were no intrinsic patient factors identified which, when accounting for the wide therapeutic window of pirtobrutinib in patients with MCL, necessitate a dose adjustment or management strategy. The effect of moderate and severe hepatic impairment is currently being studied.

The FDA's Assessment:

Hepatic Impairment

The FDA agrees with the Applicant. Study LOXO-BTK-20012 was conducted in subjects with mild (n=8), moderate (n=8), or severe hepatic impairment (n=6) (per Child-Pugh classification) and healthy subjects with normal hepatic function (n=12). Pharmacokinetic analyses were performed according to Child-Pugh classification categories as well as NCI-ODWG criteria. Table 15 shows that $AUC_{0\text{-}inf}$ did not significantly change in subjects with mild or moderate impairment (90% CIs crossed 1) and decreased by 22% in subjects with severe hepatic impairment (NCI-ODWG criteria) compared to those with normal hepatic function. C_{max} did not significantly change in subjects with mild or moderate impairment (90% CIs crossed 1) and decreased by 19% in subjects with severe hepatic impairment compared to those with normal hepatic function.

Table 15: Summary LSM Analysis of Pirtobrutinib PK Parameters in Hepatic Impairment Study

Hepatic Function per NCI-ODWG	n	GMR (90% CI) vs. Normal hepatic function	
		$AUC_{0\text{-}inf}$	C_{max}
Mild	5	0.865 (0.683, 1.10)	0.943 (0.776, 1.15)
Moderate	3	0.958 (0.714, 1.28)	1.11 (0.872, 1.42)
Severe	6	0.784 (0.635, 0.968)	0.809 (0.679, 0.963)

Adapted from Table 15 in Applicant's LOXO-BTK-20012 Study Report

Similar analyses for unbound pirtobrutinib showed no statistically significant changes in $AUC_{0\text{-}inf}$ or C_{max}. When performing these analyses using the Child-Pugh classification, $AUC_{0\text{-}inf}$ was reduced by 21% (90% CI: 4.8%, 34%) in patients with severe hepatic impairment.

No dosage adjustment is needed in patients with mild, moderate, or severe hepatic impairment.

Renal Impairment

Study LOXO-BTK-20013 was conducted in subjects with severe renal impairment (n=7) and subjects with normal renal function (n=8), per CKD-EPI formula for eGFR. Enrollment of subjects with mild and moderate renal impairment was ultimately deemed unnecessary by the Applicant upon their finding of no clinically relevant effect of severe renal impairment on the PK of pirtobrutinib. Upon FDA request, the Applicant reanalyzed their data and provided PK analyses using BSA-adjusted eGFR. Consequently, only 3 evaluable subjects were classified as having severe renal impairment.

The AUC of pirtobrutinib in subjects with severe renal impairment (eGFR 15-29 mL/min) increased by 62% and mean unbound AUC increased by 68% (90% CI: 1.02, 2.77) compared to

healthy subjects with normal renal function. Apparent clearance was reduced by 35% and the half-life increased from 22 hours to 38 hours in subjects with severe renal impairment. In the popPK analysis of patients with mild renal impairment (n=304) and moderate renal impairment (n=166), there were no clinically significant differences in the apparent clearance and predicted PK of pirtobrutinib compared to subjects with normal renal function (n=121). There was an insufficient number of patients with severe renal impairment to reliable estimate the change in apparent clearance.

In patients with severe renal impairment, the JAYPIRCA dosage should be reduced to 100 mg once daily if the current dose is 200 mg once daily and otherwise reduced by 50 mg. For dosage of 50 mg once daily, JAYPIRCA should be discontinued. No dosage adjustment is recommended for mild (60-89 mL/min) or moderate (30-59 mL/min) renal impairment.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Please see Section 6.3.1.

The Applicant's Position:

There was no effect of food or concomitant medications on the PK of pirtobrutinib which require a dose adjustment of pirtobrutinib or management strategy. Pirtobrutinib inhibited P-gp and CYP2C8 in clinical studies, and therefore, guidance for the administration of pirtobrutinib with CYP2C8 substrates and sensitive P-gp substrates is included in pirtobrutinib labeling.

The FDA's Assessment:

Food Effect
Study LOXO-BTK-20009 was the Applicant's evaluation of the effect of food on the PK of pirtobrutinib and was designed and conducted in accordance with *FDA Guidance for Industry Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations*. Results from Study LOXO-BTK-20009 showed that a high-fat, high-calorie meal (800-1000 calories, 60% from fat, 15% from protein, 25% from carbohydrates) did not have a significant effect on $AUC_{0\text{-}inf}$, decreased the C_{max} of pirtobrutinib by 23% (90% CI: 11%, 33%), and delayed t_{max} by 1 hour. **Pirtobrutinib can be administered without regards to food intake.**

Effect of Acid Reducing Agents on Pirtobrutinib PK
Study LOXO-BTK-20014 was the Applicant's evaluation of the effect of acid reducing agents on the PK of pirtobrutinib and was designed and conducted in accordance with *FDA Guidance for Industry Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents:*

Study Design, Data Analysis, and Clinical Implications. Results from Study LOXO-BTK-20014 showed that following multiple doses of omeprazole 40 mg, pirtobrutinib $AUC_{0\text{-}inf}$ increased by 11% (90% CI: 1%, 16%). Additionally, the t_{max} and $t_{1/2}$ remained similar to those seen with pirtobrutinib taken alone. These changes are not considered clinically relevant, thus pirtobrutinib can be administered concomitantly with acid reducing agents without pirtobrutinib dosage adjustment.

Effect of Strong CYP3A4 Inhibitor, Strong CYP3A4 Inducer, and Moderate CYP3A4 Inducer on Pirtobrutinib PK

Study-BTK-20006 showed that co-administration of a single 200 mg dose of pirtobrutinib with itraconazole 200 mg once daily (strong CYP3A4 inhibitor) increased pirtobrutinib $AUC_{0\text{-}inf}$ by 49% with no significant change in C_{max} (Table 16). Co-administration of a single 200 mg dose of pirtobrutinib with rifampin 600 mg once daily (strong CYP3A4 inducer) decreased pirtobrutinib $AUC_{0\text{-}inf}$ by 71% and C_{max} by 42% (Table 16). PBPK DDI simulations of co-administration of 200 mg once daily dose of pirtobrutinib to steady-state and 600 mg once daily dose of efavirenz (moderate CYP3A inducer) to steady-state decreased pirtobrutinib $AUC_{0\text{-}\tau}$ by 49% and C_{max} by 33%. Similar simulations of moderate CYP3A inducers, bosentan and modafinil, predicted decreases in $AUC_{0\text{-}inf}$ of 27% and 20% and in C_{max} of 20% and 14% (Table 16). Additional simulations of concomitant use of pirtobrutinib with moderate CYP3A inhibitors diltiazem, fluconazole, and verapamil predicted increases in $AUC_{0\text{-}inf}$ of 20%, 29%, and 30% and in Cmax of 14%, 20%, and 21% (Table 16).

Table 16: Summary of Statistical Analysis of Pirtobrutinib PK parameters During Strong or Moderate CYP3A4 Induction or Inhibition

Perpetrator Drug	GMR (90% CI) vs. 200 mg pirtobrutinib alone	
	$AUC_{0\text{-}inf}$	C_{max}
200 mg Itraconazole	1.49 (1.40, 1.58)	1.04 (0.951, 1.13)
600 mg Rifampin	0.293 (0.271, 0.316)	0.576 (0.537, 0.617)
600 mg Efavirenz (predicted)	0.51 (0.48, 0.54)	0.67 (0.65, 0.69)
125 mg BID Bosentan (predicted)	0.73 (0.72, 0.75)	0.80 (0.79, 0.81)
400 mg Modafinil (predicted)	0.80 (0.79, 0.82)	0.86 (0.85, 0.87)
Diltiazem (predicted)	1.20 (1.19, 1.21)	1.14 (1.13, 1.14)
Fluconazole (predicted)	1.29 (1.27, 1.30)	1.20 (1.19, 1.21)
Verapamil (predicted)	1.30 (1.29, 1.32)	1.21 (1.20, 1.22)

Adapted from Table 9 and Table 11 in Applicant's LOXO-BTK-20006 Study Report and 07Nov22 Clinical Information Amendment

Doses should be adjusted for concomitant administration of CYP 450 3A4 inhibitors and inducers. Given that 89% of patients with MCL enrolled in Study 18001 received the 200 mg daily dose, we recommend either avoiding concomitant therapy or adjusting the pirtobrutinib

dose during concomitant use with CYP3A modulators such that resulting exposures are similar to those of the well-studied dose of 200 mg. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the pirtobrutinib dose by 50 mg. If the current dosage is 50 mg once daily, interrupt pirtobrutinib treatment for the duration of strong CYP3A4 inhibitor use. After discontinuation of a strong CYP3A inhibitor for 5 half-lives, resume the pirtobrutinib dose that was taken prior to initiating the strong CYP3A inhibitor.

Our analysis of the pirtobrutinib exposures expected to be achieved by doses lower than 200 mg showed that a reduced efficacy cannot be excluded. A 71% decrease in exposure might result in reduced efficacy, particularly at doses below 100 mg. Refer to Section 19.4 for comprehensive review and analyses of the pirtobrutinib exposure-efficacy relationship.

FDA recommends avoiding concomitant therapy with strong and moderate CYP3A inducers; however, if concomitant use with a moderate CYP3A inducer is unavoidable and the current dosage of pirtobrutinib is 200 mg once daily, increase the dose to 300 mg. If the current dosage is 50 mg or 100 mg once daily, increase the dose by 50 mg.

Pirtobrutinib Effect on Sensitive CYP3A4 Substrate

Study LOXO-BTK-20008 showed that co-administration of pirtobrutinib 200 mg once daily with a single oral dose of midazolam 500 µg increased the midazolam $AUC_{0\text{-}inf}$ by 70% and C_{max} by 58% (Table 7). Co-administration of pirtobrutinib 200 mg once daily with a single intravenous dose of midazolam 250 µg did not have a clinically meaningful effect on midazolam exposure (Table 17).

Table 17: Summary of Statistical Analysis of Midazolam PK Parameters Following Pirtobrutinib Administration

Perpetrator Drug	GMR (90% CI) vs. 500 µg oral midazolam alone		GMR (90% CI) vs. 250 µg IV midazolam alone	
	$AUC_{0\text{-}inf}$	C_{max}	$AUC_{0\text{-}inf}$	C_{max}
200 mg pirtobrutinib	1.70 (1.55, 1.86)	1.58 (1.40, 1.78)	1.12 (1.04, 1.21)	0.993 (0.834, 1.18)

Adapted from Table 12 of Applicant's LOXO-BTK-20008 Study Report

Per *FDA Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*, these results classify pirtobrutinib as a weak inhibitor of CYP3A4. In the setting of concomitant use with sensitive CYP3A4 substrates or CYP3A4 substrates with narrow therapeutic indices, this may represent clinically relevant change that warrants caution or therapy modification. For substrates of CYP3A4 where minimal concentration changes may increase the risk of adverse reaction or loss of efficacy, providers should consult the approved product labeling.

Pirtobrutinib Effect on Sensitive CYP1A2, CYP2C9, and CYP2C19 Substrates

Study LOXO-BTK-20010 was conducted to evaluate the effects of co-administration of pirtobrutinib 200 mg once daily with single oral doses of 200 mg caffeine (sensitive CYP1A2 substrate), 40 mg omeprazole (sensitive CYP2C19 substrate), and 10 mg warfarin (sensitive CYP2C9 substrate). Pirtobrutinib increased the $AUC_{0\text{-}inf}$ and C_{max} of omeprazole (sensitive CYP2C19 substrate) by 56% (90% CI: 35%, 20%) and 49% (90% CI: 31%, 70%), respectively. Pirtobrutinib decreased the $AUC_{0\text{-}inf}$ of caffeine by 6% (90% CI: 2.4%, 9.5%) and increased the $AUC_{0\text{-}inf}$ of S-warfarin by 11% (90% CI: 8%, 14%). The effects on caffeine and S-warfarin were not clinically meaningful.

Per *FDA Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*, these results classify pirtobrutinib as a weak inhibitor of CYP2C19. In the setting of concomitant use with sensitive CYP2C19 substrates or CYP2C19 substrates with narrow therapeutic indices, this may represent clinically relevant change that warrants caution or therapy modification. For substrates of CYP2C19 where minimal concentration changes may increase the risk of adverse reaction or loss of efficacy, providers should consult the approved product labeling.

Pirtobrutinib Effect on Sensitive CYP2C8 Substrate

Study LOXO-BTK-20016 was conducted to evaluate the effects of co-administration of multiple daily doses of pirtobrutinib 200 mg with a single oral dose of repaglinide (sensitive CYP2C8 substrate). Pirtobrutinib increased the $AUC_{0\text{-}inf}$ and C_{max} of repaglinide by 130% (90% CI: 86%, 184%) and 98% (90% CI: 62%, 143%), respectively. Per *FDA Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*, these results classify pirtobrutinib as a weak inhibitor of CYP2C8. For substrates of CYP2C8 where minimal concentration changes may increase the risk of adverse reaction or loss of efficacy, providers should consult the approved product labeling.

Pirtobrutinib Effect on Sensitive BCRP and P-gp Substrates

Study LOXO-BTK-20021 was conducted to evaluate the effects of co-administration of single and multiple oral doses of pirtobrutinib on the PK of multiple oral doses of digoxin (P-gp substrate). Following multiple doses of pirtobrutinib, the AUC_{τ} and C_{max} of digoxin was increased by 35% (90% CI: 29%, 42%) and 55% (90% CI: 35%, 78%), respectively. Per *FDA Guidance for Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*, these results classify pirtobrutinib as a weak inhibitor of P-gp. For substrates of P-gp where minimal concentration changes may increase the risk of adverse reaction or loss of efficacy, providers should consult the approved product labeling.

Study J2N-MC-JZNW was conducted to evaluate the effects of the co-administration of single and multiple oral doses of pirtobrutinib on the PK of rosuvastatin (BCRP substrate). Following multiple doses of pirtobrutinib, the $AUC_{0\text{-}inf}$ and C_{max} of rosuvastatin was increased by 140% (90% CI: 121%, 162%) and 146% (90% CI: 120%, 175%), respectively. Per FDA *FDA Guidance for*

Industry Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, these results classify pirtobrutinib as a moderate inhibitor of BCRP. For substrates of BCRP where minimal concentration changes may increase the risk of adverse reaction or loss of efficacy, providers should consult the approved product labeling.

X	X
Primary Reviewer	Team Leader

7.0 Sources of Clinical Data

7.1 Table of Clinical Studies

The Applicant's Position:

The safety and efficacy for this NDA submission is primarily supported by the ongoing Study 18001, entitled "A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL)". This is an open-label, multicenter study of oral pirtobrutinib to evaluate safety and efficacy in patients with CLL/SLL and B-cell NHL, including MCL, who have failed or are intolerant to standard of care. The analyses supporting this application are based on interim data (31 January 2022) from the ongoing Study 18001. As of the data cut-off date, 725 patients had been treated with pirtobrutinib monotherapy on Study 18001, including 164 patients with MCL.

In addition to Study 18001, a comprehensive clinical pharmacology program, inclusive of 11 completed clinical pharmacology studies, was conducted in healthy subjects and subjects with severe renal impairment. Two additional clinical pharmacology studies are ongoing as of the data cut-off date; one in participants with hepatic impairment, and one DDI study in healthy participants with a BCRP substrate (rosuvastatin). There were no new significant safety findings identified in the clinical pharmacology program.

Table 18: Listing of Clinical Studies

Type of Study	Study ID	Location of Study Report	Objectives	Study Design	Dosing Regimen	Enrollment	Study Population	Duration of Treatment	Study Status; Type of Report
Efficacy	LOXO-BTK-18001[b]	5.3.5.2	To evaluate MTD, efficacy, safety, and PK	Open-label, non-randomized	Monotherapy: Phase 1: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, QD Phase 2: 200 mg, QD Combination Phase 1b: Arm A: pirtobrutinib (200 mg) plus venetoclax (400 mg QD after dose ramp-up) Arm B:pirtobrutinib (200 mg) plus venetoclax (400 mg QD after dose ramp-up) and rituximab (375 mg/m^2 first dose, then 500 mg/m^2 once per cycle; 5 cycles; total 6 doses)	725[a] (monotherapy) 25[a] (combination therapy)	Patients with histologically confirmed B-cell malignancy	Continuous 28-day cycles	Study ongoing; Interim report

[a] Enrollment as of 31 January 2022

[b] Pivotal study

The FDA's Assessment:

FDA agrees with the Applicant's description of Study LOXO-BTK-18001, which is the basis of this NDA. For the clinical pharmacology findings, refer to Section 6.0.

8.0 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL) (LOXO-BTK-18001)

Trial Design

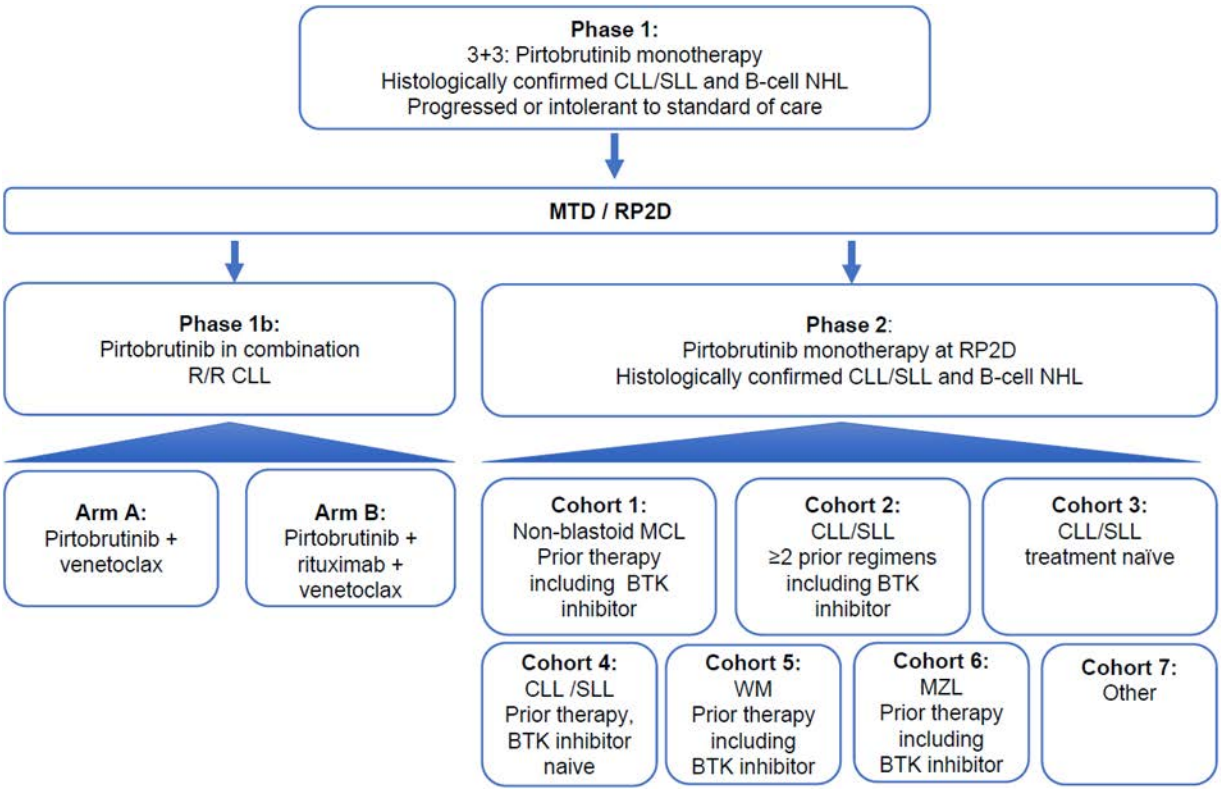
The Applicant's Description:

LOXO-BTK-18001 is an open-label, multicenter study of oral pirtobrutinib to evaluate safety and efficacy in patients with CLL/SLL and NHL who have failed or were intolerant to standard of care. This study is ongoing and includes two portions: monotherapy and combination therapy. The monotherapy portion includes Phase 1 dose escalation and dose expansion, as well as Phase 2. The combination therapy Phase 1b portion is a safety assessment and expansion of pirtobrutinib plus venetoclax with or without rituximab (or biosimilar anti-CD20 therapy).

Pirtobrutinib was self-administered in oral tablet form according to Phase 1 dose assignment (cohorts are outlined in Figure 4) and was administered at the RP2D of 200 mg QD as monotherapy in Phase 2 and at the RP2D as combination therapy in Phase 1b. Dosing was fixed as total milligram (as opposed to weight or BSA based). The starting dose of pirtobrutinib in Phase 1 was 25 mg QD. In Phase 1, an intrapatient dose escalation was allowed, provided that the patient was tolerating their current dose, and the dose level to which the patient was to be escalated had already been evaluated and was declared safe by the safety review committee.

Pirtobrutinib treatment could continue in 28-day cycles for an individual patient until PD, unacceptable toxicity, or other reasons for treatment discontinuation (LOXO-BTK-18001, Protocol Section 6.6). Patients with documented PD could continue study treatment if, in the opinion of the Investigator, the patient was deriving clinical benefit and continuation of treatment was approved by the Sponsor. Approximately 4 weeks (at least 28 days [+7 days] per protocol) after the last dose of any study treatment, all treated patients had an SFU assessment. All patients also underwent LTFU assessments every 3 months for up to 2 years, which could be conducted by telephone to assess subsequent anticancer therapy(ies) and survival status. The study schema is provided in Figure 4.

Figure 4: Study Schema



Cohort 7 included patients with CLL/SLL or NHL not otherwise specified in Cohorts 1 through 6, inclusive of CLL/SLL, Richter's transformation, or low-grade NHL with transformation, blastoid MCL, and patients with history of CNS involvement or primary CNS lymphoma.

Main Criteria for Inclusion

- Histologically confirmed B-cell malignancy (e.g., CLL/SLL, WM, NHL) failed or intolerant to either ≥ 2 prior standard of care regimens OR 1 prior BTK inhibitor-containing regimen when a BTK inhibitor is approved as first-line therapy.
- Adequate hematologic status, defined by ANC (≥ 0.75 x 10^9), platelet count (≥ 50 x 10^9), hemoglobin levels (≥ 8 g/dL). Enrollment below these levels was permitted with evidence of bone marrow involvement. Patient must be responsive to transfusion support.
- ECOG PS 0-2
- Adequate coagulation, defined by aPTT or PTT, and PT/INR not greater than 1.5 x ULN.
- Adequate hepatic function defined by AST or ALT (≤ 2.5 x ULN or ≤ 5 x ULN with liver metastases), and total bilirubin (≤ 1.5 x ULN or ≤ 3 x ULN with liver metastases)
- Adequate renal function defined by creatinine clearance ≥ 30 mL/minute using Cockcroft/Gault formula.

Main Criteria for Exclusion

- Investigational agent or anticancer therapy within 5 half-lives or 14 days of planned start of study drug, whichever is shorter
- Allogeneic or autologous SCT or CAR-T therapy within 60 days of study start
- Significant cardiovascular disease (unstable angina, myocardial infarction within 6 months, LVEF ≤ 45% within 12 months, NYHA Class 3 or 4 cardiac disease, uncontrolled or symptomatic arrhythmias)
- Prolongation of the QTcF > 470 msec
- Major bleeding event with a prior BTK inhibitor
- Requirement for therapeutic anticoagulation with warfarin

Phase 2 Dose Selection

In January 2020, based on the cumulative review of safety and PK data of enrolled patients to Phase 1/2 monotherapy cohorts, the SRC recommended that additional patients be enrolled at 300 mg QD and 200 mg QD dose levels to further evaluate safety and efficacy given that no DLTs were reported and no MTD was established. The safety profile was the same at the 300 mg QD and 200 mg QD dose levels and the inhibitory concentration was sufficient at 200 mg with no significantly greater inhibition at 300 mg. On 07 May 2020, the RP2D of pirtobrutinib was identified as 200 mg QD. Based on FDA feedback from December 2020, the Sponsor and the FDA agreed that the proposed dosing regimen of 200 mg QD was reasonable and based upon review of clinical efficacy, PK, and safety data, it was decided that further dose escalation above 300 mg QD was not medically justified and therefore, no MTD was established for pirtobrutinib.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the LOXO-BTK-18001 study, study schema, and key eligibility criteria. Regarding dose selection for Phase 2, the Agency agreed that the proposed dosing regimen appeared reasonable in the meeting held on December 10,2020 but requested additional modeling analyses to be submitted with the NDA for further characterization of body weight effect, PK, and exposure-response analyses.

The FDA does not agree with the Applicant that the safety profile was the same at the 300mg QD dose and 200mg QD dose, given the limited numbers of patients treated at doses other than 200mg QD. Refer to clinical pharmacology section 6.3.2 for additional discussion regarding dosing and safety.

Study Endpoints

The Applicant's Description:

Primary Endpoints and Secondary Endpoints

The primary endpoint for the Phase 1 portion of the study was MTD/RP2D. The primary endpoint for Phase 2 was ORR according to IRC assessment based on BOR of PR or better determined by Lugano 2014 criteria (Cheson et al. 2014). Secondary endpoints were AEs and SAEs, changes in laboratory parameters, plasma concentration of pirtobrutinib, PK parameters, ORR by Investigator assessment and other efficacy parameters including DOR, BOR, TTR, PFS and OS.

The primary efficacy endpoint of ORR, accompanied by clinically meaningful durability, has been used to demonstrate efficacy in areas of oncology with high unmet need. In high-grade NHL (which includes MCL), the primary endpoint of ORR has been shown to be an early surrogate in demonstrating clinical benefit through PFS and OS (Mangal et al. 2018, Zhu et al. 2020).

The FDA's Assessment:
The FDA agrees with the Applicant's description of the primary and secondary endpoints, but regards time-to-event efficacy endpoints such as PFS and OS as exploratory. Additionally, although ORR is an endpoint reasonably likely to predict clinical benefit, it does not necessarily correlate with PFS or OS.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The main analyses for efficacy are based on the PAS, which is comprised of the first 90 patients with MCL enrolled in the Phase 1 and Phase 2 portions of Study 18001 who meet the following criteria:

- Confirmed diagnosis of MCL based on local pathology report obtained at time of Screening and with no known CNS involvement
- Treated with prior BTK inhibitor-containing regimen
- At least 1 site of radiographically assessable disease as determined by Investigator, defined as LDi > 1.5 cm, or extra nodal site > 1.0 cm in LDi by CT
- Received 1 or more doses of pirtobrutinib monotherapy (regardless of starting dose)

The primary analysis was evaluated by an IRC in order to minimize bias and variability in the assessment of clinical response. ORR was determined using images attained via CT scan, with or without FDG-PET images, and pertinent clinical data.

An ORR of ≥ 40% was hypothesized when pirtobrutinib is administered to patients in the proposed indication. A sample size of 65 patients was estimated to provide approximately 95% power to achieve a lower boundary of a 2-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. The sample size in the PAS was increased to N = 90 following FDA feedback received during the pre-NDA FDA meeting. A cut-off date of 31 January 2022 was chosen to ensure that the vast majority of responders in the PAS have at least 9 months of follow-up from the onset of response. Ruling out a lower limit of 20% for ORR is considered clinically meaningful for MCL patients pretreated with a BTK inhibitor, as ORRs between 20% to 30% were reported in clinical studies supporting the approval of agents given as monotherapy in BTK inhibitor-naïve advanced MCL (temsirolimus, 22% [Hess et al. 2009]; bortezomib, 31% [VELCADE USPI]; lenalidomide, 28% [Goy et al. 2015]). In addition to the PAS, the Sponsor has analyzed the efficacy data of PAS patients who have received a starting dose equal to 200 mg QD ('PAS = 200 subgroup', N = 77).

DOR was evaluated for patients with CR or PR as a BOR. DOR was defined as the number of months from the start date of the first documented response to the earlier of the documentation of PD or death from any cause. A DOR of 9 months is considered clinically meaningful in the PAS because the survival of patients with MCL following progression on BTK inhibitors is very poor with a median OS of 2.5 months to 8.4 months (Martin et al. 2016; Cheah et al. 2015; Epperla et al. 2017).

The FDA's Assessment:
The FDA agrees with the Applicant's description of the eligibility criteria for the PAS and the description of the planned sample size. The FDA disagrees with the proposed analysis population and the description of the duration of follow-up for the responders within the analysis population.

- Analysis Population*:* The Applicant identified the PAS based on the eligibility criteria noted above and included patients treated at variable doses across Phases 1 and 2 of study. In Phase 1, patients were treated with starting doses ranging from 25mg PO daily to 200mg PO daily and intrapatient dose escalation was permitted to doses up to 300mg PO daily. In Phase 2, patients were treated at the 200mg PO daily starting dose without intrapatient dose escalation.

  The FDA does not agree with the inclusion of patients who received doses other than the intended 200mg daily dose in the efficacy populations. Inclusion of patients receiving variable doses in the efficacy analysis population would not allow for an accurate assessment of efficacy at the intended dose.

  The FDA's revised analysis set for efficacy includes patients from the PAS + SAS1 populations who were treated with the 200mg starting dose and either did not undergo dose escalation or underwent dose escalation only after an IRC-assessed PD event or

permanent IRC censoring (n=120). The SAS1 patients who were included in the analysis set had the same eligibility criteria as patients in the PAS, but these patients were enrolled after the data cut-off for PAS eligibility, so duration of follow up was limited in this subset of the efficacy population.

- Duration of Follow-Up: The FDA agrees that in general, the vast majority of responders should have at least 9 months of follow-up from the onset of response in order to inform efficacy. However, the FDA disagrees that the data submitted include 9 months of follow-up in the majority of responders. With the modification of the efficacy analysis population, as described in 'Analysis Population' above, the median duration of follow-up is 7.3 months and demonstrates less follow-up than originally requested. The median duration of follow up was slightly higher, 8.2 months, in the efficacy population that only includes patients in the PAS (n=74), thus the PAS-only efficacy population is also being used to inform durability of response.

Protocol Amendments

The Applicant's Description:

Table 19: Changes to the Protocol

Version	Major Changes to the Protocol
Version 2.0	The following revisions were made based on FDA IND review: Revised Phase 1 patient eligibility criteria to require at least 2 lines of prior therapy. DLT criteria were revised to state that any toxicity that is a potential DLT will be considered a DLT if the SRC determines it is related to study drug.
Version 3.0	The following revisions were made in accordance with 21 CFR 312.30: Revised eligibility criteria and prohibited concomitant medications to exclude patients on strong P-gp inhibitors and prohibit use of strong P-gp inhibitors on study.
Version 5.1	The following revisions were made in accordance with 21 CFR 312.30: Updated the eligibility criteria to require 2 or more prior regimens or 1 prior BTKi-containing regimen when a BTK inhibitor is approved as first-line therapy. Updated dosing schedule section based on current patient data.
Version 6.0/7.0/8.0	The following revisions were made to update the Phase 2 design for LOXO-305 monotherapy, which reflected the Sponsor's intent of the study to support registration: Primary purpose: revised the Objectives of Phase 1/2 pirtobrutinib monotherapy in order to support registration. Redefined Phase 2 cohorts to be disease specific rather than by BTK mutational status Updated to include that the RP2D was determined to be 200 mg QD. Added assessment of LVEF during Screening in selected patients who had a history of

	LVEF < 45%. Revised dose modifications for pirtobrutinib monotherapy
Version 9.0/10.0	Revisions were made to the SoA for disease assessment to align with description of disease assessment and timing defined in v8.0.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the key changes made in the protocol amendments.

8.1.2 Study Results

Compliance with Good Clinical Practices

Data and the Applicant's Position:

Study 18001 was conducted in accordance with US FDA and ICH Guidelines for GCP, with the ethical principles originating in the Declaration of Helsinki, and standard clinical operating procedures for Loxo Oncology, Inc.

The FDA's Assessment:
FDA agrees that a statement indicating compliance with GCP was provided in the application. No concerns were identified during the clinical site inspections or inspection of the Applicant.

Financial Disclosure

The Applicant's Position:

Financial disclosure information was collected for all 922 Investigators and Sub-Investigators participating in LOXO-BTK-18001. See Appendix 19.2 for detail.

The FDA's Assessment:
Financial disclosure information was provided for 923 investigators and sub-investigators, 3 of whom were noted to have disclosable financial interests. The reason for disclosable financial interest for one investigator was 'compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study'; this investigator was hired by Loxo Oncology in (b) (6) . The reason for disclosable financial interest for two sub-investigators was 'significant payments of other sorts' (b) (6) . The Applicant has provided a description of steps that have been taken to minimize potential bias from these reported financial interests.

Patient Disposition

Data:

The efficacy analysis sets are outlined in Table 20.

Table 20: Analysis Sets for MCL

Analysis Set	Analysis Set Description	Number of Patients
PAS	Confirmed diagnosis of MCL based on local pathology report obtained at time of Screening and with no known active CNS involvement.	90
	Treated with prior BTK inhibitor-containing regimen.	
	At least 1 site of radiographically assessable disease as determined by Investigator, defined as LDi > 1.5 cm, or extra nodal site > 1.0 cm in LDi by CT.	
	Received 1 or more doses of pirtobrutinib monotherapy (regardless of starting dose).	
SAS1	MCL patients who meet the PAS eligibility criteria but were enrolled after the 90th PAS patient by the data cut-off date.	46
SAS2	MCL patients who were treated with prior BTK inhibitor-containing regimen but do not meet at least 1 of the other PAS criteria.	14
SAS3	MCL patients who were not treated with prior BTK inhibitor-containing regimen.	14

Table 21: Patient Disposition

	PAS (N = 90)	PAS=200 Subgroup* (N = 77)	All MCL Patients (N = 164)
Pirtobrutinib treatment status, n (%)			
Subjects continuing to receive pirtobrutinib	18 (20.0)	17 (22.1)	55 (33.5)
Subjects discontinued from pirtobrutinib treatment	72 (80.0)	60 (77.9)	109 (66.5)
Progressive disease	49 (54.4)	40 (51.9)	78 (47.6)
Adverse events	11 (12.2)	9 (11.7)	13 (7.9)
Requirement for alternative treatment in the opinion of the Investigator	3 (3.3)	3 (3.9)	4 (2.4)
Withdrawal of consent by the patient	2 (2.2)	2 (2.6)	3 (1.8)
Death	5 (5.6)	5 (6.5)	7 (4.3)
Other	2 (2.2)	1 (1.3)	4 (2.4)

	PAS (N = 90)	PAS=200 Subgroup* (N = 77)	All MCL Patients (N = 164)
Study Status, n (%)			
Subjects still on study	46 (51.1)	41 (53.2)	100 (61.0)
Subjects discontinued study	44 (48.9)	36 (46.8)	64 (39.0)
Withdrawal of consent	9 (10.0)	7 (9.1)	15 (9.1)
Death	30 (33.3)	26 (33.8)	43 (26.2)
Other	5 (5.6)	3 (3.9)	6 (3.7)

*The PAS=200 subgroup is the PAS subgroup who received a starting dose of 200 mg QD.
Source: SCE Table 14.1.2

As of the data cut-off date on 31 January 2022, 164 patients with MCL received at least one dose of pirtobrutinib, including 90 patients in the PAS (Table 21). Of the 164 patients with MCL, 55 patients (33.5%) were still on treatment with pirtobrutinib. Among all patients with MCL, 109 (66.5%) patients discontinued treatment with pirtobrutinib. The most common reasons for discontinuation from pirtobrutinib treatment were PD (78 [47.6%] patients) and AE (13 [7.9%]) patients. The patient disposition in the PAS subgroup who received a starting dose of 200 mg QD (PAS=200; N = 77) was generally consistent with the observations in the PAS population (N = 90) and the overall MCL population (N = 164).

The FDA's Assessment:

The FDA disagrees with the analysis populations identified by the Applicant. The primary analysis set includes patients who were not treated at the intended registrational dose of 200mg daily. The PAS 200mg subgroup represents an analysis set of only patients who received a starting dose of 200mg daily but includes patients who dose-escalated to a higher dose of pirtobrutinib during the study. Efficacy analysis populations should consist only of patients with consistent eligibility criteria whose response assessments reflect dosing at the 200mg daily registrational dose.

Thus, the FDA analysis sets for efficacy are:

- PAS subgroup: Patients within the PAS who received the 200mg dose throughout study or received the 200mg starting dose and dose-escalated only after PD or permanent censoring (n=74)
- PAS + SAS1 subgroup: Patients within the PAS + SAS1 who received the 200mg dose throughout study or received the 200mg starting dose and dose-escalated only after PD or permanent censoring (n=120)

The disposition of the patients in these two analysis sets is shown in Table 22 below.

In the primary efficacy population, the PAS + SAS1 subgroup (n=120), 38 patients (31.7%) were remained on treatment with pirtobrutinib as of the January 31, 2022 data cut-off. Across both

analysis populations, >68% of patients discontinued pirtobrutinib treatment, most commonly due to progressive disease, adverse events, or death. Study disposition was also similar in both analysis populations, with more than half of patients remaining on study and the remainder having discontinued study, most commonly due to death.

Table 22: Patient Disposition of the FDA's Efficacy Populations

	PAS Subgroup (N = 74)	PAS + SAS1 Subgroup (N=120)
Pirtobrutinib treatment status, n (%)		
Subjects continuing to receive pirtobrutinib	16 (21.6)	38 (31.7)
Subjects discontinued from pirtobrutinib treatment	58 (78.4)	82 (68.3)
Progressive disease	39 (52.7)	59 (49.2)
Adverse events	9 (12.2)	10 (8.3)
Requirement for alternative treatment	4 (5.4)	4 (3.3)
Withdrawal of consent by the patient	1 (1.4)	1 (<1)
Death	5 (6.8)	7 (5.8)
Other	0	1 (<1)
Study Status, n (%)		
Subjects still on study	40 (54.1)	73 (60.8)
Subjects discontinued study	34 (45.9)	47 (39.2)
Death	25 (33.8)	34 (28.3)
Withdrawal of consent	6 (8.1)	9 (7.5)
Other	3 (4.1)	4 (3.3)

Source: FDA analysis based on ADSL.xpt

Protocol Violations and Deviations

Data:

Important protocol deviations of the study, defined by ICH guidelines as "a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being", were identified prior to data cut-off (and prior to database lock) and included CSR-reportable deviations related to investigational product, Inclusion/Exclusion Criteria, SAE reporting, restricted concomitant medication changes, study procedures, and informed consent.

There was a total of 79 (10.9%) patients with at least 1 major (same as important deviations per ICH guidance) protocol deviation in the OMTSAS. The highest number of major protocol deviations in patients receiving monotherapy in the OMTSAS were errors with study procedures (55 patients), mainly study assessments (47 patients). Of note, there were 8 major protocol deviations due to COVID-19 in 5 patients total (3 patients in the 200 mg QD starting dose cohort and 1 each in the 150 mg QD and 250 mg QD dose cohorts); all 8 were errors with study assessments.

Major protocol deviations were reported for 8 BTK-inhibitor pretreated MCL patients. These were due to errors with the study procedures (3 patients), investigational product (2 patients), and safety reporting/follow-up (2 patients), and errors with study assessment (1 patient).

The Applicant's Position:

Overall, the protocol deviations were not considered to have a meaningful impact on the safety or efficacy outcomes of the study.

The FDA's Assessment:
Based on FDA analysis, major protocol deviations were reported in 11% (81/725) of patients with B-cell malignancies and in 6% (10/164) of patients with MCL treated on the study. The majority of protocol deviations in both populations were due to errors in study assessments, reporting and follow up, dispensing/accountability, and inclusion/exclusion criteria. Based on the categories within which the major deviations occurred, the FDA agrees that it is unlikely that the protocol deviations had a meaningful impact on safety or efficacy outcomes from the study.

Demographic Characteristics

Data:

Table 23: Demographics – MCL Patients by Analysis Sets

	PAS (N = 90)	PAS=200 Subgroup (N = 77)	All MCL Patients (N = 164)
Age at Enrollment (years)			
Median (Range)	70.0 (46, 87)	71.0 (46, 87)	70.0 (46, 88)
< 65 years, n (%)	24 (26.7)	18 (23.4)	47 (28.7)
≥ 65 years, n (%)	66 (73.3)	59 (76.6)	117 (71.3)
≥ 75 years, n (%)	27 (30.0)	25 (32.5)	47 (28.7)
≥ 85 years, n (%)	3 (3.3)	3 (3.9)	8 (4.9)
Sex, n (%)			
Male	72 (80.0)	63 (81.8)	128 (78.0)
Female	18 (20.0)	14 (18.2)	36 (22.0)
Race, n (%)			
American Indian or Alaskan Native	0	0	2 (1.2)
Asian	6 (6.7)	6 (7.8)	20 (12.2)
Black or African American	1 (1.1)	1 (1.3)	3 (1.8)
Native Hawaiian or Pacific Islander	0	0	0
White	76 (84.4)	64 (83.1)	129 (78.7)
Other	7 (7.8)	6 (7.8)	10 (6.1)

Source: SCE Table 14.2.1

The Applicant's Position:

Demographics

Patients with MCL enrolled in Study 18001 are generally representative of patients with pretreated MCL in the real world setting as reflected by age and gender.

No clinically meaningful differences in demographics were observed between the overall MCL population, the PAS, and the PAS subgroup receiving the 200 mg QD starting dose (PAS = 200). Demographics are summarized in Data:

Table 23, Table 25, and Table 26.

The FDA's Assessment:
As described above in 'Patient Disposition', the FDA does not agree with the analysis sets

identified by the Applicant. For efficacy, the FDA's analysis sets are the PAS subpopulation (n=74) and PAS + SAS1 subpopulation (n=120). Demographics for each of these analysis sets are shown in Table 24 below.

Table 24: Demographics of the FDA's Efficacy Populations

	PAS Subgroup (N = 74)	PAS + SAS1 Subgroup (N=120)
Age at Enrollment (years)		
Median (Range)	71 (46, 87)	71 (46, 88)
< 65 years, n (%)	16 (21.6)	27 (22.5)
≥ 65 years, n (%)	58 (78.4)	93 (77.5)
≥ 75 years, n (%)	25 (33.8)	39 (32.5)
≥ 85 years, n (%)	3 (4.1)	6 (5.0)
Sex, n (%)		
Male	61 (82.4)	95 (79.2)
Female	13 (17.6)	25 (20.8)
Race, n (%)		
American Indian or Alaskan Native	0	2 (1.7)
Asian	6 (8.1)	17 (14.2)
Black or African American	1 (1.4)	2 (1.7)
Native Hawaiian or Pacific Islander	0	0
White	61 (82.4)	93 (77.5)
Other	6 (8.1)	6 (5.0)
Ethnicity, n (%)		
Hispanic or Latino	3 (4.1)	3 (2.5)
Not Hispanic or Latino	67 (90.5)	113 (94.2)
Unknown	4 (5.4)	4 (3.3)

Source: FDA analysis based on ADSL.xpt

The median age of patients in the primary efficacy population (n=120) was 71 and the majority of patients were male.

The demographics of patients with MCL diagnosed between 1992 and 2009 per the surveillance, epidemiology and end results 9 (SEER 9) database are as follows: 89% White, 4.1%

Black, 3.7% Asian Pacific Islander, and 3.7% Hispanic (Wang and Ma, 2014). Compared to the U.S. population of patients with MCL referenced, there was limited representation of Black patients and adequate representation of Hispanic and Asian patients in the efficacy populations of the BRUIN trial.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Baseline disease characteristics and time on treatment are summarized in Table 25 and Table 26.

Table 25: Baseline Disease Characteristics and Prior Therapies

	PAS (N = 90)	PAS = 200 Subgroup (N = 77)	All MCL Patients (N = 164)
ECOG Score at Baseline, n (%)			
0	61 (67.8)	51 (66.2)	97 (59.1)
1	28 (31.1)	25 (32.5)	63 (38.4)
2	1 (1.1)	1 (1.3)	4 (2.4)
Time Since Initial Diagnosis of Primary Cancer to First Pirtobrutinib Dose (months)			
n	89	76	163
Median (Min, Max)	70.34 (4.5, 183.7)	74.35 (4.5, 183.7)	72.38 (4.5, 209.6)
sMIPI Score[a], n (%)			
Low Risk	20 (22.2)	13 (16.9)	32 (19.5)
Intermediate Risk	50 (55.6)	47 (61.0)	84 (51.2)
High Risk	20 (22.2)	17 (22.1)	48 (29.3)
Tumor Bulk (cm)[b], n (%)			
< 5	59 (65.6)	47 (61.0)	100 (61.0)
≥ 5	24 (26.7)	23 (29.9)	41 (25.0)
Nonmeasurable Lymph Node	7 (7.8)	7 (9.1)	23 (14.0)
Extranodal Disease, n (%)			
Yes	35 (38.9)	33 (42.9)	63 (38.4)
No	55 (61.1)	44 (57.1)	101 (61.6)

	PAS (N = 90)	PAS = 200 Subgroup (N = 77)	All MCL Patients (N = 164)
Bone Marrow Involvement[c], n (%)			
Yes	46 (51.1)	41 (53.2)	84 (51.2)
No	44 (48.9)	36 (46.8)	80 (48.8)
MCL Histology[d], n (%)			
Classic/Leukemic	70 (77.8)	60 (77.9)	129 (78.7)
Blastoid	8 (8.9)	8 (10.4)	16 (9.8)
Pleomorphic	12 (13.3)	9 (11.7)	19 (11.6)
Median Number of Lines of Prior Systemic Therapy (Range), n (%)	3 (1–8)	3 (1–8)	3 (1-9)
1	6 (7)	6 (7.8)	13 (7.9)
2	35 (39)	29 (37.7)	60 (36.6)
3	18 (20)	15 (19.5)	34 (20.7)
≥ 4	31 (34)	27 (35.1)	57 (34.8)
Prior Systemic Therapies, n (%)			
Prior BTK inhibitor[e]	90 (100.0)	77 (100.0)	14 (100.0)
Prior BCL2 inhibitor	14 (15.6)	12 (15.6)	2 (14.3)
Prior Chemotherapy	79 (87.8)	66 (85.7)	13 (92.9)
Prior Anti-CD20 Antibody	86 (95.6)	73 (94.8)	14 (100.0)
Prior PI3K Agent	3 (3.3)	3 (3.9)	0
Prior Immunomodulator	19 (21.1)	17 (22.1)	2 (14.3)
Prior CAR-T	4 (4.4)	4 (5.2)	2 (14.3)
Prior Stem Cell Transplant	19 (21.1)	17 (22.1)	6 (42.9)
Auto-SCT	17 (18.9)	15 (19.5)	6 (42.9)
Allo-SCT	4 (4.4)	4 (5.2)	0
Other Systemic Therapy	22 (24.4)	21 (27.3)	4 (28.6)
Prior proteasome inhibitors	14 (15.6)	13 (16.9)	25 (15.2)
Median Number of Lines of Prior BTK Inhibitor (Range)[e], n (%)	1.0 (1-3)	1.0 (1-3)	1.0 (0-3)
0	0	0	14 (8.5)
1	72 (80.0)	61 (79.2)	122 (74.4)

	PAS (N = 90)	PAS = 200 Subgroup (N = 77)	All MCL Patients (N = 164)
2	17 (18.9)	15 (19.5)	24 (14.6)
≥ 3	1 (1.1)	1 (1.3)	4 (2.4)
Reason for Discontinuation from the Most Recent Prior BTK Inhibitor, n (%)			
Disease Progression	73 (81.1)	63 (81.8)	125 (76.2)
Intolerance/Toxicity	12 (13.3)	10 (13.0)	15 (9.1)
Other Reason for Discontinuation	5 (5.6)	4 (5.2)	8 (4.9)
Missing	0	0	2 (1.2)
Relapsed/Refractory on Most Recent Prior BTK Inhibitor[f], n (%)	83 (92.2)	72 (93.5%)	142 (86.6)
Discontinued Any Prior BTK Inhibitor Due to Intolerance/Toxicity, n (%)	16 (17.8)	14 (18.2)	20 (12.2)

Source: SCE Table 14.2.2 and SCE Table 14.2.3
[a] Based on baseline assessment. [b] Assessed by Sponsor based on Investigator selected lymph node target lesions at Screening. [c] Based on assessment of bone marrow aspirate and/or biopsy at Screening. [d] Based on local pathology results at Screening; not confirmed centrally. [e] All prior BTK inhibitors were confirmed to be covalent, except for in 3 patients enrolled at Japanese site 1101 where details about prior investigational agents could not be provided.
[f] Discontinued due to disease progression or had documented disease progression on or after treatment and before starting a new therapy.

Table 26: Pirtobrutinib Starting Doses and Time on Treatment

Starting Dose, n (%)	PAS (N = 90)	PAS = 200 Subgroup (N = 77)	All MCL Patients (N = 164)
25 mg QD	3 (3.3)	0	3 (1.8)
50 mg QD	0	0	0
100 mg QD	2 (2.2)	0	3 (1.8)
150 mg QD	1 (1.1)	0	1 (0.6)
200 mg QD	77 (85.6)*	77 (100.0)*	148 (90.2)
250 mg QD	2 (2.2)	0	3 (1.8)
300 mg QD	5 (5.6)	0	6 (3.7)
Median Time on Treatment (months, range)	5.24 (0.2, 337)	5.49 (0.3, 27.3)	4.52 (0.2, 33.7)

*Among the 77 PAS patients receiving the 200 mg QD starting dose, duration of exposure was at least 6 months for 45.5% of patients, at least 9 months for 27.3% of patients, at least 12 months for 15.6% of patients, and at least 18 months for 11.7% of patients.

Source: SCE Table 14.1.2, SCS Table 14.3.1.2

The Applicant's Position:

MCL is a rare and aggressive subtype of B-cell NHL and is incurable with current therapies. MCL is considered an orphan condition (Howlader et al. 2021; ECIS 2021), is more common in males than in females, and is typically diagnosed in patients aged 60 to 70 years old (Cheah et al. 2016; Swerdlow et al. 2016). The typical clinical presentation of MCL is aggressive with treatment required at the time of diagnosis for most patients. Blastoid and pleomorphic histologies portend particularly aggressive disease and sMIPI classification of intermediate or high risk is associated with poor prognosis. Available upfront therapy for MCL includes chemotherapy and anti-CD20 immunotherapy. While PFS in first-line therapy can exceed 4 years, cure with this approach is rare and relapse is nearly universal (Kumar et al. 2019). Covalent BTK inhibitors (e.g., ibrutinib) are the most established therapy for relapsed MCL but is not curative and when patients relapse, outlook is poor and subsequent treatment options are not well defined (NCCN 2022). The patients with R/R MCL who received pirtobrutinib in Study 18001 are representative of the typical population of MCL patients in age, clinical presentation, and prior treatment experience who would be recommended for treatment after a BTK inhibitor.

The FDA's Assessment:

As described above in 'Patient Disposition', the FDA does not agree with the analysis sets identified by the Applicant. For efficacy, the FDA's analysis sets are the PAS subpopulation (n=74) and PAS + SAS1 subpopulation (n=120). Disease characteristics are shown in Table 27 and a summary of prior therapies is shown in Table 28 below.

Table 27: Baseline Disease Characteristics of FDA's Efficacy Populations

	PAS Subgroup (N = 74)	PAS + SAS1 Subgroup (N=120)
ECOG Score at Baseline, n (%)		
0	50 (67.6)	70 (58.3)
1	23 (31.1)	47 (39.2)
2	1 (1.4)	3 (3.5)
Time Since Initial Diagnosis of Primary Cancer to First Pirtobrutinib Dose (months)		
n	73	119
Median (Min, Max)	73.0 (4.5, 183.7)	72.4 (4.5, 209.6)
sMIPI Score[a], n (%)		
Low Risk	13 (17.6)	18 (15.0)
Intermediate Risk	45 (60.8)	71 (59.2)
High Risk	16 (21.6)	31 (25.8)
Tumor Bulk (cm)[b], n (%)		
< 5	45 (60.8)	75 (62.5)
≥ 5	23 (31.1)	35 (29.2)
Nonmeasurable Lymph Node	6 (8.1)	10 (8.3)
Extranodal Disease, n (%)		
Yes	31 (41.9)	50 (41.7)
No	43 (58.1)	70 (58.3)
Bone Marrow Involvement[c], n (%)		
Yes	38 (51.4)	61 (50.8)
No	36 (48.6)	59 (49.2)
MCL Histology[d], n (%)		
Classic/Leukemic	58 (78.4)	93 (77.5)
Blastoid	7 (9.5)	13 (10.8)
Pleomorphic	9 (12.2)	14 (11.7)

Source: FDA analysis based on ADSL.xpt

Although the study population appears to be representative of the overall patient population with MCL with respect to disease characteristics, with the majority of patients on the study having intermediate or high risk sMIPI scores at baseline, extranodal disease, and classic/leukemic histology, selection bias is inherent due to the study requirements. Thus, many patients with R/R MCL may not meet study requirements based on end-organ function, comorbidities, concomitant medications, or other factors.

Table 28: Prior Therapies in FDA's Efficacy Populations

	PAS Subgroup (N = 74)	PAS + SAS1 Subgroup (N=120)
Number of Lines of Prior Systemic Therapy (Range), n (%)		
Median (range)	3 (1–8)	3 (1–9)
1	6 (8.1)	9 (7.5)
2	27 (36.5)	41 (34.2)
3	15 (20.3)	24 (20.0)
≥ 4	26 (35.1)	46 (38.3)
Prior Systemic Therapies, n (%)		
Prior BTK inhibitor	74 (100.0)	120 (100.0)
Prior BCL2 inhibitor	11 (14.9)	19 (15.8)
Prior Chemotherapy	63 (85.1)	106 (88.3)
Prior Anti-CD20 Antibody	70 (94.6)	115 (95.8)
Prior PI3K Agent	3 (4.1)	6 (5.0)
Prior Immunomodulator	17 (23.0)	22 (18.3)
Prior CAR-T	4 (5.4)	11 (9.2)
Prior Stem Cell Transplant	16 (21.6)	24 (20.0)
Auto-SCT	14 (18.9)	21 (17.5)
Allo-SCT	4 (5.4)	7 (5.8)
Other Systemic Therapy	21 (28.4)	32 (26.7)
Prior proteasome inhibitors	13 (17.6)	21 (17.5)
Lines of Prior BTK Inhibitor (Range), n (%)		
Median (range)	1 (1–3)	1 (1–3)
0	0	0

	PAS Subgroup (N = 74)	PAS + SAS1 Subgroup (N=120)
1	59 (79.7)	98 (81.7)
2	14 (18.9)	19 (15.8)
3	1 (1.4)	3 (2.5)
Reason for Discontinuation from the Most Recent Prior BTK Inhibitor, n (%)		
Disease Progression	61 (82.4)	100 (83.3)
Intolerance/Toxicity	9 (12.2)	12 (10)
Other Reason for Discontinuation	4 (5.4)	6 (5.0)
Missing	0	2 (1.7)
Relapsed/Refractory to Any Prior BTK Inhibitor, n (%)	71 (95.9)	116 (96.7)
Discontinued Any Prior BTK Inhibitor Due to Intolerance/Toxicity, n (%)	13 (17.6)	16 (13.3)

Source: FDA analysis based on ADSL.xpt

The characteristics of prior therapies received were similar across the two analysis populations. In the PAS + SAS1 subgroup, subjects had a median of 3 prior lines of therapy (range 1-9); 7.5% of patients had 1 prior line of therapy, while 92.5% had 2 or more prior lines of therapy. All patients in both efficacy analysis sets received a prior BTK inhibitor. The other most common prior therapies received by patients on the study were anti-CD20 antibodies (95.8%) and chemotherapy (88.3%). Most patients received 1 prior BTK inhibitor (81.7%), 15.8% received 2 prior BTK inhibitors, and 2.5% received 3 prior BTK inhibitors. The most common reason for discontinuation of the most recent BTK inhibitor was disease progression (83.3%). The majority of patients had R/R disease to any prior BTK inhibitor (96.7%), while a minority of patients experienced intolerance to any prior BTK inhibitor, resulting in discontinuation (13.3%).

Pirtobrutinib dosing and duration of exposure is summarized in Table 29 below.

Table 29: Duration of Exposure in FDA's Efficacy Populations

	PAS Subgroup (N = 74)	PAS + SAS1 Subgroup (N = 120)
Starting Dose, n (%)		
200 mg QD	74 (100)	120 (100)
Dose Escalation (After PD or Censoring), n (%)		
Yes	2 (2.7)	5 (4.2)
No	72 (97.3)	115 (95.8)
Maximum Dose Received, n(%)		
200 mg QD	72 (97.3)	115 (95.8)
250 mg QD	1 (1.4)	1 (<1)
300 mg QD	1 (1.4)	4 (3.3)
Median Time on Treatment (months)		
Median (Q1, Q3)	4.1 (1.7–7.5)	5.3 (1.7, 9.3)
Treatment Duration (months)		
≥6 months	32 (43.2)	43 (35.8)
≥9 months	20 (27.0)	20 (16.7)
≥12 months	11 (14.9)	11 (9.2)

Source: FDA analysis based on ADSL.xpt

The FDA analysis sets include only patients who were treated at the 200mg dose throughout study treatment and those who received the 200mg starting dose and dose escalated only after progressive disease or permanent censoring, such that the efficacy outcomes reflect treatment with pirtobrutinib at 200mg daily. The majority of patients received the 200mg dose throughout study treatment (96% in the PAS + SAS1subgroup); the other 4% underwent dose escalation to doses of 250mg daily or 300mg daily following progressive disease or permanent IRC-censoring.

There was limited duration of exposure to pirtobrutinib, with a median duration of exposure of 5.3 months in the PAS + SAS1 subgroup. In the PAS + SAS1 subgroup, 64% of patients received less than 6 months of treatment with pirtobrutinib. The limited duration of exposure appears to be related to the rates of treatment discontinuation due to progressive disease and to the limited amount of follow up at the time of the data cut-off.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

Patients were required to keep a daily diary to record dosing compliance of oral study

treatment. Compliance was also assessed at each clinic visit by means of a tablet count in the returned bottle(s). There were no patients in the Phase 2 MCL cohort who discontinued the study due to serious noncompliance.

Concomitant Medications

The most common concomitant medications were antibacterials, antivirals, and analgesics. Consistent with high occurrence of infections in this patient population (due to inherent risk factors such as underlying disease and age-related factors as well as on-target immunosuppressive effects of study drug), antibiotics and antiviral use were seen in 61.0% and 56.7% of patients, respectively.

Additionally, multiple concomitant medications were reported in patients in the OMTSAS consistent with a population of advanced age with a baseline increased risk for cardiovascular disease, including antithrombotic agents (218 [30.1%]), lipid modifying agents (195 [26.9%]), beta blocking agents (177 [24.4%]), agents acting on the renin-angiotensin system (170 [23.4%]), diuretic (135 [18.6%]), and calcium channel blockers (131 [18.1%]).

Generally, the other concomitant medications used were in line with standard clinical practice in the treatment of MCL, CLL/SLL, and other NHLs. The use of the concomitant therapies did not appear to affect the overall safety profile of pirtobrutinib.

Rescue Medications

Not applicable.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of treatment compliance and concomitant medications.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Primary Analysis Set – MCL

The PAS includes the first 90 MCL patients treated in the Phase 1 and Phase 2 portions of the Study 18001. PAS patients had a confirmed MCL diagnosis based on local pathology report, with no known active CNS involvement, prior treatment with a BTK inhibitor, and at least 1 site of radiographically assessable disease as determined by Investigator, and patients received 1 or more doses of pirtobrutinib monotherapy on study.

The primary endpoint was ORR by IRC assessment. Investigator assessed ORR was a secondary endpoint.

Overall Response Rate

The ORR in the PAS was 57.8% (52/90; 95% CI: 46.9, 68.1) by IRC assessment. Consistent with the PAS results, the ORR in the PAS subgroup receiving a starting dose of 200 mg QD was 58.4% (45/77; 95% CI: 46.6, 69.6) by IRC assessment (Table 30:). The results are clinically meaningful for this population, where available therapies in relapsed BTK inhibitor-naïve MCL yield ORR of 20% to 30% (Goy et al. 2009, Trněný et al. 2016, Hess et al. 2009). Statistical significance was demonstrated as the estimated lower bound of the 2-sided 95% CI of ORR by IRC assessment exceeded the prespecified threshold of 20%.

Table 30: Best Overall Response and Overall Response Rate – IRC Assessment

	PAS (N = 90)	PAS Subgroup 200 mg QD Starting Dose (N = 77)
Best Overall Response, n (%)		
CR	18 (20.0)	15 (19.5)
PR	34 (37.8)	30 (39.0)
SD	14 (15.6)	13 (16.9)
PD	15 (16.7)	10 (13.0)
NE	9 (10.0)	9 (11.7)
Overall Response Rate		
n (%)	52 (57.8)	45 (58.4)
95% Confidence Interval	46.9, 68.1	46.6, 69.6

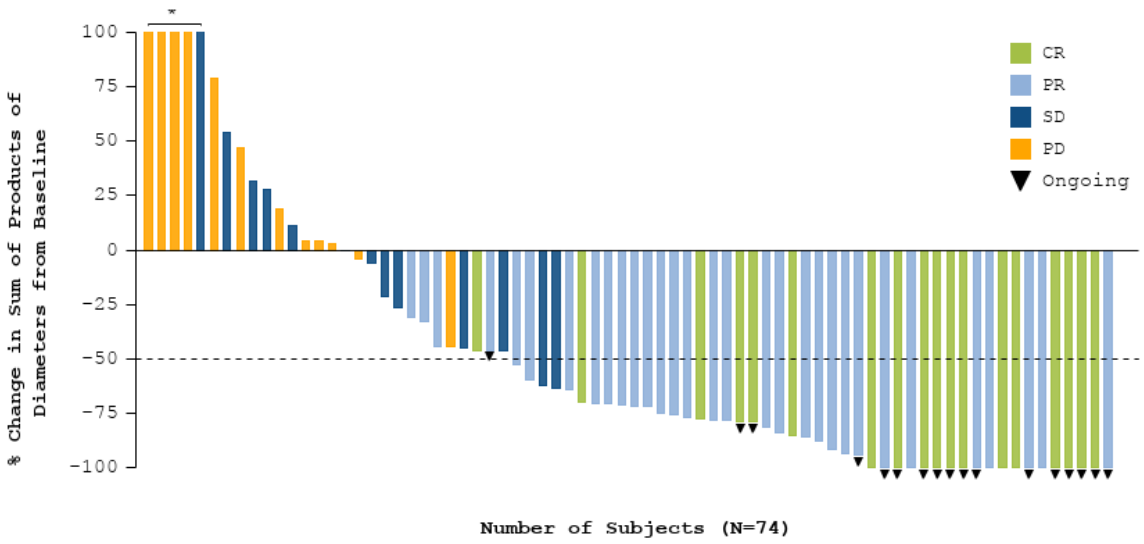
Sources: SCE Table 14.3.1.1.1

Agreement between IRC and Investigator BOR assessments in the PAS was achieved in 83 of 90 patients (46 responders, 37 nonresponders) for a concordance rate of 92.2% (95% CI: 84.6, 96.8%). Agreement between IRC and Investigator BOR assessments in the PAS=200 subgroup was achieved in 73 of 77 patients (41 responders, 32 nonresponders) for a concordance rate of 94.8% (95% CI: 87.2, 98.6%).

A waterfall plot for the PAS illustrating best change in tumor size and BOR by IRC is shown in Figure 5. Response was determined based on Lugano Treatment Response Criteria (Cheson et al. 2014).

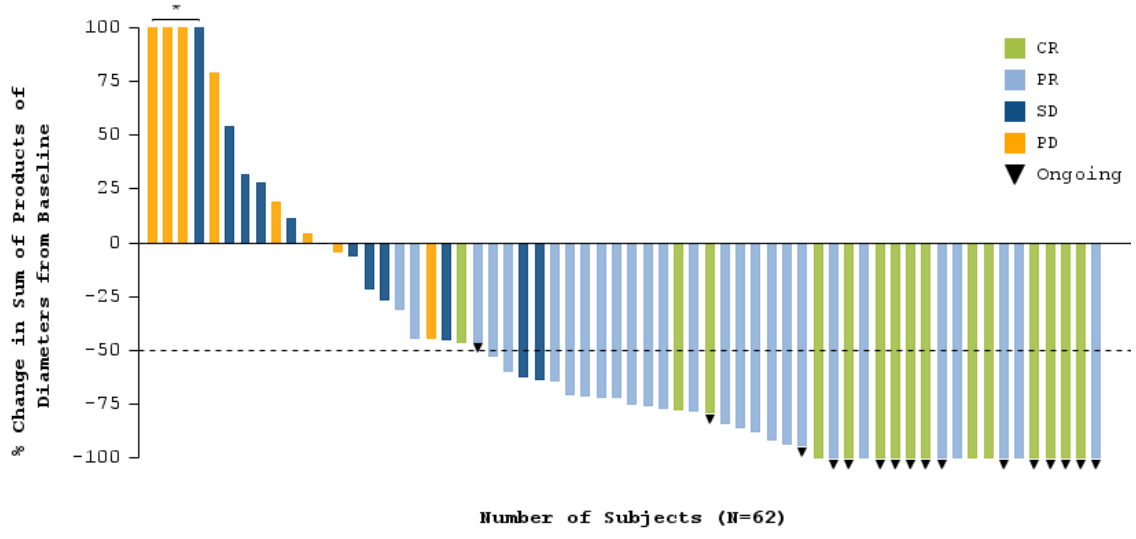
Figure 5: Waterfall Plot of Best Change in Tumor Size Based on IRC Assessments

a) Primary Analysis Set



BOR for each patient is represented by color.
Waterfall plot includes subjects with baseline and at least one evaluable post baseline tumor measurement.
* Indicates patients with >100% increase in sum of the products diameters, and the corresponding percent change from baseline is 385.1, 199.3, 183.9, 180.8, and 117.6, respectively.

b) PAS Subgroup – 200 mg QD Starting Dose



BOR for each patient is represented by color.
Waterfall plot includes subjects with baseline and at least one evaluable post baseline tumor measurement.
* Indicates patients with >100% increase in SPD, and the corresponding % change from baseline is 199.3, 183.9, 180.8, and 117.6, respectively
Source: SCE Figure 14.2.1 and SCE Figure 14.2.1.1

The Applicant's Position:

The efficacy of pirtobrutinib in patients with pretreated MCL was established based on interim data from Study 18001. The efficacy data supports a clinically meaningful benefit for the use of pirtobrutinib as a single agent in the treatment of patients with MCL who were previously treated with a BTK inhibitor, irrespective of the number and types of prior therapy.

The FDA's Assessment:

As described above in "Patient Disposition", FDA does not agree with the analysis sets identified by the Applicant. For efficacy, the FDA's primary analysis set is the PAS+SAS1 subpopulation (n=120). The PAS subpopulation (n=74) was also analyzed due to the longer duration of follow-up.

As PET was used by IRC for the response assessments in only 41% of patients in the primary efficacy population, BOR by Lugano criteria (incorporating PET data when available) and BOR by CT-based assessments in all subjects were both evaluated. Table 31 shows the Lugano-based BOR per IRC, which was adjudicated by the FDA and incorporates PET data, when available.

Table 32 shows the CT-only based BOR per IRC, also adjudicated by the FDA.

The Lugano-based ORR by IRC assessment was 50% (95% CI: 41, 59) in the primary efficacy population and 57% (95% CI: 45, 68) in the PAS subgroup. The median TTR per IRC was 1.8 months in both efficacy populations. The IRC-assessed response rates using CT-based criteria were similar to the response rates that incorporated PET data where available (Table 32). In the primary efficacy population, CT-based ORR per IRC was 48% (95% CI: 38, 57) with a CR rate of 13%.

The concordance rate between Lugano-based BOR by IRC and Investigator BOR assessments was 90.8% in the primary analysis population and 94.6% in the PAS.

Table 31: Lugano-Based BOR per IRC, FDA Adjudicated (N=120 and N=74)

	PAS+SAS1 Subgroup (N=120)	PAS Subgroup (N=74)
BOR per IRC, FDA, n (%)		
CR	15 (12.5)	13 (17.6)
PR	45 (37.5)	29 (39.2)
SD	26 (21.7)	13 (17.6)
PD	28 (23.3)	14 (18.9)
NE	6 (5.0)	5 (6.8)
Overall Response Rate		
n (%)	**60 (50.0)**	**42 (56.8)**
95% CI	**40.7, 59.3**	**44.7, 68.2**
Time to Response per IRC, months		
Median (range), months	**1.8 (0.8, 4.2)**	**1.8 (1.0, 4.2)**
Q1, Q3, months	**1.8, 1.9**	**1.8, 1.9**

Source: FDA analysis based on ADEFF.xpt submitted on 12/1/2022

Table 32: CT-Based BOR per IRC, FDA Adjudicated (N=120 and N=74)

	PAS+SAS1 Subgroup (N=120)	PAS Subgroup (N=74)
CT BOR per IRC, FDA, n (%)		
CR	16 (13.3)	11 (14.9)
PR	41 (34.2)	27 (36.5)
SD	26 (21.7)	14 (18.9)
PD	31 (25.8)	17 (23.0)
NE	6 (5.0)	5 (6.8)
Overall Response Rate		
n (%)	**57 (47.5)**	**38 (51.4)**
95% CI	**38.3, 56.8**	**39.4, 63.1**

Source: FDA analysis based on ADEFF.xpt submitted on 12/1/2022

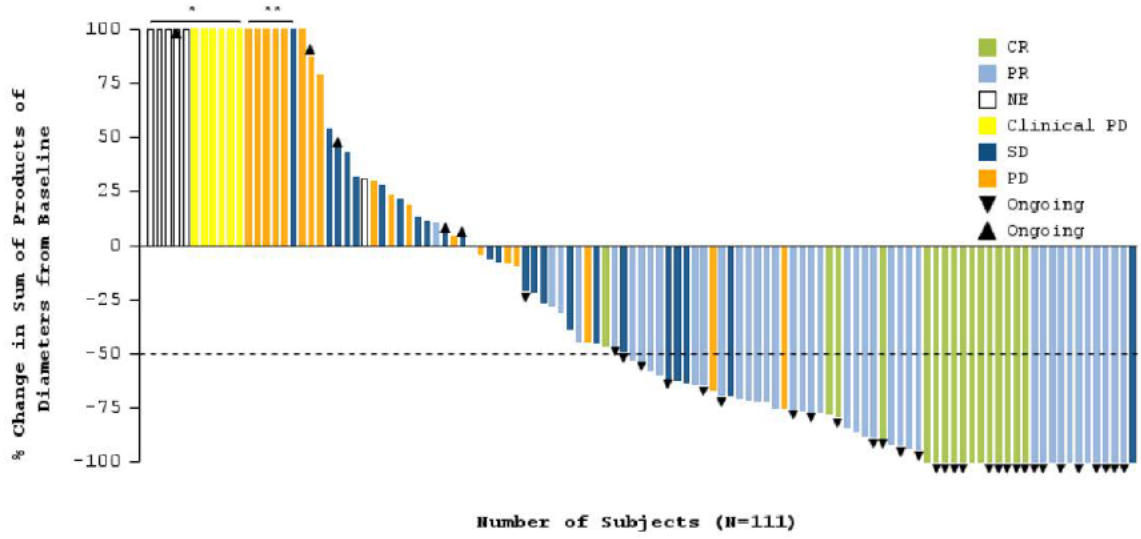
Table 33: BOR per Investigator

	PAS+SAS1 Subgroup (N=120)	PAS Subgroup (N=74)
Best Overall Response, n (%)		
CR	26 (21.7)	20 (27.0)
PR	31 (25.8)	18 (24.3)
SD	23 (19.2)	12 (16.2)
PD	30 (25.0)	15 (20.3)
NE	10 (8.3)	9 (12.2)
Overall Response Rate		
n (%)	**57 (47.5)**	**38 (51.4)**
95% CI	**38.3, 56.8**	**39.4, 63.1**

Source: FDA analysis based on ADEFF.xpt submitted on 12/1/2022

A waterfall plot of BOR per IRC per Lugano, incorporating PET data when available and as adjudicated by FDA, is shown in Figure 6 below.

Figure 6: Waterfall Plot of BOR per IRC in the PAS + SAS1 Population (n=120)



Source: Applicant's analysis, in response to IR sent on 12/1/2022.
9 patients who had IRC assessed responses of radiographic PD or BOR of SD or better but didn`t have measurable disease at baseline or had an incomplete evaluation of post-baseline target lesions are not displayed on this plot.
*Indicates patients with NE or Clinical PD who didn`t have measurable disease at baseline or at least one evaluable post baseline tumor measurement, percent change of SPDs are imputed as 100% to represent an arbitrary maximal change in SPD.
**Indicates patients with >100% increase in SPD, and the corresponding % change from baseline is 214.9, 209.1, 199.3, 183.9, 180.8, 117.6, respectively.

Clinical reviewer's comments:

- ***FDA adjudication of BOR identified several subjects whose final FDA-adjudicated response assessments differed from those originally reported by the Applicant. There were changes made to Lugano-based BOR in 8 subjects and to CT-only based BOR in 21 subjects. The rationales for the changes are described below:***
  - ***Change from non-evaluable status to 'PD': Several subjects who were considered non-evaluable for response by the Applicant were reported to have clinical disease progression. The FDA considers the totality of data, including clinical data, to inform response assessments and adjudicated these cases accordingly.***
  - ***Change from 'CR' to 'PR': Several subjects who were considered to have CR by the Applicant had pre-treatment bone marrow involvement and either were missing post-treatment bone marrow evaluations or had evidence of bone marrow involvement on post-treatment bone marrow. These subjects were downgraded from CR to PR based on FDA-adjudication.***
- ***As noted above, only 41% of patients in the primary efficacy population (n=120) had PET data utilized in their assessment of BOR per Lugano Criteria, while the remainder had CT-only based assessment of BOR. Given the substantial heterogeneity in the disease assessments across the efficacy population, the BOR using CT scans only across the efficacy population was also evaluated. Lugano based ORR and CR rate (ORR 50% with 95% CI: 41, 59; CR rate 13%) and CT-only based ORR and CR rate (ORR 48 with 95% CI: 38, 57; CR rate 13%) were similar. Given that response by Lugano was the pre-specified analysis in the protocol and given that the radiologists performing CT-only BOR evaluations also had access to the PET scan results, potentially affecting their interpretation of CT-only BOR, the decision was made to report PET-based BOR as the primary assessment of efficacy in the efficacy table of the label. However, given the heterogeneity in disease assessments using Lugano-based criteria, the CT-only BOR is also being reported in a footnote under the table.***

Efficacy Results – Secondary and Other Relevant Endpoints

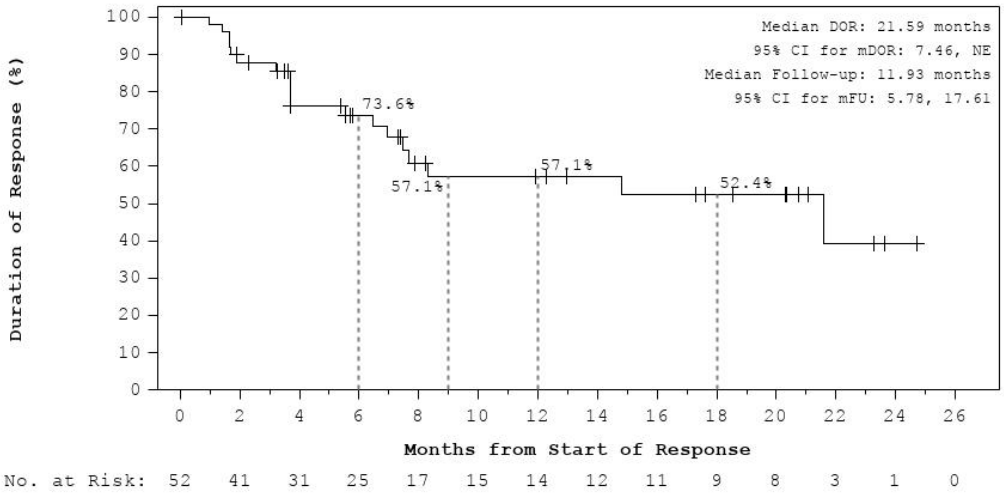
Data:

Table 34: Duration of Response – Primary Analysis Set – IRC Assessment

	PAS (N = 90)	PAS Subgroup 200 mg QD Starting Dose (N = 77)
Number of Responders	52	45
Overall Response Status, n (%)		
Disease Progression	15 (28.8)	13 (28.9)
Died (No Disease Progression Beforehand)	4 (7.7)	4 (8.9)
Censored	33 (63.5)	28 (62.2)
Reason Censored, n (%)		
Alive without documented PD on or before Data Cut-off	18 (34.6)	16 (35.6)
Subsequent Anticancer Therapy without Documented PD	9 (17.3)	9 (20.0)
Documented PD or Death after Subsequent Anticancer Therapy	3 (5.8)	0
Discontinued from Study without Documented PD or Death	2 (3.8)	2 (4.4)
Death or PD after Two or More Missed Disease Assessments	1 (1.9)	1 (2.2)
Duration of Response (months)		
Median (95% CI)	21.59 (7.46, NE)	21.59 (6.93, NE)
Minimum, Maximum	0.03+, 24.71+	0.99, 23.26+
Duration of Follow-up (months)		
Median (Q1, Q3)	11.93 (5.55, 20.34)	8.21 (5.55, 20.30)
Rate (%) of Duration of Response (95% CI)		
6 months or more	73.6 (58.0, 84.2)	72.6 (55.7, 83.9)
9 months or more	57.1 (39.3, 71.5)	52.7 (33.3, 68.8)
12 months or more	57.1 (39.3, 71.5)	52.7 (33.3, 68.8)
18 months or more	52.4 (33.9, 67.9)	52.7 (33.3, 68.8)

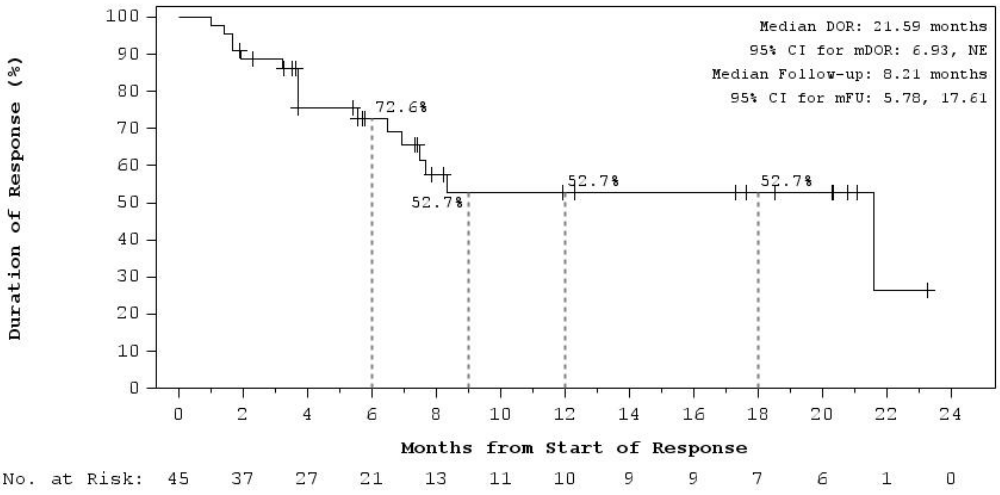
Sources: SCE Table 14.3.2.1.1

Figure 7: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – Primary Analysis Set



Source: SCE Figure 14.3.1

Figure 8: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment – Primary Analysis Set – 200 mg QD Starting Dose



Source: SCE Figure 14.3.1.1

Subgroup analyses were also performed by baseline disease characteristics, prior therapy, and starting dose for patients in the PAS. Efficacy results for ORR and DOR by those subgroups were generally consistent with the observations in the overall PAS population (Table 35).

Table 35: Subgroup Analysis by Baseline Disease Characteristics, Prior Therapy, and Pirtobrutinib Starting Dose Based on IRC Assessment – PAS

Parameter	Number of patients (N)	Responders (n)	ORR (%)	95% CI	Median DOR (months)	95% CI
ECOG Status at Baseline						
0	61	36	59.0	45.7, 71.4	21.59	8.31, NE
1	28	16	57.1	37.2, 75.5	7.46	1.91, NE
≥ 2	1	0	0.0	0.0, 97.5	-	-
Ann Arbor Staging for Lymphoma						
Stage I-III	19	12	63.2	38.4, 83.7	NE	14.82, NE
Stage IV	69	38	55.1	42.6, 67.1	8.31	6.47, NE
Simplified MCL International Prognostic Index						
Low Risk (0 to 3)	20	15	75.0	50.9, 91.3	NE	3.68, NE
Intermediate Risk (4 to 5)	50	32	64.0	49.2, 77.1	NE	6.93, NE
High Risk (6 to 11)	20	5	25.0	8.7, 49.1	8.31	0.99, NE
Tumor Bulk (largest diameter)						
< 5 cm	59	34	57.6	44.1, 70.4	21.59	7.66, NE
≥ 5 cm	24	11	45.8	25.6, 67.2	6.93	3.68, NE
Extranodal Disease						
Yes	35	24	68.6	50.7, 83.1	7.46	3.71, NE
No	55	28	50.9	37.1, 64.6	21.59	8.31, NE
Bone Marrow Involvement						
Yes	46	25	54.3	39.0, 69.1	21.59	5.55, NE
No	44	27	61.4	45.5, 75.6	7.66	6.47, NE
Gastrointestinal Involvement						
Yes	7	3	42.9	9.9, 81.6	7.66	3.71, NE
No	83	49	59.0	47.7, 69.7	21.59	7.46, NE
MCL Histology						
Classic/Leukemic	70	40	57.1	44.7, 68.9	21.59	7.46, NE
Blastoid	8	6	75.0	34.9, 96.8	NE	1.41, NE
Pleomorphic	12	6	50.0	21.1, 78.9	NE	3.68, NE

Parameter	Number of patients (N)	Responders (n)	ORR (%)	95% CI	Median DOR (months)	95% CI
Prior Lines of Systemic Therapies						
≤ 3 versus > 3						
≤3	59	30	50.8	37.5, 64.1	NE	7.66, NE
>3	31	22	71.0	52.0, 85.8	7.46	3.71, NE
Prior BCL2						
Yes	14	7	50.0	23.0, 77.0	3.71	1.41, NE
No	76	45	59.2	47.3, 70.4	21.59	7.46, NE
Prior Stem Cell Transplant						
Yes	19	11	57.9	33.5, 79.7	NE	3.68, NE
No	71	41	57.7	45.4, 69.4	21.59	7.46, NE
Prior Anti-CD20 and Chemo						
Yes	79	49	62.0	50.4, 72.7	21.59	7.46, NE
No	11	3	27.3	6.0, 61.0	NE	3.71, NE
Prior CAR-T						
Yes	4	2	50.0	6.8, 93.2	8.31	NE, NE
No	86	50	58.1	47.0, 68.7	21.59	6.93, NE
Reason for Discontinuation from the Most Recent Prior BTK inhibitor						
Disease Progression	73	36	49.3	37.4, 61.3	7.66	3.71, NE
Toxicity	12	11	91.7	61.5, 99.8	NE	7.46, NE
Other	5	5	100.0	47.8, 100.0	NE	1.64, NE
Starting Dose						
< 200 mg QD	6	3	50.0	11.8, 88.2	NE	NE, NE
200 mg QD	77	45	58.4	46.6, 69.6	21.59	6.93, NE
> 200 mg QD	7	4	57.1	18.4, 90.1	14.82	1.71, NE

Source: SCE Table 14.3.7.1

Time to Response and Time to Best Response

In the overall PAS, the median TTR by IRC assessment was 1.84 (Q1, Q3: 1.84, 1.87) months with most patients demonstrating response at the first disease assessment. The median TTBR by IRC assessment was 1.87 (Q1, Q3: 1.84, 2.05) months. In the PAS subgroup receiving at starting dose of 200 mg QD, the median TTR by IRC assessment was 1.84 (Q1, Q3: 1.84, 1.87) months with most patients demonstrating response at the first disease assessment. The median TTBR by IRC assessment was 1.87 (Q1, Q3: 1.84, 1.91) months.

Progression Free Survival

The KM estimate of median PFS was 7.36 months (95% CI: 5.32, 12.45) by IRC assessment in the PAS. By KM estimates, the probability of being progression-free at 9 and 12 months in the PAS were 44.7% (95% CI: 32.5, 56.1%) and 40.0% (95% CI: 27.7, 52.0%) based on IRC assessment.

Overall Survival

The median OS was not estimable (95% CI: 14.75, NE) in the PAS (N = 90) with 30 deaths observed after a median duration of follow-up of 16.56 months. At 12 months, the KM estimate for OS rate was 67.6% (95% CI: 55.7, 77.0%).

The Applicant's Position:

As of the data cut-off, a follow-up of 9 months or more from the onset of response was reached for 90.4% responders in the PAS and for 88.9% in the PAS subgroup who received 200 mg QD as their starting dose (PAS=200). Therefore, the follow-up time available enables assessment of a clinically meaningful DOR relative to other available therapies post-BTK inhibitors, which from the limited available data have a median OS ranging from only 2.5 months to up to 8.4 months (Martin et al. 2016; Cheah et al. 2015; Epperla et al. 2017).

The additional secondary endpoints of BOR and TTR were supportive of the clinical benefit. PFS and OS data supported the durability of the observed clinical benefit.

The FDA's Assessment:

As described above in "Patient Disposition", the FDA does not agree with the analysis sets identified by the Applicant. For efficacy, the FDA's analysis sets are the PAS+SAS1 subpopulation (n=120) which is the primary analysis set, and the PAS subpopulation (n=74) which informs DOR with longer follow-up. Additionally, FDA does not agree that most responders in the originally defined PAS had at least 9 months of follow-up for DOR, as the majority of responders were censored before 6 months as evident in Figure 8. The limitations with the DOR follow-up were a significant review issue.

ORR supported by durability is an endpoint that is reasonably likely to predict clinical benefit, but is not a direct measure of clinical benefit in this setting. FDA does not agree that PFS and OS data support clinical benefit in this trial; PFS and OS are difficult to interpret in single-arm trials and cannot be used to support efficacy claims.

Duration of Response after FDA Adjudication

The DOR data per IRC incorporating FDA-adjudication are shown in Table 36.

The median DOR by KM estimate was 8.3 months (95% CI: 5.7, NE) in the PAS + SAS1 population and 11.9 months (95% CI: 6.5, NE) in the PAS population.

There was a notable degree of early censoring in both efficacy populations, with 60% of patients in the PAS + SAS1 population censored, most commonly due to being alive without PD before the data cutoff (72% of all censored patients).

With the notable degree of early censoring in both populations, as seen in the Kaplan-Meier plots of DOR (Figure 9 through Figure 12) the median DOR estimates are being skewed by outliers with longer durations of response. Thus, the median DOR estimates on their own are not necessarily representative of the data and must be interpreted in the context of the limited number of patients with DOR events and the degree of early censoring and early failures. In particular, the estimated median DOR of 11.9 months in the PAS population does not mirror the appearance of the Kaplan-Meier plot, which would suggest a shorter median DOR.

Table 36: Duration of Response per IRC after Adjudication in the FDA's Efficacy Populations

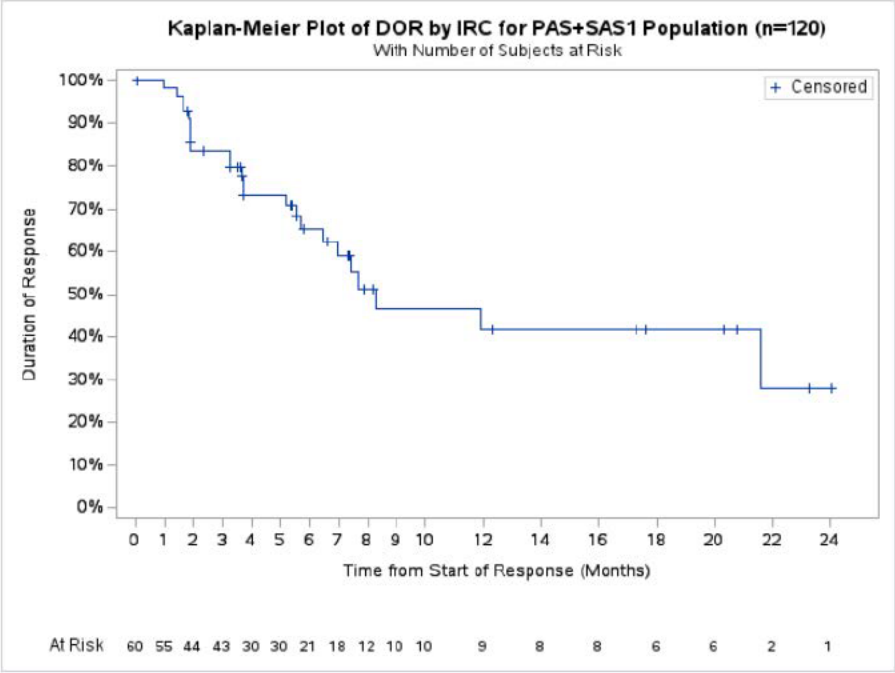
	PAS+SAS1 (N=120)	**PAS (N=74)**
ORR per IRC, n (%)[a]	60 (50.0)	42 (56.8)
DOR per IRC[a]		
DOR estimates, median (95% CI)[b, c]		
Median, mo (95% CI)	8.3 (5.7, NE)	11.9 (6.5, NE)
6-month DOR estimate, % (95% CI)	65.3 (49.8, 77.1)	70.9 (53.4, 82.9)
9-month DOR estimate, % (95% CI)	46.4 (28.7, 62.4)	50.3 (30.7, 67.1)
DOR events or censoring status, n (%)		
Censored	36 (60)	24 (57)
Progressive disease	19 (32)	14 (33)
Death	5 (8)	4 (10)
Reasons for Censoring, n (% of patients censored)		
Alive without PD before data cutoff	26 (72)	14 (58)
Subsequent therapy without PD	7 (19)	7 (29)
Discontinued study without PD or death	2 (6)	2 (8)
Death or PD after ≥2 missed assessments	1 (3)	1 (4)

[a] Incorporating FDA adjudication
[b] By Kaplan-Meier estimate

[c] The estimated median duration of follow-up for DOR was 7.3 months in the PAS+SAS1 population and 8.2 months in the PAS population, by the reverse KM method.
Source: FDA analysis based on ADAE.xpt and ADTTE2.xpt datasets

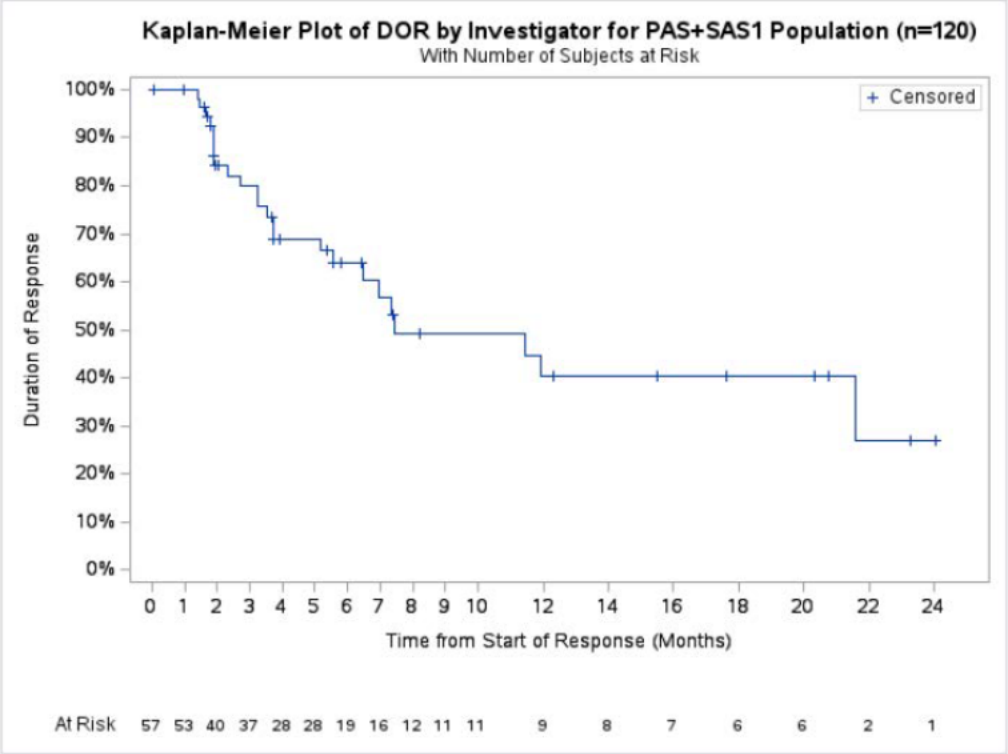
KM plots of DOR per IRC and per investigator for the PAS + SAS1 population (n=120) are shown in the figures below. By the KM method, the estimated 6-month DOR rate per IRC was 65.3% (95% CI: 49.8, 77.1). Of the 60 patients who achieved an objective response, a total of 35% (based on proportions) maintained responses for at least 6 months and 15% maintained responses for at least 12 months.

Figure 9: Kaplan-Meier Plot of DOR by IRC for the PAS+SAS1 Population (n=120)



Source: FDA analysis based on ADTTE2.xpt submitted on 12/7/2022 reflecting FDA adjudication

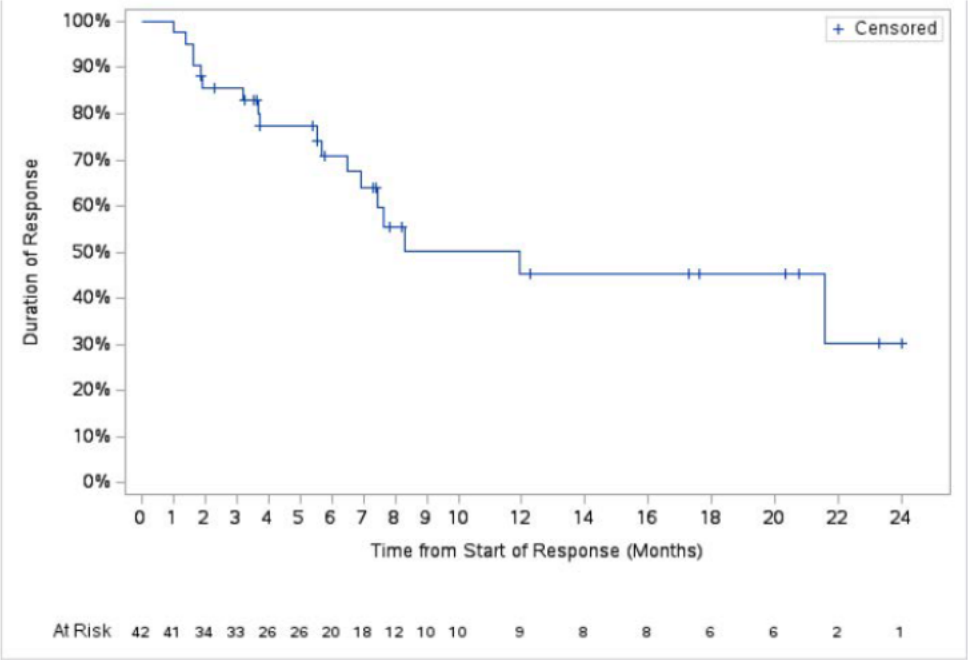
Figure 10: Kaplan-Meier Plot of DOR by Investigator for the PAS+SAS1 Population (n=120)



Source: FDA analysis based on ADTTE2.xpt submitted on 12/7/2022

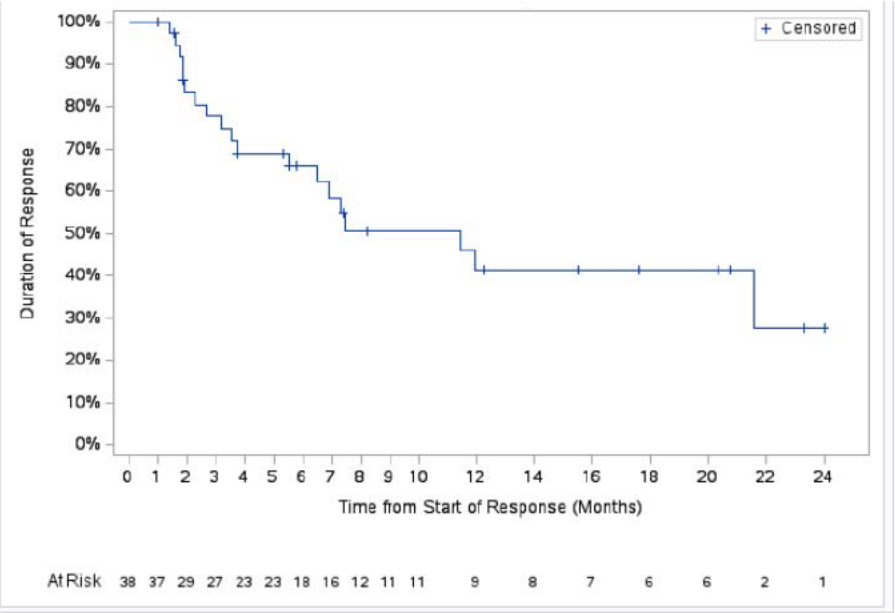
KM plots of DOR per IRC and per investigator for the PAS population (n=74) are shown in the figures below. By the KM method, the estimated 6-month DOR rate per IRC was 70.9% (95% CI: 53.4, 82.9).

Figure 11: Kaplan-Meier Plot of DOR by IRC for the PAS Population (n=74), FDA Adjudicated



Source: FDA analysis based on ADTTE2.xpt submitted on 12/7/2022 reflecting FDA adjudication

Figure 12: Kaplan-Meier Plot of DOR by INV for PAS Population (n=74)



Source: FDA analysis based on ADTTE2.xpt submitted on 12/7/2022

Other Descriptive Endpoints

Time to Best Response

In the primary analysis set of 120 (PAS+SAS1) subjects, the median TTBR by IRC assessment was 1.9 (Q1, Q3: 1.8, 1.9) months. In the 74-subject PAS population, the median TTBR by IRC assessment was 1.8 (Q1, Q3: 1.8, 1.9) months.

Progression-Free Survival

In the primary analysis population (n=120), the KM estimate of median PFS was 5.5 months (95% CI: 3.8, 8.3) by IRC assessment. By KM estimates, the probability of being progression-free at 9 and 12 months was 36.2% (95% CI: 25.6, 46.9%) and 31.0% (95% CI: 20.2, 42.5%) based on IRC assessment, respectively.

In the 74-subject PAS population, The KM estimate of median PFS was 7.3 months (95% CI: 4.0, 9.5) by IRC assessment. By KM estimates, the probability of being progression-free at 9 and 12 months were 41.4% (95% CI: 28.4%, 53.9%) and 35.5% (95% CI: 22.5%, 48.8%) based on IRC assessment.

Overall Survival

In the primary analysis population (n=120), the median OS was not estimable (95% CI: 13.3, NE), with 34 deaths observed after a median duration of follow-up of 9.3 months. At 12 months, the KM estimate for OS rate was 63.8% (95% CI: 51.6%, 73.7%).

In the 74-subject PAS population, the median OS was not estimable (95% CI: 13.3, NE), with 25 deaths observed after a median duration of follow-up of 14.0 months. At 12 months, the KM estimate for OS rate was 65.7% (95% CI: 52.3, 76.1%).

Clinical reviewer's comments:

- ***There was a notable degree of early censoring of responders. In the primary efficacy population (PAS + SAS1; n=120), of the responders who were censored (n=36), 61% were censored within 6 months of onset of response and 78% were censored within 9 months. Due to these limitations in duration of follow up for response in responders, the median estimates are skewed by outliers, and it is challenging to accurately estimate the durability of response with pirtobrutinib.***
- ***There was a high degree of discordance between IRC-assessed and investigator-assessed median DOR when initially analyzed. At the time of FDA's initial analysis of DOR, the efficacy population being used was the PAS population receiving the 200mg starting dose, regardless of dose escalation (n=77); in this population, the median DOR per IRC was 21.6 months (95% CI: 6.9, NE) and median DOR per INV was 7.5 months (95% CI: 3.7, NE). Based on the discordance noted, FDA adjudication of DOR was performed.***

Five changes were made to the DOR data initially submitted by the Applicant; these were based on review of radiology reports and clinical data provided by the Applicant. Four of the changes made were changes to the censor code and one was a change to the duration of response value. The changes to censor code were changes from censoring to 'PD' for subjects in whom there was clear and unequivocal evidence of disease progression based on a review of radiographic and/or clinical findings. Following adjudication of DOR, and based on the final primary efficacy population, the IRC-assessed and investigator-assessed median DOR became more similar, with median DOR per IRC of 8.3 months (95% CI: 5.7, NE) and median DOR per INV of 7.5 months (95% CI: 5.6, NE).

- ***Given that the data are from a single-arm trial, time-to-event endpoints such as PFS and OS are considered exploratory.***

Dose/Dose Response

Data:

Please see Sections **6.2.1** and **8.1.1** for discussions of the doses tested.

The FDA's Assessment:
Refer to the clinical pharmacology assessment.

Persistence of Effect

Data:

Not applicable.

The FDA's Assessment:
Persistence of effect is not applicable, because it refers to persistence of the treatment effect after the drug is discontinued, and pirtobrutinib is administered continuously.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data:

PRO endpoints have not been analyzed in the 18001 study.

The FDA's Assessment:
PRO assessments collected for patients with NHL in the 18001 study were the Worst Pain Numerical Rating Score, the Patient Global Impression of Severity scale, and the Patient Global Impression of Change scale. These questionnaires were only collected for patients in countries where the questionnaires were translated into the region's native language(s) and for patients who were fluent in an available translated language. PRO data

were not submitted in the study's interim CSR or in datasets with the NDA submission.

Additional Analyses Conducted on the Individual Trial

Data:

Supplemental Analysis Sets

Three supplemental analysis sets provide supportive data to the primary analysis. The supplemental analysis sets are defined in Table 20.

Overall Response Rate – Supplemental Analysis Sets

For BTK inhibitor-pretreated patients in SAS1, the ORR by IRC assessment was 39.1% (95% CI: 25.1, 54.6%). The lower ORR compared to the PAS is likely due to the shorter follow-up duration for patients in SAS1 compared to the PAS. For BTK inhibitor pretreated patients in SAS2, the ORR by IRC assessment was 28.6% (95% CI: 8.4, 58.1%). However, the small number of patients and differences in patient eligibility in the SAS2 limit the comparisons of the observed ORR to the PAS. Despite these differences, the ORRs in the SAS1 and SAS2 are still considered meaningful. For patients in SAS3, the ORR was 85.7% (95% CI: 57.2, 98.2%), notably higher than that of the PAS. This is not unexpected because patients in SAS3 are BTK inhibitor-naïve and have fewer prior lines of therapy (median 2, range 1 to 3 compared to PAS median 3, range 1 to 8). Similar ORRs are observed in the BTK inhibitor-naïve population treated with covalent BTK inhibitors (65.8% ibrutinib, 80% acalabrutinib, 84% zanubrutinib).

Duration of Response - Supplementary Analysis Sets

The median DOR by IRC assessment was not estimable for any of the supplemental analysis sets (SAS1 95% CI: 1.87 NE; SAS2 95% CI: 1.28, NE, and SAS3 95% CI: NE, NE). Patient numbers are small and at the time of this interim analysis the median duration of follow-up by IRC assessment was 3.71 months for SAS1, 7.20 months for SAS2, and 7.06 months for SAS3.

The FDA's Assessment:
The FDA primary efficacy analysis set (n=120) includes patients who were pooled between the PAS and SAS1, as these sets had consistent eligibility criteria and contained only BTK inhibitor-pretreated patients.

The FDA did not adjudicate the responses of patients in the SAS2 and SAS3 analysis sets. FDA does not consider evaluation of efficacy in the SAS2 set to be informative, given the differences in eligibility criteria between this analysis set and the FDA primary analysis set; given the inclusion of patients without radiographically assessable disease into SAS2, these subjects would not be considered evaluable for response. FDA also does not consider evaluation of efficacy in the SAS3 set to be informative of the efficacy determination for the intended

population, given that the patients in SAS3 were BTK inhibitor-naïve.

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

The efficacy of pirtobrutinib monotherapy in patients with R/R MCL is based on the LOXO-BTK 18001 study, a single-arm study of adults with previously treated CLL/SLL or non-Hodgkin Lymphoma, including MCL. The MCL efficacy population (n=120) consisted of patients who had received a prior BTK inhibitor and who were treated at the 200mg once daily dosage throughout treatment, or who received the 200mg starting dose and dose escalated only after permanent censoring or disease progression. Thus, analysis of the defined efficacy population represents efficacy outcomes at the registrational dose of pirtobrutinib.

Of the 120-patient efficacy population the median age was 71 and the median number of prior systemic therapies was 9 (range 1-9), with 34% of patients receiving 2 prior systemic therapies, 20% receiving 3 prior systemic therapies, and 38% receiving 4 or more prior systemic therapies. Eighty-three percent of patients discontinued the most recent prior BTK inhibitor due to disease progression, while 10% discontinued the most recent prior BTK inhibitor due to intolerance or toxicity, and 5% discontinued for other reasons. Ninety-seven percent of patients had relapsed or refractory disease to any prior BTK inhibitor.

Efficacy was based on ORR and DOR per IRC assessment using Lugano 2014 criteria, and incorporated adjudication by FDA. In the PAS + SAS1 population (n=120), the IRC-assessed ORR was 50% (95% CI: 41, 59) and CR rate was 13%, with median time to response of 1.8 months. The Kaplan-Meier estimate of median DOR per IRC was 8.3 months (95% CI: 5.68, NE) and the Kaplan-Meier estimate of 6-month DOR was 65.3% (95% CI: 49.8, 77.1).

In the PAS population (n=74), the IRC-assessed ORR was 57% (95% CI: 45, 68) and CR rate was 18%. The Kaplan-Meier estimate of median DOR per IRC was 11.9 months (95% CI: 6.5, NE) and the Kaplan-Meier estimate of 6-month DOR was 70.9% (95% CI: 53.4, 82.9).

Due to the notable degree of censoring within 6-9 months of onset of response, the assessment of durability of response with pirtobrutinib is limited. Additionally, there are notable rates of disease progression in responders within the first 6-9 months of treatment and there are limited numbers of patients who maintained responses beyond 6 months. Nevertheless, the efficacy population represents a refractory patient population with prior BTK inhibitor treatment, so the response rate, which is coupled with adequate demonstration of durability in the limited number of responders with follow-up greater than 6 months, is supportive of clinically meaningful efficacy in patients with relapsed or refractory MCL after at least 2 prior lines of therapy including a BTK inhibitor.

8.1.4 Assessment of Efficacy Across Trials

This section is not applicable as the indication is supported by a single clinical trial.

8.2 Review of Safety

The Applicant's Position:

The results of Study 18001 demonstrate that pirtobrutinib was well tolerated in a representative patient population of advanced age, with multiple comorbidities, and heavily pretreated severe underlying disease. The findings are generally consistent with the known drug class effects seen with BTK inhibitor therapy across disease types enrolled in the study, including patients with MCL. Thus, for the primary analysis of pirtobrutinib safety, the OMTSAS was used. This is a comprehensive safety dataset comprised of 725 patients with B-cell malignancies who enrolled to Study 18001 and received pirtobrutinib monotherapy.

The FDA's Assessment:
The FDA agrees that pirtobrutinib was generally well tolerated in the study population, with a safety profile that is generally consistent with the known class effect with the BTK inhibitor drug class. However, longer-term tolerability remains to be defined, given the relatively short duration of exposure to pirtobrutinib.

The FDA disagrees with the Applicant's safety population, which includes patients treated at variable dosages of pirtobrutinib. To assess the safety profile for the intended registrational dose of pirtobrutinib, 200mg once daily, the FDA has restricted the safety populations to those who received the 200mg daily starting dose without subsequent dose escalation. The safety population of patients with B-cell malignancies is comprised of 583 patients treated uniformly at the 200mg dose. The safety population of patient with MCL is comprised of patients who received a prior BTK inhibitor and were treated uniformly at the 200mg dose.

8.2.1 Safety Review Approach

The Applicant's Position:

The primary safety analysis set is based on patients irrespective of B-cell malignancy, who received at least one dose of pirtobrutinib as monotherapy, at any dose level, as of the data cut-off of 31 January 2022 and is referred to as the Overall Monotherapy Safety Analysis Set (OMTSAS; n = 725). Although B-cell malignancies differ in nature and aggressiveness, the safety and tolerability of pirtobrutinib across the various disease types is expected to be similar and, thus, facilitates aggregate consideration. This is consistent with currently available covalent BTK inhibitors, which utilize aggregate population safety findings across B-cell malignancies to

inform their respective safety profiles (Janssen Biotech, 2013 [ibrutinib]; AstraZeneca, 2017 [acalabrutinib]; BeiGene USA, 2019 [zanubrutinib]). A separate safety analysis for the patient population with MCL (MSAS; n = 164) was also performed to investigate whether there were any notable differences in the safety profile of pirtobrutinib in this individual tumor type compared to the OMTSAS. An additional subgroup of 148 MCL patients who received a starting dose of 200 mg QD (MSAS-200) was reviewed and provided supportive safety data. No notable differences in the safety profile of pirtobrutinib between the OMTSAS, MSAS, and MSAS-200 were identified. Throughout, safety data is summarized from the OMTSAS, unless otherwise specified.

The Sponsor considers the data presented here to reasonably characterize the safety profile of pirtobrutinib in patients with B-cell malignancies and demonstrates that pirtobrutinib has a tolerable and manageable safety profile.

The FDA's Assessment:
As noted above, the FDA safety analysis sets are restricted to patients who were treated with the 200mg daily starting dose without subsequent dose escalation, in order to inform safety and tolerability of the registrational dose. There are limitations in the safety database due to the relatively short duration of exposure of pirtobrutinib in the BRUIN trial, which is further characterized in the 'Review of the Safety Database' section below. These limitations will be addressed through two post-marketing requirements to characterize the longer-term safety profile of pirtobrutinib (Section 13.0).

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Pirtobrutinib Safety Database

The primary safety data comes from an interim analysis of patients receiving pirtobrutinib monotherapy on Study 18001 (Table 37). Patient safety data from Phase 1, all dose levels, and Phase 2 monotherapy data are pooled.

Table 37: Study 18001 Patient Data Contributing to the OMTSAs

Study / Description	Patient Description	Number of Patients
Study 18001 / Patients treated with pirtobrutinib monotherapy as of data cut-off of 31 January 2022	MCL	164
	CLL/SLL	311
	Total[1]	725

[1] Includes patients with other NHL (e.g., DLBCL, MZL, Richter's Transformation, FL, WM) as presented in the Study 18001 CSR.

The median time on treatment in Study 18001 was 8.05 months (range: 0, 34.0) across all treated monotherapy patients (OMTSAS), 4.52 months (range: 0.2, 33.7) in all MCL patients (MSAS), and 4.52 months (range: 0.3, 27.3) in the MSAS-200 subgroup. Thus, this study describes extensive experience with the proposed 200 mg QD dose. A summary of exposure to pirtobrutinib is provided in the table below.

Table 38: Exposure to Pirtobrutinib

Parameter	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Starting Dose, n (%)			
25 mg QD	3 (1.8)	0	5 (0.7)
50 mg QD	0	0	6 (0.8)
100 mg QD	3 (1.8)	0	9 (1.2)
150 mg QD	1 (0.6)	0	20 (2.8)
200 mg QD (proposed dose)	148 (90.2)	148 (100)	640 (88.3)
250 mg QD	3 (1.8)	0	25 (3.4)
300 mg QD	6 (3.7)	0	20 (2.8)
Median time on treatment, months (range)	4.52 (0.2, 33.7)	4.52 (0.3, 27.3)	8.05 (0, 34.0)
Relative dose intensity, mean (SD)	95.64 (8.825)	95.58 (8.784)	95.99 (9.195)
Duration of exposure, n (%)			
< 3 months	57 (34.8)	49 (33.1)	174 (24.0)
≥ 3 and < 6 months	41 (25.0)	40 (27.0)	128 (17.7)
≥ 6 and < 9 months	31 (18.9)	31 (20.9)	84 (11.6)
≥ 9 and < 12 months	13 (7.9)	12 (8.1)	99 (13.7)
≥ 12 and < 18 months	5 (3.0)	5 (3.4)	118 (16.3)
≥ 18 and < 24 months	10 (6.1)	8 (5.4)	81 (11.2)
≥ 24 and < 30 months	4 (2.4)	3 (2.0)	31 (4.3)
≥ 30 months	3 (1.8)	0	10 (1.4)

Source: SCS Table 14.1.2, SCS Table 14.3.1

Of the 198 Phase 1 patients in the OMTSAS, a total of 39 patients (19.7%) underwent intrapatient dose escalation, including 4 patients with MCL (4/40; 10.0%) (Table 39).

Table 39: Intrapatient Dose Escalation for Phase 1 Patients [a]

		Starting Dose (mg QD)						Total N = 198
		25 N = 5	50 N = 6	100 N = 9	150 N = 20	200 N = 113	250 N = 25	
Maximum Dose (mg QD)	100		3					3
	150	1						1
	200	2[b]	1	2	2			7
	250		1	1	1	3[b]		6
	300	1[b]		2	1	14[b]	4	22
	Total	4	5	5	4	17	4	39

[a] Four MCL patients underwent dose escalation. [b] Includes 1 patient with MCL.

Demographic and Other Characteristics of Study Population

Data:

The OMTSAS had a total of 725 patients and the MSAS had 164 patients (Table 37, Table 40). The demographic characteristics were consistent across analysis sets and in the MSAS-200 subgroup. Demographic information and baseline characteristics for the OMTSAS, the MSAS, and the MSAS-200 subgroup treated in Study 18001 are summarized in the tables below (Table 40 and Table 41).

Table 40: Patient Demographics

Parameter	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Sex, n (%)			
Male	128 (78.0)	116 (78.4)	482 (66.5)
Female	36 (22.0)	32 (21.6)	243 (33.5)
Race, n (%)			
White	129 (78.7)	114 (77.0)	628 (86.6)
Black or African American	3 (1.8)	3 (2.0)	22 (3.0)
Native Hawaiian or Other Pacific Islander	0	0	3 (0.4)
Asian	20 (12.2)	20 (13.5)	42 (5.8)
American Indian or Alaska Native	2 (1.2)	2 (1.4)	3 (0.4)
Other	10 (6.1)	9 (6.1)	26 (3.6)
Unknown	0	0	1 (0.1)
Ethnicity, n (%)			

Parameter	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Hispanic or Latino	3 (1.8)	3 (2.0)	27 (3.7)
Not Hispanic or Latino	154 (93.9)	138 (93.2)	667 (92.0)
Unknown	7 (4.3)	7 (4.7)	31 (4.3)
Age at Enrollment, years			
Median (Range)	70.0 (46, 88)	70.5 (46, 88)	68.0 (27, 95)
< 50 years	1 (0.6)	1 (0.7)	31 (4.3)
≥ 65 years, n (%)	117 (71.3)	108 (73.0)	471 (65)
≥ 75 years, n (%)	47 (28.7)	45 (30.4)	177 (24.4)
≥ 85 years, n (%)	8 (4.9)	8 (5.4)	24 (3.3)

Source/Program: SCS Table 14.2.1

Table 41: Baseline Disease Characteristics

Parameter	MSAS (N = 164)	MSAS-200 (N = 148)	OMTSAS (N = 725)
Time since initial diagnosis to first dose (months)			
n	163	147	724
Mean (SD)	74.77 (48.167)	76.01 (48.591)	108.24 (76.762)
Median	72.38	73.23	97.95
Range	4.5, 209.6	4.5, 209.6	0.5, 739.4
ECOG performance status at enrollment, n (%)			
0	97 (59.1)	84 (56.8)	364 (50.2)
1	63 (38.4)	60 (40.5)	320 (44.1)
2	4 (2.4)	4 (2.7)	40 (5.5)
Tumor Bulk (cm)[a], n (%)			
< 5	100 (61.0)	87 (58.8)	--
≥ 5	41 (25.0)	39 (26.4)	--
Missing	23 (14.0)	22 (14.9)	--
Bone marrow involvement (MSAS)[b], n (%)			
Yes	84 (51.2)	79 (53.4)	--
No	80 (48.8)	69 (46.6)	--
Ann Arbor staging for Lymphoma at enrollment (MSAS)[c], n (%)			
I	4 (2.4)	4 (2.7)	--
II	11 (6.7)	11 (7.4)	--
III	22 (13.4)	18 (12.2)	--
IV	124 (75.6)	112 (75.7)	--

Missing	3 (1.8)	3 (2.0)	--
MCL histology (MSAS)[d], n (%)			
Classic or Leukemic	129 (78.7)	116 (78.4)	--
Blastoid	16 (9.8)	16 (10.8)	--
Pleomorphic	19 (11.6)	16 (10.8)	--

Source/Program: SCS Table 14.2.2

[a] Assessed by Sponsor based on Investigator selected lymph node target lesions at Screening. [b] Based on assessment of bone marrow aspirate and/or biopsy at Screening. [c] Based on baseline assessment. [d] Based on local pathology results at Screening; not confirmed centrally.

Prior Cancer Treatment

Among the OMTSAS and the MSAS, patients had a median of 3 prior systematic therapies and patients in the MSAS as well as the MSAS-200 subgroup received similar prior lines of therapy to the OMTSAS. A summary of prior cancer treatments in the OMTSAS, the MSAS, and the MSAS-200 subgroup is provided below (Table 42).

Table 42: Summary of Prior Cancer Treatments

Parameter	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Prior Systemic Therapies, n (%)			
Prior BTK inhibitor	150 (91.5)	137 (92.6)	566 (78.1)
Prior BCL2	24 (14.6)	22 (14.9)	203 (28.0)
Prior chemotherapy	149 (90.9)	133 (89.9)	629 (86.8)
Prior anti-CD20 antibody	159 (97.0)	143 (96.6)	676 (93.2)
Prior PI3K agent	7 (4.3)	7 (4.7)	117 (16.1)
Prior immunomodulator	27 (16.5)	24 (16.2)	97 (13.4)
Prior CAR-T	13 (7.9)	13 (8.8)	50 (6.9)
Prior stem cell transplant	40 (24.4)	35 (23.6)	67 (9.2)
Auto-SCT	37 (22.6)	32 (21.6)	55 (7.6)
Allo-SCT	7 (4.3)	7 (4.7)	17 (2.3)
Other systemic therapy[1]	39 (23.8)	37 (25.0)	200 (27.6)
Number of lines of prior systemic therapy			
Median (range)	3.0 (1, 9)	3.0 (1, 9)	3.0 (0, 13)
0	0	0	1 (0.1)
1	13 (7.9)	13 (8.8)	48 (6.6)
2	60 (36.6)	52 (35.1)	199 (27.4)
3	34 (20.7)	30 (20.3)	153 (21.1)

Parameter	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
≥ 4	57 (34.8)	53 (35.8)	324 (44.7)
Number of lines of prior BTK inhibitor treatment, n (%)			
0	14 (8.5)	11 (7.4)	159 (21.9)
1	122 (74.4)	111 (75.0)	454 (62.6)
2	24 (14.6)	22 (14.9)	93 (12.8)
≥ 3	4 (2.4)	4 (2.7)	19 (2.6)
Reason for discontinuation from most recent prior BTK inhibitor, n (%)			
Disease progression	125 (76.2)	115 (77.7)	425 (58.6)
Toxicity	15 (9.1)	13 (8.8)	95 (13.1)
Other	8 (4.9)	7 (4.7)	41 (5.7)

[1] Other systemic therapies included: mTOR inhibitors, immunotherapies excluding anti-CD20, PD/PDL1 immunotherapies, proteasome inhibitors, and other molecular pathways/small molecule inhibitors.
Source/Program: SCS Table 14.2.3

The FDA's Assessment:

As noted above, the FDA's safety analysis sets are restricted to patients who received the 200mg dose and did not undergo dose escalation, in order to inform the safety profile of the intended registrational dose of pirtobrutinib. Further, the MCL safety analysis population is restricted to those who received a prior BTK inhibitor, to inform safety in the intended patient population.

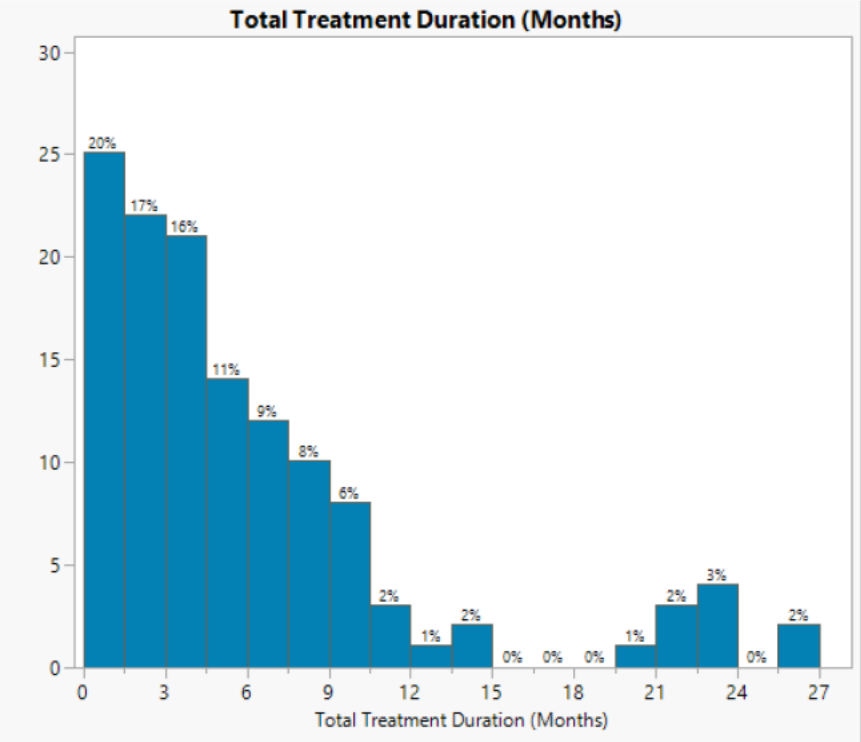
Table 43: FDA Safety Analysis Sets in Study 18001

Study / Description	Patient Description	Number of Patients
Study 18001 / Patients treated with pirtobrutinib monotherapy as of data cut-off of 31 January 2022	MCL	128
	B-cell Malignancies[1]	583

[1] Includes patients with CLL/SLL and other NHL (e.g., DLBCL, MZL, Richter's Transformation, FL, WM).
Source: FDA analysis based on ADSL.xpt

The median time on treatment in Study 18001 was 7.5 months (range: 0-27.1) across the pooled safety population and 3.8 months (range: 0.3, 26.9) in the MCL safety population. There was limited duration of exposure to pirtobrutinib in this study, particularly in patients with MCL, which limits the assessment of the safety and tolerability of pirtobrutinib. In the MCL safety population, 64% of patients were treated for less than 6 months, as shown in Figure 13 and Table 44 below.

Figure 13: Total Treatment Duration of Pirtobrutinib in FDA's MCL Safety Population



Source: FDA analysis based on ADSL.xpt

Table 44: Exposure to Pirtobrutinib in FDA's Safety Populations

Parameter	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Median time on treatment, months (range)	3.8 (0.3, 26.9)	7.5 months (0-27.1)
Relative dose intensity, mean (SD)	94.8 (9.2)	95.8 (9.4)
Duration of exposure, n (%)		
< 3 months	47 (36.7)	150 (25.7)
≥ 3 and < 6 months	35 (27.3)	107 (18.4)
≥ 6 and < 9 months	22 (17.2)	68 (11.7)
≥ 9 and < 12 months	11 (8.6)	87 (14.9)
≥ 12 and < 18 months	3 (2.3)	97 (16.6)
≥ 18 and < 24 months	8 (6.3)	68 (11.7)
≥ 24 and < 30 months	2 (1.6)	6 (1.0)

Source: FDA analysis based on ADSL.xpt

The demographics for the patients in the MCL safety population and pooled safety population were similar and are shown in Table 45 below. There was limited representation of Black patients and adequate representation of Hispanic and Asian patients, in comparison to the

demographics of U.S. patients diagnosed with MCL between 1992 and 2009 per the SEER 9 database (89% White, 4.1% Black, 3.7% Asian Pacific Islander, and 3.7% Hispanic) (Wang and Ma, 2014).

Table 45: Demographics of FDA's Safety Populations

Parameter	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Sex, n (%)		
Male	102 (79.7)	387 (66.4)
Female	26 (20.3)	196 (33.6)
Race, n (%)		
White	100 (78.1)	498 (85.4)
Black or African American	3 (2.3)	17 (2.9)
Native Hawaiian or Other Pacific Islander	0	3 (0.5)
Asian	18 (14.1)	42 (7.2)
American Indian or Alaska Native	2 (1.6)	2 (0.3)
Other	5 (3.9)	21 (3.6)
Unknown	0	0
Ethnicity, n (%)		
Hispanic or Latino	3 (2.3)	25 (4.3)
Not Hispanic or Latino	121 (94.5)	531 (91.1)
Unknown	4 (3.1)	27 (4.6)
Age at Enrollment, years		
Median (Range)	71 (46-88)	70.5 (46, 88)
< 50 years	1 (0.8)	23 (3.9)
≥ 65 years, n (%)	98 (76.6)	392 (67.2)
≥ 75 years, n (%)	43 (33.6)	153 (26.2)
≥ 85 years, n (%)	7 (5.5)	21 (3.6)

Source: FDA analysis based on ADSL.xpt

The baseline disease characteristics of the two safety populations are shown below in Table 46.

Table 46: Baseline Disease Characteristics of FDA's Safety Populations

Parameter	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Time since initial diagnosis to first dose (months)		
n	127	582
Mean (SD)	73.2 (49.9)	109.9 (80.1)
Median	73.2	98.5
Range	4.5, 209.6	0.5, 739.4
ECOG performance status at enrollment, n (%)		
0	77 (60.2)	293 (50.3)
1	49 (38.3)	257 (44.1)
2	2 (1.6)	32 (5.5)
Tumor Bulk (cm)[a], n (%)		
< 5	77 (60.2)	230 (39.5)
≥ 5	31 (24.2)	112 (19.2)
Missing	20 (15.6)	241 (41.3)
Bone marrow involvement (MSAS)[b], n (%)		
Yes	69 (53.9)	73 (12.5)
No	59 (46.1)	510 (87.5)
Ann Arbor staging for Lymphoma at enrollment (MCL Safety Population), n (%)		
I	4 (3.1)	=
II	10 (7.8)	=
III	12 (9.4)	=
IV	100 (78.1)	-
Missing	2 (1.6)	-
MCL histology (MSAS)[d], n (%)		
Classic or Leukemic	101 (78.9)	-
Blastoid	14 (10.9)	-
Pleomorphic	13 (10.1)	-

Source: FDA analysis based on ADSL.xpt

A summary of prior cancer therapies received in both safety populations is shown below in Table 47. The most common prior therapies received were anti-CD20 antibodies, chemotherapy, and BTK inhibitors. The most common reason for discontinuation of the most recent prior BTK inhibitor was disease progression (84.4% in the MCL safety population), with a minority of patients having discontinued any prior BTK inhibitor due to intolerance (13.3% in the MCL safety population).

Table 47: Summary of Prior Cancer Treatments in FDA's Safety Populations

Parameter	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Prior Systemic Therapies, n (%)		
Prior BTK inhibitor	128 (100)	457 (78.4)
Prior BCL2	21 (16.4)	161 (27.6)
Prior chemotherapy	113 (88.3)	500 (85.8)
Prior anti-CD20 antibody	123 (96.1)	541 (92.8)
Prior PI3K agent	5 (3.9)	92 (15.8)
Prior immunomodulator	22 (17.2)	76 (13.0)
Prior CAR-T	12 (9.4)	38 (6.5)
Prior SCT	28 (21.9)	52 (8.9)
Auto-SCT	25 (19.5)	42 (7.2)
Allo-SCT	7 (5.5)	14 (2.4)
Other systemic therapy[1]	36 (28.1)	166 (28.5)
Number of lines of prior systemic therapy		
Median (range)	3 (1, 9)	3 (0-13)
0	0	1 (0.2)
1	9 (7.0)	46 (7.9)
2	44 (34.4)	161 (27.6)
3	25 (19.5)	115 (19.7)
≥ 4	50 (39.1)	260 (44.6)
Number of lines of prior BTK inhibitor treatment, n (%)		
0	0	126 (21.6)
1	103 (80.5)	364 (62.4)
2	21 (16.4)	76 (13.0)
≥ 3	4 (3.1)	17 (2.9)
Reason for discontinuation from most recent prior BTK inhibitor, n (%)		
n	128	452
Disease progression	108 (84.4)	345 (59.2)
Toxicity	12 (9.4)	76 (13.0)
Other	8 (6.3)	31 (5.3)
Discontinued Any Prior BTK Inhibitor Due to Intolerance/Toxicity, n (%)		
n	128	457

Parameter	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Yes	17 (13.3)	96 (16.5)
No	109 (85.2)	356 (61.1)
Unknown	2 (1.6)	5 (0.9)

Source: FDA analysis based on ADSL.xpt

Relevant Characteristics of the Safety Population:

The Applicant's Position:

Please see tables in the previous section (Table 41 and Table 42) for the relevant characteristics of the Safety Population.

The FDA's Assessment:

The tables and descriptions in the previous section summarize the relevant characteristics of the safety population.

Adequacy of the Safety Database:

Data:

As of the data cut-off date, 31 January 2022, in the OMTSAS, a total of 725 patients had been treated with pirtobrutinib and 360 (49.7%) patients were continuing to receive treatment. The median time on treatment was 8.05 months (range: 0, 34.0); 655 (90.3%) patients had received at least one dose of pirtobrutinib at the proposed dose of 200 mg QD and 699 (96.4%) patients received 200 mg QD or higher. The median age of patients receiving pirtobrutinib was 68.0 years (range: 27, 95) and the population was heavily pretreated, having received a median of 3 prior lines of therapy (range: 0, 13). Most patients (566 [78.1%]) had received previous BTK inhibitor therapy, including 95 (13.1%) patients who had discontinued their most recent prior BTK inhibitor therapy due to intolerance/toxicity.

Safety data, across safety analysis sets, demonstrate that pirtobrutinib is well tolerated with a safety profile that is consistent with the BTK inhibitor drug class and/or the underlying disease setting and reflects the high degree of selectivity of pirtobrutinib. Toxicities were manageable per protocol guidance, which form the basis of proposed labeling. The Sponsor considers the data sufficient to characterize the safety profile of pirtobrutinib.

The FDA's Assessment:

As previously noted, the FDA disagrees with the Applicant's safety analysis sets, which include patients treated at variable doses of pirtobrutinib. The FDA's MCL analysis set includes patients with MCL who received a prior BTK inhibitor and received the 200mg starting dose, without

subsequent dose escalation (n=128). The FDA's pooled analysis set includes patients with B-cell malignancies who received the 200mg starting dose, without subsequent dose escalation (n=583). Thus, the number of patients in the safety populations is lower than that originally analyzed by the Applicant.

In the pooled safety population, the median time on pirtobrutinib was 7.5 months (range: 0 27.1) in the pooled safety population and 3.8 months (range: 0.3, 26.9) in the MCL safety population. This demonstrates that there was limited duration of exposure, likely related to the rates of disease progression and the limited follow-up on study prior to data cut-off, for a drug intended for continuous administration.

Demographic characteristics were notable for underrepresentation of Black patients, with adequate representation of other racial and ethnic minorities, and were otherwise generally representative of the MCL population. Baseline characteristics and summary of prior therapies of subjects treated with pirtobrutinib 200mg daily were generally representative of the MCL population. The number of subjects in each analysis set are adequate to inform safety of pirtobrutinib but the evaluation of safety data requires interpretation in the context of the limited duration of exposure. Overall, the safety database is adequate to provide an assessment of adverse reactions but will need to be supported by longer term safety data which is being requested through two post-marketing requirements (Section 13.0).

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

There were no data quality or integrity issues identified. This NDA submission contains all the required components of the eCTD. Analysis-ready, efficacy and safety datasets, which support the efficacy and safety of pirtobrutinib from Study 18001, are provided.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Categorization of Adverse Event

The Applicant's Position:

In Study 18001, the reported verbatim AE term was assigned a PT using MedDRA Version 24.0 and categorized by SOC. For each patient, recording of AEs began at the time that written informed consent was obtained. TEAEs were defined as those with onset after administration of

the first dose of study treatment (more simply referred to as "AEs" in this document). AEs were assessed for their potential relationship to study treatment by the Investigator (more simply referred to as "related" or "unrelated" to study treatment in this document) unless indicated otherwise. Conventional summary statistics (number and percent of patients) were generated for incidence of the following AE categories: all, related to study treatment, by maximum severity, serious, related serious, those resulting in treatment interruption, reduction, or discontinuation, and fatal.

The severity of each AE was graded according to CTCAE Version 5.0. AEs in special groups and circumstances were also analyzed, including by age group, sex, race, and previous BTK inhibitor treatment status. If a patient experienced repeat episodes of the same AE (as defined by the MedDRA SOC and PT), then the event with the highest reported severity grade and the strongest causal relationship to study treatment was used for purposes of incidence tabulations. In the event multiple actions taken with study treatment were reported for the same AE, the most significant action taken with study treatment was reported by the Investigator and used for purposes of incidence tabulations. The significance order (from most to least) of the action taken with drug is withdrawn, reduced, interrupted.

SAEs were defined as any AE that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event.

AESI for pirtobrutinib were identified based on the known class effects of BTK inhibitors and included infections (including serious and fatal infections), cytopenia (neutropenia, anemia, and thrombocytopenia), bleeding (including bruising and hemorrhage), and atrial fibrillation and atrial flutter. AEPCS were identified based on known occurrence in this patient population with possible contribution of BTK inhibitor drug class effect or based on regulatory request. The AEPCS included second primary malignancies, TLS, lymphocytosis, CV events (heart failure, supraventricular arrhythmias, ventricular arrhythmias, and hypertension), and rash.

To assess the impact of COVID-19 on the safety analysis, COVID-19-related events were evaluated and summarized, including frequency of COVID-19 AEs as well as serious and fatal events, events leading to study treatment modification or study treatment discontinuation, and other potential impacts.

Aggregate analyses were conducted for AESI, AEPCS, and COVID-19, where component PTs were aggregated under composite terms based on SMQ, SOC, or select PT analyses.

The FDA's Assessment:

For increased sensitivity of AE reporting, the FDA used a combination of individual MedDRA PTs and custom groupings of PTs, as defined in Appendix 19.5, which was adopted by the Applicant for reporting of safety results in labeling. Of note, the FDA analysis of safety does not distinguish between AEs that were determined to be "related" or "unrelated" to study

treatment by Investigator, and all AEs, regardless of causality, are reported.

Routine Clinical Tests

The Applicant's Position:

Analyses of data from clinical laboratory evaluations were consistent with the analyses of AEs reported in OMTSAS for Study 18001. Hematology (neutrophils, hemoglobin, platelets, lymphocytes) laboratory abnormalities were present at baseline; while some worsened while on treatment, these changes were transient with most returning to baseline or better as of the last postbaseline value recorded. No additional significant safety signals were identified from clinical laboratory evaluations.

The FDA's Assessment:
The FDA disagrees with the Applicant's statement that laboratory abnormalities were present at baseline. While some patients had laboratory abnormalities at baseline, which worsened while on treatment, others had normal values at baseline which became abnormal during study treatment. These categories of abnormalities were both captured as treatment-emergent laboratory abnormalities, in addition to those laboratory abnormalities which were unknown to have worsened from baseline.

The FDA also disagrees with the Applicant's statement that clinical laboratory evaluations did not identify any significant safety findings; the notable safety findings are summarized in Section 8.2.4.

8.2.4 Safety Results

Deaths

Data:

Among the 725 treated patients in the OMTSAS, 155 (21.4%) had died as of the data cut-off date; fewer of which (68/155 [43.9%]) were within 28 days of last study drug dose. Overall, the most common cause of death in the OMTSAS was progressive disease (86 [11.9%] patients). Consistent with these results, among the 640 patients in the OMTSAS treated at a starting dose of 200 mg QD, 133 (20.8%) had died as of the data cut-off date; fewer of which (65/133 [48.9%]) were within 28 days of last study drug dose with progressive disease being the most common cause of death (73 [11.4%] patients) overall.

In the OMTSAS, 45 (6.2%) patients experienced fatal AEs including 4 (0.6%) with fatal AEs that were assessed as being related to study treatment. Fatal AEs that occurred in more than 1 patient included COVID-19 pneumonia (9 [1.2%] patients); COVID-19 (6 [0.8%] patients); and

dyspnoea, multiple organ dysfunction syndrome, pneumonia, respiratory failure, sepsis, and septic shock (2 [0.3%] patients each). Three of the 45 fatal AEs had an onset date that was prior to the data cut-off but the date of death was after the data cut-off date; this included 1 of the 4 fatal AEs that were considered related to study drug (pneumonia necrotising). Notably, 29 of the 45 (64.4%) fatal AEs were in the SOC Infections and Infestations (Table 48) and approximately half (15 of 29 [51.7%]) of these were related to COVID-19.

The 4 fatal AEs that were assessed as being related to study treatment were all infectious in nature and included COVID-19 pneumonia, pneumonia necrotising, respiratory failure, and *Enterococcus faecium*-related septic shock. Of note, the fatal events pneumonia necrotising and respiratory failure both occurred in the setting of COVID-19 pneumonia. In all events, the Investigators did not deem pirtobrutinib directly causative to these fatal events, but the study treatment was believed to have significantly contributed to the event severity, considering the increased infectious risk associated with the drug class.

Deaths while receiving pirtobrutinib or within 28 days of their last dose prior to the cut-off date were assessed per the SAP. There were 68 (9.4%) patients who died either while receiving pirtobrutinib or within 28 days of their last dose prior to the cut-off date. Of these deaths, 30 (4.1%) were attributed to disease progression, and 38 (5.2%) were attributed to an AE including 3 (0.4%) that, as mentioned above, were deemed related to study treatment (respiratory failure, COVID-19 pneumonia, and *Enterococcus faecium*-related septic shock).

Table 48: Deaths on Treatment Due to AE Within 28 Days of Last Dose of Pirtobrutinib Administration (n = 38)

Patient	Pirtobrutinib starting dose	Disease Type	Total days of treatment	Study day of death	Days from last dose	SOC/PT/VERBATIM	Start date of AE	Relationship[1] of death to Pirtobrutinib
AE related to pirtobrutinib								
(b) (6)	200 mg QD	CLL	183	197	14	Respiratory, Thoracic and Mediastinal Disorders/Respiratory failure/DEATH, ITSELF, IS DUE TO HYPOXIC RESPIRATORY FAILURE IN SETTING OF COVID PNEUMONIA	197	Related
	200 mg QD	CLL	84	108	24	Infections and Infestations/COVID-19 pneumonia/COVID-19 LUNG INFECTION	89	Related
	200 mg QD	CLL	23	31	8	Infections and Infestations/Septic shock/ENTEROCOCCUS FAECIUM RELATED SEPTIC SHOCK	24	Related
AE not related to pirtobrutinib								
(b) (6)	200 mg QD	CLL	36	48	12	Infections and Infestations/Pneumonia fungal/FUNGAL PNEUMONIA	47	Not Related
	200 mg QD	CLL	241	247	6	Infections and Infestations/Septic shock/INFECTIONS AND INFESTATIONS-SEPTIC SHOCK	246	Not Related
	200 mg QD	CLL	15	19	4	Vascular Disorders/Shock/BLOOD AND LYMPHATIC DISORDERS - HEMODYNAMIC SHOCK	18	Not Related
	200 mg QD	B-PLL	5	8	3	Respiratory, Thoracic and Mediastinal Disorders/Respiratory failure/RESPIRATORY FAILURE	4	Not Related

Patient	Pirtobrutinib starting dose	Disease Type	Total days of treatment	Study day of death	Days from last dose	SOC/PT/VERBATIM	Start date of AE	Relationship[1] of death to Pirtobrutinib
(b) (6)	200 mg QD	CLL	14	16	2	Injury, Poisoning and Procedural Complications/Splenic rupture/SPLENIC RUPTURE	16	Not Related
	200 mg QD	CLL	159	160	1	Metabolism and Nutrition Disorders/Failure to thrive/FAILURE TO THRIVE	160	Not Related
	200 mg QD	DLBCL	94	119	25	Respiratory, Thoracic and Mediastinal Disorders/Dyspnoea/DYSPNEA	119	Not Related
	200 mg QD	MCL	56	79	23	Respiratory, Thoracic and Mediastinal Disorders/Respiratory failure/RESPIRATORY FAILURE	63	Not Related
	200 mg QD	MCL	686	713	27	Infections and Infestations/COVID-19 pneumonia/COVID-19 PNEUMONIA	696	Not Related
	200 mg QD	MCL	34	36	2	Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)/Malignant pleural effusion/MALIGNANT PLEURAL EFFUSION	35	Not Related
	200 mg QD	MCL	21	22	1	General Disorders and Administration Site Conditions/Sudden death/SUDDEN DEATH NOS	22	Not Related
	200 mg QD	WM	445	461	16	Infections and Infestations/COVID-19 pneumonia/COVID-19 PNEUMONIA	448	Not Related
	200 mg QD	MCL	26	33	7	General Disorders and Administration Site Conditions/Multiple organ dysfunction syndrome/MULTI-ORGAN FAILURE	26	Not Related
	200 mg QD	MCL	243	266	23	Cardiac Disorders/Cardiac arrest/CARDIAC ARREST	266	Not Related

Patient	Pirtobrutinib starting dose	Disease Type	Total days of treatment	Study day of death	Days from last dose	SOC/PT/VERBATIM	Start date of AE	Relationship[1] of death to Pirtobrutinib
(b) (6)	200 mg QD	CLL	173	185	12	General Disorders and Administration Site Conditions/Multiple organ dysfunction syndrome/MULTISYSTEM ORGAN FAILURE (RESPIRATORY AND RENAL FAILURE)	185	Not Related
	300 mg QD	CLL	542	561	19	Infections and Infestations/COVID-19/COVID-19 Infection	542	Not Related
	200 mg QD	MCL	201	210	9	Infections and Infestations/Mucormycosis/ MUCORMYCOSIS	204	Not Related
	200 mg QD	CLL	401	424	23	Infections and Infestations/Sepsis/SEPSIS	410	Not Related
	200 mg QD	MCL	38	51	13	Infections and Infestations/Streptococcal infection/INFECTIOUS AND INFESTATIONS OTHER, STREPTOCOCCUS, SALIVARIUS AND GORDONII	32	Not Related
	200 mg QD	CLL	27	37	10	Infections and Infestations/Legionella infection/LEGIONELLA PNEUMOPHILA BACTERIAL INFECTION	28	Not Related
	200 mg QD	MCL	28	45	17	Respiratory, Thoracic and Mediastinal Disorders/Respiratory failure/RESPIRATORY FAILURE	36	Not Related
	200 mg QD	CLL	235	254	19	Infections and Infestations/COVID-19/SARS-COV-2	235	Not Related
	200 mg QD	CLL	562	570	8	Infections and Infestations/Escherichia sepsis/E. COLI SEPSIS	563	Not Related
	200 mg QD	CLL	276	279	3	Infections and Infestations/COVID-19 pneumonia/COVID-19 PNEUMONIA	269	Not Related

Patient	Pirtobrutinib starting dose	Disease Type	Total days of treatment	Study day of death	Days from last dose	SOC/PT/VERBATIM	Start date of AE	Relationship[1] of death to Pirtobrutinib
(b) (6)	200 mg QD	CLL	125	128	3	Infections and Infestations/COVID-19/SARS-COV-2 INFECTION	128	Not Related
	200 mg QD	SLL	10	19	9	Infections and Infestations/COVID-19/SARS-COV-2 INFECTION	9	Not Related
	200 mg QD	RICHTER SYNDROME/ TRANSFORMATION	297	318	21	Infections and Infestations/COVID-19 pneumonia/SARS-COV-2 PNEUMONIA	297	Not Related
	200 mg QD	CLL	446	458	12	Infections and Infestations/COVID-19/COVID 19	446	Not Related
	200 mg QD	CLL	292	315	23	Infections and Infestations/Sepsis/SEPSIS	292	Not Related
	200 mg QD	CLL	106	126	20	Infections and Infestations/COVID-19 pneumonia/COVID RELATED PNEUMONIA	106	Not Related
			106	126	20	Nervous System Disorders/Cerebrovascular accident/MASSIVE CVA STROKE	124	Not Related
	200 mg QD	WM	305	320	15	Infections and Infestations/Bacterial sepsis/MORGANELLA MORGANII-RELATED SEPSIS	307	Not Related
	200 mg QD	CLL	532	534	2	Infections and Infestations/COVID-19 pneumonia/COVID-19 PNEUMONIA	531	Not Related
	200 mg QD	CLL	43	53	10	Infections and Infestations/COVID-19 pneumonia/COVID 19 PNEUMONIA	41	Not Related
	200 mg QD	CLL	6	25	19	Infections and Infestations/Infectious pleural effusion/E.COLI RELATED RIGHT PLEURAL EFFUSION	5	Not Related

Patient	Pirtobrutinib starting dose	Disease Type	Total days of treatment	Study day of death	Days from last dose	SOC/PT/VERBATIM	Start date of AE	Relationship[1] of death to Pirtobrutinib
(b) (6)	200 mg QD	MCL	56	56	0	Vascular Disorders/Haemorrhage/MASSIVE HAEMORRHAGE	56	Not Related

[1] Per Investigator assessment.

Source/Program: SCS Listing 16.2.3.2

The Applicant's Position:

Overall, the deaths in Study 18001 are largely related to the study disease of the patient population.

The FDA's Assessment:

FDA disagrees with the Applicant's assessment of attribution of fatal AEs. All fatalities occurring within the 28-day window following treatment with pirtobrutinib, with the exception of those attributed to disease progression or those that occurred following subsequent anticancer therapy, are considered fatal AEs. The FDA classified deaths occurring in the context of untreated PD as deaths due to PD.

Table 49 summarizes all reported deaths with causes in the MCL safety population. Fatal AEs (within 30 days of the last dose of pirtobrutinib) occurred in 7% of patients treated with pirtobrutinib, most commonly infections, and included cases of pneumonia, mucormycosis infection, and streptococcal infection.

Table 49: Summary of Deaths in FDA's MCL Safety Population

	Number (%) of Subjects
Deaths, n (%)	35 (27.3)
Primary Cause of Death	
Disease Progression	20 (15.6)
Adverse Event	9 (7.0)
Other	6 (4.7)
Categories of Fatal AEs	
Infection[1]	6 (4.7)
Respiratory Failure	1 (0.8)
Bleeding Disorder[2]	1 (0.8)
General[3]	1 (0.8)

[1] Fatal infections included COVID-19 pneumonia, mucormycosis infection, and streptococcal infection. One of the COVID-19 fatalities was also associated with complications related to pulmonary embolism.
[2] The fatal bleeding event was a massive hemorrhage of unknown location.
[3] The general event was an event of sudden death with unknown cause.
Source: FDA analysis based on ADAE.xpt

Serious Adverse Events

Data:

In the OMTSAS, 255 (35.2%) patients experienced one or more SAEs, and SAEs considered to be related to study treatment occurred in 41 (5.7%) patients (Table 50).

No SAEs were reported in more than 5% of the overall safety population. The most common SOC category for SAEs was Infections and Infestations and the most common SAE by preferred term was pneumonia.

There were 31 (4.3%) patients who had SAEs leading to discontinuation, 8 (1.1%) of which were treatment-related (2 of COVID-19 pneumonia, and 1 each of cholecystitis, febrile neutropenia, myelodysplastic syndrome, neuropathy peripheral, respiratory failure, septic shock, and staphylococcal sepsis). There were 45 (6.2%) patients who had fatal SAEs including 9 (1.2%) with COVID-19 pneumonia, 6 (0.8%) with COVID-19, 4 (0.6%) with respiratory failure, and 2 (0.3%) each with multiple organ dysfunction syndrome, pneumonia, sepsis, and septic shock. All other fatal SAEs occurred in only 1 patient each.

The frequency and nature of SAEs was similar between the MSAS, the MSAS subgroup receiving a starting dose of 200 mg QD, and OMTSAS. The SOC in which SAEs were most commonly reported was Infections and Infestations (129 [17.8%] patients).

Table 50: Serious Adverse Events Occurring in ≥ 1% of Patients by Preferred Term in Order of Decreasing Incidence in the OMTSAS

	MSAS (N = 164)		MSAS-200 Subgroup (N = 148)		OMTSAS (N = 725)	
PT, n (%)	**All**	**Related**	**All**	**Related**	**All**	**Related**
Any SAE	55 (33.5)	8 (4.9)	52 (35.1)	6 (4.1)	255 (35.2)	41 (5.7)
Pneumonia	13 (7.9)	3 (1.8)	11 (7.4)	2 (1.4)	34 (4.7)	8 (1.1)
COVID-19 pneumonia	5 (3.0)	0	5 (3.4)	0	28 (3.9)	2 (0.3)
COVID-19	2 (1.2)	0	2 (1.4)	0	17 (2.3)	0
Febrile neutropenia	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)	13 (1.8)	8 (1.1)
Anaemia	1 (0.6)	0	1 (0.7)	0	12 (1.7)	2 (0.3)
Pyrexia	1 (0.6)	0	1 (0.7)	0	11 (1.5)	1 (0.1)
Sepsis	3 (1.8)	1 (0.6)	3 (2.0)	1 (0.7)	11 (1.5)	2 (0.3)
Acute kidney injury	2 (1.2)	0	2 (1.4)	0	10 (1.4)	0
Bacteraemia	1 (0.6)	0	1 (0.7)	0	7 (1.0)	1 (0.1)
Pleural effusion	3 (1.8)	0	3 (2.0)	0	7 (1.0)	0
Respiratory failure	2 (1.2)	0	2 (1.4)	0	7 (1.0)	1 (0.1)
Urinary tract infection	0	0	0	0	7 (1.0)	0

Source/Program: SCS Table 14.4.14, SCS Table 14.4.15

The FDA's Assessment:

In the pooled safety population, 34.1% of patients experienced one or more SAEs. The most common SAEs in the pooled safety population were infections (which included pneumonia, COVID-19, and sepsis), and febrile neutropenia. The rates and types of SAEs seen in the MCL safety population were similar to those seen in the pooled safety population. In the pooled safety population, there were 25 (4.3%) patients who had SAEs leading to treatment discontinuation, most commonly due to pneumonia, sepsis, and COVID-19. There were 37 (6.3%) patients who had fatal SAEs, also most commonly due to pneumonia, sepsis, and COVID-19.

Table 51: Serious Adverse Events in FDA's Safety Populations

	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Any SAE, n (%)	49 (38.3)	199 (34.1)
Any Grade ≥3 SAE	47 (36.7)	181 (31.0)
Any Grade ≥4 SAE	15 (11.7)	52 (8.9)
SAEs with ≥2% Incidence in the Pooled Safety Population		
Pneumonia	18 (14.1)	54 (9.3)
Sepsis	3 (2.3)	19 (3.3)
COVID-19	1 (0.8)	14 (2.4)
Febrile Neutropenia	2 (1.6)	14 (2.4)

Source: FDA analysis based on ADAE.xpt

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

In the OMTSAS, 45 (6.2%) patients experienced an AE that led to permanent treatment discontinuation (Table 52). Of the AEs that led to permanent treatment discontinuation, only COVID-19 pneumonia (4 [0.6%]), COVID-19 and myelodysplastic syndrome (3 [0.4%] each), and pneumonia, sepsis, and squamous cell carcinoma (2 [0.3%] each) occurred in more than one patient. However, multiple AEs leading to discontinuation represent events of an infectious nature and second primary malignancy. The SOCs with the highest incidences of AEs leading to treatment discontinuation were Infections and Infestations (17 [2.3%]) followed by Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) (8 [1.1%]). No other SOCs had AEs leading to treatment discontinuation with incidences ≥ 1%.

There were 15 (2.1%) patients who had treatment permanently discontinued for an AE related to study treatment in the OMTSAS. Each study treatment-related AE that led to discontinuation occurred in 1 (0.1%) patient only (Table 52). The incidences of study treatment-related AEs that

led to the treatment discontinuation were generally similar across analysis sets (MSAS: 5 [3.0%] patients; MSAS-200: 3 [2.0%] patients; OMTSAS: 15 [2.1%] patients).

Table 52: Adverse Events Leading to Treatment Discontinuation in Any Analysis Set in Order of Decreasing Incidence in the OMTSAS[1]

	MSAS (N = 164)		MSAS-200 Subgroup (N = 148)		OMTSAS (N = 725)	
PT, n (%)	**All**	**Related**	**All**	**Related**	**All**	**Related**
Any AE leading to discontinuation of study treatment	15 (9.1)	5 (3.0)	12 (8.1)	3 (2.0)	45 (6.2)	15 (2.1)
COVID-19*	1 (0.6)	0	1 (0.7)	0	7 (1.0)	1 (0.1)
Myelodysplastic syndrome	1 (0.6)	0	1 (0.7)	0	3 (0.4)	1 (0.1)
Neutropenia*	2 (1.2)	2 (1.2)	1 (0.7)	1 (0.7)	3 (0.4)	3 (0.4)
Pneumonia	2 (1.2)	0	2 (1.4)	0	2 (0.3)	0
Sepsis	1 (0.6)	0	1 (0.7)	0	2 (0.3)	0
Squamous cell carcinoma	0	0	0	0	2 (0.3)	0
Abdominal pain	0	0	0	0	1 (0.1)	0
Acute kidney injury	1 (0.6)	0	1 (0.7)	0	1 (0.1)	0
Acute myeloid leukaemia	0	0	0	0	1 (0.1)	0
Acute myocardial infarction	1 (0.6)	0	1 (0.7)	0	1 (0.1)	0
Alopecia	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.1)	1 (0.1)
Anaemia*	0	0	0	0	1 (0.1)	1 (0.1)
Anal squamous cell carcinoma	1 (0.6)	0	0	0	1 (0.1)	0
Anxiety	0	0	0	0	1 (0.1)	0
Bacterial sepsis	0	0	0	0	1 (0.1)	0
Blood alkaline phosphatase increased	0	0	0	0	1 (0.1)	0
Cholecystitis	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.1)	1 (0.1)
Chronic respiratory failure	0	0	0	0	1 (0.1)	0
Dyspnoea	0	0	0	0	1 (0.1)	0
Eyelid ptosis	0	0	0	0	1 (0.1)	0
Fatigue	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.1)	1 (0.1)
Gastrointestinal haemorrhage	0	0	0	0	1 (0.1)	0
Hyperkalaemia	0	0	0	0	1 (0.1)	0

	MSAS (N = 164)		MSAS-200 Subgroup (N = 148)		OMTSAS (N = 725)	
PT, n (%)	**All**	**Related**	**All**	**Related**	**All**	**Related**
Infective aneurysm	1 (0.6)	0	1 (0.7)	0	1 (0.1)	0
Mucormycosis	1 (0.6)	0	1 (0.7)	0	1 (0.1)	0
Multiple organ dysfunction syndrome	1 (0.6)	0	1 (0.7)	0	1 (0.1)	0
Myalgia	0	0	0	0	1 (0.1)	1 (0.1)
Neuropathy peripheral	0	0	0	0	1 (0.1)	1 (0.1)
Pancreatic duct rupture	0	0	0	0	1 (0.1)	0
Pancytopenia	0	0	0	0	1 (0.1)	0
Pneumonitis	1 (0.6)	1 (0.6)	0	0	1 (0.1)	1 (0.1)
Rash*	0	0	0	0	1 (0.1)	1 (0.1)
Respiratory failure	0	0	0	0	1 (0.1)	1 (0.1)
Septic shock	0	0	0	0	1 (0.1)	1 (0.1)
Staphylococcal sepsis	0	0	0	0	1 (0.1)	1 (0.1)
Stent-graft endoleak	1 (0.6)	0	1 (0.7)	0	1 (0.1)	0
Streptococcal infection	1 (0.6)	0	1 (0.7)	0	1 (0.1)	0
Tumour pain	0	0	0	0	1 (0.1)	0
Urosepsis	0	0	0	0	1 (0.1)	0
Weight decreased	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.1)	1 (0.1)

[1] Based on Adverse Events Analysis Dataset.

*Anaemia includes anaemia and aplastic anaemia; neutropenia includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; COVID-19 includes COVID-19, COVID-19 pneumonia, SARS-CoV2 test positive, Coronavirus test positive, and post-acute COVID-19 syndrome; rash includes rash, rash maculo-papular, rash macular, rash pruritic, rash popular, rash pustular, rash erythematous, injection site rash, medical device site rash

Source/Program: SCS Table 14.4.12, SCS Table 14.4.13; SCS Table 14.4.17.1.1, SCS Table 14.4.17.2.1, SCS Table 14.4.17.3.1

The FDA's Assessment:

In the pooled safety population, 35 (6.0%) patients permanently discontinued study treatment due to an AE. The most common AEs leading to treatment discontinuation were pneumonia, sepsis, and COVID-19 in more than 1 patient each; the remainder of AEs leading to treatment discontinuation occurred in 1 patient each. Table 53 shows the AEs leading to treatment discontinuation (with a threshold of ≥2% in the pooled safety population) in each safety population.

Table 53: AEs Leading to Treatment Discontinuation in FDA's Safety Populations

	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
AE Leading to Treatment Discontinuation, n (%)	12 (9.4)	35 (6.0)
Pneumonia	3 (2.3)	7 (1.2)
Sepsis	1 (0.8)	5 (0.9)
COVID-19	0	2 (<0.1)

Source: FDA analysis based on ADAE.xpt

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

The tables below provide a summary of dose interruptions (Table 54) and dose reductions (Table 55). Overall, reasons for dose modifications due to AEs were similar and comparable in the OMTSAS, the MSAS, and the MSAS-200 subgroup.

Table 54: Adverse Events Leading to Dose Interruption Occurring in ≥ 1% of Patients in Order of Decreasing Incidence in the OMTSAS[1]

	MSAS (N = 164)	MSAS-200 mg Subgroup (N = 148)	OMTSAS (N = 725)
PT, n (%)			
Any AE leading to dose interruption	47 (28.7)	43 (29.1)	252 (34.8)
COVID-19*	4 (2.4)	4 (2.7)	45 (6.2)
Neutropenia*	8 (4.9)	8 (5.4)	44 (6.1)
Pneumonia	8 (4.9)	7 (4.7)	23 (3.2)
Anaemia*	3 (1.8)	3 (2.0)	14 (1.9)
Diarrhoea	1 (0.6)	1 (0.7)	12 (1.7)
Lipase increased	0	0	8 (1.1)
Thrombocytopenia*	4 (2.4)	3 (2.0)	8 (1.1)
Rash*	2 (1.2)	2 (1.4)	8 (1.1)
Acute kidney injury	1 (0.6)	1 (0.7)	7 (1.0)
Alanine aminotransferase increased	2 (1.2)	2 (1.4)	7 (1.0)
Fatigue	0	0	7 (1.0)
Pyrexia	0	0	7 (1.0)
Upper respiratory tract infection	4 (2.4)	4 (2.7)	7 (1.0)

[1] Based on Adverse Events Analysis Dataset.

*Anaemia includes anaemia and aplastic anaemia; neutropenia includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; thrombocytopenia includes platelet count decreased and thrombocytopenia; COVID-19 includes COVID-19, COVID-19 pneumonia, SARS-CoV2 test positive, Coronavirus test positive, and post-acute COVID-19 syndrome; rash includes rash, rash maculo-papular, rash macular, rash pruritic, rash popular, rash pustular, rash erythematous, injection site rash, medical device site rash.

Source/Program: SCS Table 14.4.8, SCS Table 14.4.17.1.1, SCS Table 14.4.17.2.1, SCS Table 14.4.17.3.1

Table 55: Adverse Events Leading to Dose Reduction Occurring in >1 Patient in Order of Decreasing Incidence in the OMTSAS[1]

PT, n (%)	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Any AE leading to dose reduction	8 (4.9)	6 (4.1)	37 (5.1)
Neutropenia*	2 (1.2)	1 (0.7)	13 (1.8)
Fatigue	0	0	3 (0.4)
Anaemia*	0	0	2 (0.3)
Thrombocytopenia*	1 (0.6)	1 (0.7)	2 (0.3)
Rash*	1 (0.6)	1 (0.7)	2 (0.3)

[1] Based on Adverse Events Analysis Dataset.
*Anaemia includes anaemia and aplastic anaemia; neutropenia includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; thrombocytopenia includes platelet count decreased and thrombocytopenia; rash includes rash, rash maculo-papular, rash macular, rash pruritic, rash popular, rash pustular, rash erythematous, injection site rash, medical device site rash
Source/Program: SCS Table 14.4.10, SCS Table 14.4.17.1.1, SCS Table 14.4.17.2.1

The FDA's Assessment:

In the pooled safety population, 194 (33.3%) patients interrupted study treatment due to an AE. The most common AEs leading to treatment interruption were neutropenia, pneumonia, and COVID-19. Table 56 shows the AEs leading to treatment interruption (with a threshold of ≥1.5% in the pooled safety population) in each safety population.

Table 56: Dose Interruptions Due to AEs in FDA's Safety Populations

	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
AE Leading to Treatment Interruption, n (%)	41 (32.0)	194 (33.3)
Neutropenia	7 (5.5)	34 (5.8)
Pneumonia	10 (7.8)	33 (5.6)
COVID-19	2 (1.6)	21 (3.6)
Anemia	3 (2.3)	12 (2.1)
Diarrhea	1 (0.8)	9 (1.5)
Sepsis	1 (0.8)	9 (1.5)

Source: FDA analysis based on ADAE.xpt

In the pooled safety population, 24 (4.1%) patients had dose reductions of study treatment due to AEs. AEs leading to dose reduction that occurred in more than one patient each were neutropenia, rash, fatigue, and musculoskeletal pain; the remainder occurred in one patient each. Table 57 shows the AEs leading to dose reduction (with a threshold of ≥1 patient each in the pooled safety population) in each safety population.

Table 57: Dose Reductions Due to AEs Occurring in FDA's Safety Populations

	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
AE Leading to Dose Reductions, n (%)	6 (4.7)	24 (4.1)
Neutropenia	1 (0.8)	8 (1.4)
Rash	1 (0.8)	3 (0.5)
Fatigue	0	2 (0.3)
Musculoskeletal Pain	0	2 (0.3)

Source: FDA analysis based on ADAE.xpt

The Applicant's Position:

Adverse Events of Special Interest

AESIs were identified based on the known safety profile of covalent BTK inhibitor therapies, nonclinical toxicology, and emerging safety data during the conduct of the study. Aggregate analysis was conducted as part of the analysis of AESI to characterize the safety profile of these events and included the following composite terms: cytopenia (specifically, neutropenia, anemia, and thrombocytopenia), infections, bleeding (including bruising and hemorrhage), and atrial fibrillation and atrial flutter.

The most common AESIs (occurring in ≥ 15% of patients) included infections (342 [47.2%]), bruising (168 [23.2%]), and neutropenia (165 [22.8%]) (Table 58).

There were no notable differences observed in the MSAS analysis set or the MSAS-200 subgroup compared to the OMTSAS in the analysis of the AESI.

Table 58: Summary of Adverse Events of Special Interest

Composite term, n (%)	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Infection (including COVID-19)			
Any grade	59 (36.0)	53 (35.8)	342 (47.2)
Grade 3 or 4	24 (14.6)	23 (15.5)	99 (13.7)
Grade 5	4 (2.4)	3 (2.0)	29 (4.0)
Infection (excluding COVID-19)			
Any grade	54 (32.9)	48 (32.4)	300 (41.4)
Grade 3 or 4	20 (12.2)	19 (12.8)	81 (11.2)
Grade 5	3 (1.8)	2 (1.4)	14 (1.9)
Bleeding			
Bruising[1]			
Any grade	27 (16.5)	22 (14.9)	168 (23.2)
Grade 3 or 4	0	0	0
Hemorrhage			
Any grade	25 (15.2)	21 (14.2)	126 (17.4)
Grade 3 or 4	5 (3.0)	5 (3.4)	15 (2.1)
Grade 5	1 (0.6)	1 (0.7)	1 (0.1)
Neutropenia[1]			
Any grade	23 (14.0)	21 (14.2)	165 (22.8)
Grade 3 or 4	22 (13.4)	20 (13.5)	143 (19.7)
Anemia[1]			
Any grade	21 (12.8)	21 (14.2)	102 (14.1)
Grade 3 or 4	8 (4.9)	8 (5.4)	57 (7.9)
Thrombocytopenia[1]			
Any grade	24 (14.6)	23 (15.5)	94 (13.0)
Grade 3 or 4	11 (6.7)	10 (6.8)	48 (6.6)
Atrial fibrillation/flutter[1]			
Any grade	6 (3.7)	6 (4.1)	19 (2.6)
Grade 3 or 4	2 (1.2)	2 (1.4)	7 (1.0)

[1] No Grade 5 AESI was reported for this category in Study 18001.

Source/Program: SCS Table 14.4.17.1

Adverse Events of Potential Clinical Significance

AEPCS were identified for routine surveillance throughout the pirtobrutinib clinical program and were assessed during Study 18001. These AEPCS do not necessarily represent known on-

target safety risks of the BTK inhibitor drug class but are potentially clinically significant based on general risks associated with anticancer treatment in this patient population, or on-target effects of the BTK inhibitor drug class that are potential, but not identified, risks. Aggregate analysis was conducted as part of the analysis of AEPCS and included the following composite terms: lymphocytosis, TLS, second primary malignancies, CV events (heart failure, supraventricular arrhythmias, ventricular arrhythmias, and hypertension), and rash. A summary of AEPCS is displayed in Table 59.

There were no notable differences observed in the MSAS analysis set or the MSAS-200 subgroup compared to the OMTSAS in the analysis of the AEPCS.

Table 59: Summary of Adverse Events of Potential Clinical Significance[1]

n (%)	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Rash			
Any grade	14 (8.5)	13 (8.8)	89 (12.3)
Grade 3 or 4	1 (0.6)	1 (0.7)	3 (0.4)
Cardiovascular events			
Hypertension			
Any grade	6 (3.7)	6 (4.1)	69 (9.5)
Grade 3 or 4	0	0	20 (2.8)
Heart failure			
Any grade	1 (0.6)	1 (0.7)	10 (1.4)
Grade 3 or 4	0	0	5 (0.7)
Ventricular tachyarrhythmias			
Any grade	1 (0.6)	1 (0.7)	5 (0.7)
Grade 3 or 4	0	0	0
Supraventricular tachyarrhythmias[2]			
Any grade	4 (2.4)	4 (2.7)	21 (2.9)
Grade 3 or 4	0	0	4 (0.6)
Second primary malignancy			
Any grade	6 (3.7)	5 (3.4)	48 (6.6)
Grade 3 or 4	1 (0.6)	1 (0.7)	9 (1.2)
Second primary malignancy: nonmelanoma skin cancer			
Any grade	3 (1.8)	3 (2.0)	33 (4.6)

n (%)	MSAS (N = 164)	MSAS-200 Subgroup (N = 148)	OMTSAS (N = 725)
Grade 3 or 4	0	0	1 (0.1)
Second primary malignancy: excluding nonmelanoma skin cancer			
Any grade	4 (2.4)	3 (2.0)	17 (2.3)
Grade 3 or 4	1 (0.6)	1 (0.7)	8 (1.1)
Lymphocytosis			
Any grade	10 (6.1)	9 (6.1)	35 (4.8)
Grade 3 or 4	7 (4.3)	6 (4.1)	22 (3.0)
TLS			
Any grade	1 (0.6)	1 (0.7)	3 (0.4)
Grade 3 or 4	1 (0.6)	1 (0.7)	3 (0.4)

[1] No Grade 5 AEPCS was reported in Study 18001.

[2] Supraventricular tachyarrhythmias excludes adverse events of atrial fibrillation and atrial flutter.

Source/Program: SCS Table 14.4.17.2

The FDA's Assessment:

The adverse events of special interest that were evaluated were infections, cytopenias, hemorrhage, cardiac arrhythmias including atrial fibrillation or flutter, and SPMs, and are summarized below for the MCL safety population and the pooled safety population. Of note, the analysis of infection excluding cases of COVID-19 was not performed by FDA. The FDA considers that the overall 'Infection' grouping should include all infections, including COVID-19.

Table 60: Adverse Events of Special Interest in FDA's Safety Populations

AE Term, n (%)	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Infection (including COVID-19)		
Any grade	50 (39.1)	241 (41.3)
Grade 3 or 4	24 (18.8)	83 (14.2)
Grade 5	3 (2.3)	24 (4.1)
Bleeding		
Bruising*		
Any grade	21 (16.4)	114 (19.6)
Grade 3 or 4	0	0
Hemorrhage		
Any grade	16 (12.5)	81 (13.9)

AE Term, n (%)	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Grade 3 or 4	4 (3.1)	11 (1.9)
Grade 5	1 (0.8)	1 (0.2)
Neutropenia*^		
Any grade	45 (36.0)	231 (40.8)
Grade 3 or 4	20 (16.0)	133 (23.5)
Anemia*^		
Any grade	53 (41.7)	212 (37.1)
Grade 3 or 4	11 (8.6)	64 (11.2)
Thrombocytopenia*^		
Any grade	47 (38.5)	149 (26.6)
Grade 3 or 4	17 (13.9)	60 (10.7)
Atrial fibrillation/flutter*		
Any grade	6 (3.7)	16 (2.7)
Grade 3 or 4	2 (1.2)	6 (1.0)
Second primary malignancies		
Any grade	4 (3.1)	34 (5.8)
Grade 3 or 4	1 (0.8)	6 (1.0)
Grade 5	0	0

* No Grade 5 AESI was reported for this category.
^ Analysis of laboratory AEs was based on lab-shift data
Source: FDA analysis based on ADAE.xpt

8.2.4.1 Analyses of Selected AESIs

Detailed analyses of each AESI warranting a more thorough evaluation are provided below.

8.2.4.1.1 *Infections*

In the pooled safety population, there was a 41.3% incidence of any-grade infection, with a 16.5% incidence of Grade ≥3 infection. A summary of the types of infection that occurred ≥1% of the pooled safety population are shown in Table 61 below. The most common infections of any grade were pneumonia, COVID-19, and URI. The most common fatal infections were COVID-19, pneumonia, and sepsis. Opportunistic infections included herpesvirus infection (1.7%), aspergillus infection (0.3%), and extrapulmonary tuberculosis (0.2%).

Table 61: Types of Infections in the Pooled Safety Population

Type of infection	Pooled Safety Population (n=583)		
	Any Grade n (%)	Grade 3-4 n (%)	Grade 5
Pneumonia	74 (12.7)	46 (7.9)	10 (1.7)
COVID-19	65 (11.1)	21 (3.6)	11 (1.9)
Upper Respiratory Tract Infection	57 (9.8)	4 (0.7)	0
Urinary Tract Infection	41 (7.0)	4 (0.7)	0
Sepsis	25 (4.3)	18 (3.1)	6 (1.0)
Respiratory Tract Infection	21 (3.6)	2 (0.3)	0
Herpesvirus Infection	10 (1.7)	1 (0.2)	0
Lower Respiratory Tract Infection	9 (1.5)	1 (0.2)	0
Skin Infection	9 (1.5)	1 (0.2)	0

Source: FDA analysis based on ADAE.xpt

8.2.4.1.2 *Hemorrhage*

In the pooled safety population, major bleeding, defined as serious or Grade ≥3 bleeding, or any grade of CNS or retinal bleed, occurred in 2.7%, with gastrointestinal bleeding as the leading site. Excluding Grade 2 nonserious retinal bleeding, this incidence was 2.4%.

Table 62: Sites of Major Bleeding in Pooled Safety Population

Site	N patients (16 total)	% (from N of 583)
GI	8	1.4
Retinal	3	0.5
Unspecified	3	0.5
Mucosal*	1	0.2
Intracranial	1	0.2
Soft tissue	1	0.2

*Mucosal bleeding refers to a case of epistaxis
Source: FDA analysis based on ADAE.xpt

The incidence of any-grade bleeding in FDA's safety populations is described in Table 66.

8.2.4.1.3 *Cardiac Arrhythmias*

In the pooled safety population, there was a 2.7% incidence of atrial fibrillation and flutter. Due to the known association of other BTK inhibitors with cardiac arrhythmias, including ventricular arrhythmias, FDA also analyzed the incidence of cardiac arrhythmias, including conduction disorders, and ventricular arrhythmias. Given that PACs and PVCs may not be clinically significant and since PVCs were generally low-grade and asymptomatic, they were excluded

from this analysis. Approximately half of all cardiac arrhythmias were atrial fibrillation or flutter and there was a low incidence of Grade 3 or greater cardiac arrhythmias. There was a low incidence of ventricular arrhythmias; the one Grade 5 event that was identified through the 'Ventricular arrhythmia and cardiac arrest' HLT was a case of Grade 5 cardiac arrest of unknown etiology.

Table 63: Cardiac Arrhythmias in MCL and Pooled Safety Populations

AE Term, n (%)	MCL Safety Population (N=128)	Pooled Safety Population (N=583)
Cardiac arrhythmias*		
Any grade	8 (6.3)	27 (4.6)
Grade 3 or 4	2 (1.6)	6 (1.0)
Grade 5	1 (0.8)	1 (0.2)
Ventricular arrhythmias and cardiac arrest^		
Any grade	3 (2.3)	4 (0.7)
Grade 3 or 4	0	1 (0.2)
Grade 5	1 (0.6)	1 (0.2)

* Cardiac arrythmias were identified using the 'Cardiac arrhythmia' high level group term, excluding PACs, PVCs, bradycardia, and tachycardia
^ Ventricular arrhythmias and cardiac arrest were identified using the 'Ventricular arrhythmia and cardiac arrest' high level term, excluding PVCs
Source: FDA analysis based on ADAE.xpt

Clinical reviewer's comments:

- ***The data are limited by the relatively short duration of exposure to pirtobrutinib and from experience with other BTK inhibitors, it is known that cardiac arrythmias may develop after longer-term exposure following 1 year or more (Bhat et al. 2022). However, given the current data with pirtobrutinib, there is no clear signal for overall cardiac toxicity or ventricular arrhythmias. A safety PMR is being issued to characterize the longer-term safety profile of pirtobrutinib, including the risk of cardiac arrythmias with at least 24 months of follow up..***

8.2.4.1.4 *Second Primary Malignancies*

There was a 5.8% incidence of SPMs in the pooled safety population. Table 64 summarizes the types of SPMs that occurred, more the half of which were non-melanoma skin cancers. Other types of SPMs that occurred (in decreasing frequency) were melanoma, solid tumors (including breast and GU cancers), and hematologic malignancies (including AML and MDS).

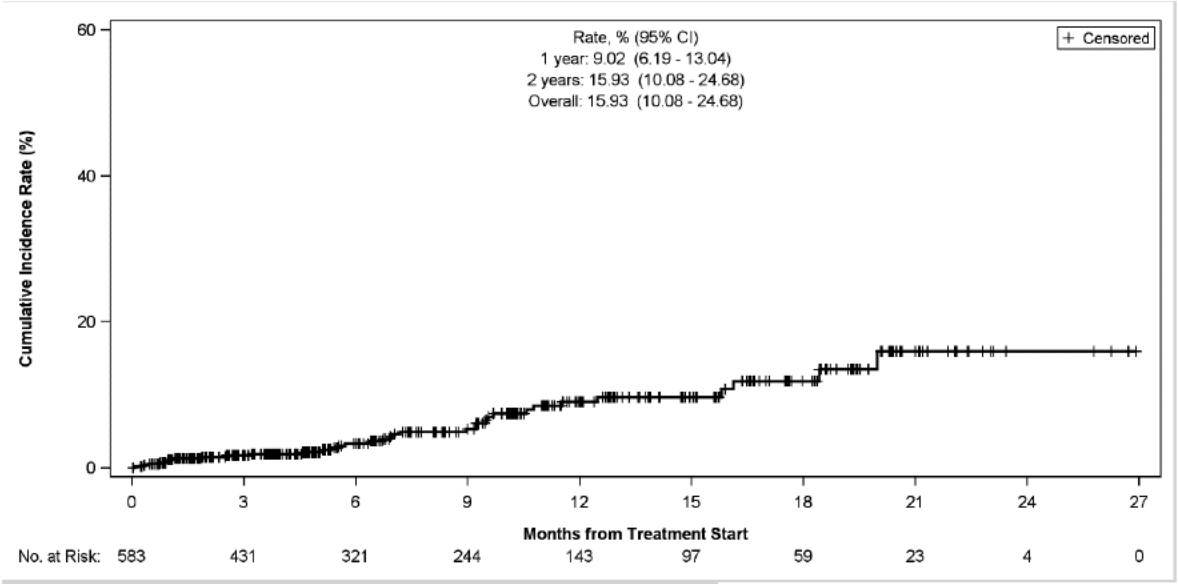
Table 64: Types of SPMs

Second Primary Malignancies	MCL 200 mg population (n=128)	Pooled 200mg population (n=583)
Number of patients, n (%)	5 (3.9)	34 (5.8)
Time from First Dose to First SPM, mo (median, range)	11.6 (1.5, 18.4)	6.9 (0.1, 20.0)
Skin cancer, n (%)	3 (2.3)	27 (4.6)
Non-melanoma	2 (1.6)	22 (3.8)
Melanoma	1 (0.8)	4 (0.7)
Unknown	0	1 (0.2)
Non-melanoma solid tumor, n (%)	1 (0.8)	4 (0.7)
Genitourinary	1 (0.8)	2 (0.3)
Breast	0	2 (0.3)
Hematologic malignancy*, n (%)	1 (0.8)	2 (0.3)
Unspecified carcinomas, n (%)	------	2 (0.3)

* Hematologic malignancies included AML and MDS
SPM: second primary malignancy; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome, SCC: squamous cell carcinoma
Source: FDA analysis based on ADAE.xpt

Figure 14 below shows the estimated cumulative incidence of development of SPMs based on time-to-first-event analysis.

Figure 14: Kaplan-Meier Estimate of the Cumulative Incidence Rate of SPMs in the Pooled Safety Population



Source: Applicant's Analysis, in response to IR sent on 11/14/2022

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Among patients in the OMTSAS, the most common AEs (occurring in ≥ 15% of patients) were fatigue (191 [26.3%]), diarrhoea (160 [22.1%]), and contusion (138 [19.0%]). It is notable that these events were also frequently reported in the medical history of the OMTSAS (fatigue [30.2%], diarrhoea [10.3%], contusion [7.9%]), suggesting that they are possibly a reflection of underlying disease characteristics rather than solely study treatment induced.

In general, the most common AEs (occurring in ≥ 20% of patients) in the MSAS as well as the MSAS-200 subgroup were similar to the OMTSAS. The most common AEs in patients in the MSAS and MSAS-200 were fatigue (49 [29.9%] and 38 [25.7%]) and diarrhoea (35 [21.3%] and 27 [18.2%]).

Aggregate analysis using composite terms was conducted as part of the analysis of AESI and AEPCS based on the known class effects of BTK inhibitors and underlying disease characteristics. Some of these composite terms when considered in aggregate, such as infections, bruising/bleeding, and neutropenia, have incidences in the range of the most common AEs listed above.

The overall AE profile is reflective of the disease characteristics of B-cell hematological malignancies and/or existing covalent BTK inhibitor drug class toxicity. The predominantly

uniform findings across populations analyzed support using the OMTSAS as the main analysis set for assessing the safety of pirtobrutinib.

Table 65: Adverse Events Occurring in ≥ 10% of Patients by Preferred Term and Maximum Severity in Order of Decreasing Incidence in the OMTSAS

PT, (n %)	MSAS (N = 164)		MSAS–200 Subgroup (N = 148)		OMTSAS (N = 725)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any AE	146 (89.0)	76 (46.3)	131 (88.5)	68 (45.9)	681 (93.9)	385 (53.1)
Fatigue	49 (29.9)	4 (2.4)	38 (25.7)	2 (1.4)	191 (26.3)	12 (1.7)
Bruising*	27 (16.5)	0	22 (14.9)	0	168 (23.2)	0
Neutropenia*	23 (14.0)	22 (13.4)	21 (14.2)	20 (13.5)	165 (22.8)	143 (19.7)
Diarrhoea	35 (21.3)	0	27 (18.2)	0	160 (22.1)	6 (0.8)
Nausea	18 (11.0)	0	16 (10.8)	0	108 (14.9)	1 (0.1)
Cough	20 (12.2)	0	16 (10.8)	0	107 (14.8)	0
Anaemia*	21 (12.8)	8 (4.9)	21 (14.2)	8 (5.4)	102 (14.1)	57 (7.9)
Dyspnoea	27 (16.5)	3 (1.8)	23 (15.5)	3 (2.0)	99 (13.7)	7 (0.7)
Thrombocytopenia*	24 (14.6)	11 (6.7)	23 (15.5)	10 (6.8)	94 (13.0)	48 (6.6)
Arthralgia	15 (9.1)	1 (0.6)	14 (9.5)	1 (0.7)	94 (13.0)	3 (0.4)
Constipation	18 (11.0)	0	17 (11.5)	0	93 (12.8)	2 (0.3)
COVID-19*	10 (6.1)	7 (4.3)	10 (6.8)	7 (4.7)	92 (12.7)	44 (6.1)
Back pain	21 (12.8)	2 (1.2)	17 (11.5)	2 (1.4)	91 (12.6)	4 (0.6)
Rash*	14 (8.5)	1 (0.6)	13 (8.8)	1 (0.7)	89 (12.3)	3 (0.4)
Headache	11 (6.7)	1 (0.6)	8 (5.4)	1 (0.7)	88 (12.1)	2 (0.3)
Pyrexia	19 (11.6)	0	17 (11.5)	0	87 (12.0)	6 (0.8)
Oedema peripheral	14 (8.5)	0	12 (8.1)	0	83 (11.4)	1 (0.1)
Abdominal pain	14 (8.5)	1 (0.6)	13 (8.8)	1 (0.7)	80 (11.0)	6 (0.8)
Myalgia	17 (10.4)	0	16 (10.8)	0	46 (6.3)	0

*Anaemia includes anaemia and aplastic anaemia; bruising includes contusion, petechiae, ecchymosis, increased tendency to bruise; neutropenia includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; thrombocytopenia includes platelet count decreased and thrombocytopenia; COVID-19 includes COVID-19, COVID-19 pneumonia, SARS-CoV2 test positive, Coronavirus test positive, and post-acute COVID-19 syndrome; rash includes rash, rash maculo-papular, rash macular, rash pruritic, rash popular, rash pustular, rash erythematous, injection site rash, medical device site rash
Source/Program: SCS Table 14.4.3, SCS Table 14.4.4, SCS Table 14.4.6; SCS Table 14.4.17.1; SCS Table 14.4.17.2

The FDA's Assessment:

Table 66 summarizes all-cause treatment-emergent AEs, excluding laboratory terms, in each safety population within the primary safety window, using a threshold of ≥10% in the MCL safety population. Slight differences in some AE incidences by FDA and Applicant analysis are not unexpected due to methodologic differences; refer to the USPI for final agreed-upon numbers.

In the MCL safety population, the most common non-laboratory AEs (≥ 15%) were fatigue, musculoskeletal pain, diarrhea, edema, dyspnea, pneumonia, and bruising. In the pooled safety population, the most common non-laboratory AEs (≥ 15%) were fatigue, musculoskeletal pain, diarrhea, bruising, rash, and edema.

Table 66: Most Common Treatment-Emergent Adverse Events in FDA's Safety Populations

SOC or Main SOC /Grouped PT	MCL Safety Population (n=128)		Pooled Safety Population (n=583)	
	Any grade, %	G 3-4, % [a]	Any grade, %	G 3-4, % [a]
General Conditions				
Fatigue	29	1.6	27	1.2
Edema	18	0.8	15	0.3
Fever	13	0	12	0.7
Musculoskeletal, Connective Tissue				
Musculoskeletal pain	27	3.9	25	1.9
Arthritis or Arthralgia	12	0.8	14	0.7
Gastrointestinal				
Diarrhea	19	0	20	0.9
Constipation	13	0	12	0
Abdominal pain	11	0.8	12	1.0
Nausea	11	0	14	0.2
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	17	2.3	13	1.0
Cough	14	0	14	0
Injury				
Bruising	16	0	20	0
Infections				
Pneumonia	16[a]	14	13[b]	9.4
Upper respiratory tract infections	10	0.8	10	0.7
Nervous system disorders				
Peripheral neuropathy	14	0.8	10	0.9
Dizziness	10	0	10	0.2
Skin and subcutaneous disorders				
Rash	14	0	16	0.3
Vascular disorders				

SOC or Main SOC /Grouped PT	MCL Safety Population (n=128)		Pooled Safety Population (n=583)	
	Any grade, %	G 3-4, % [a]	Any grade, %	G 3-4, % [a]
Hemorrhage	11[c]	3.1	14[d]	2.1

[a] Includes 1 case of fatal pneumonia
[b] Includes 10 cases of fatal pneumonia
[c] Includes 1 case of fatal hemorrhage
[d] Includes 1 case of fatal hemorrhage
Source: FDA analysis based on ADAE.xpt

Other clinically relevant AEs in <10% of patients included:

- **Neurologic disorders:** memory changes (3.3% in pooled safety population, 7% in MCL safety population), headache (10% in pooled safety population, 5% in MCL safety population)
- **Infection:** urinary tract infection (7% in pooled safety population, 5% in MCL safety population), sepsis (4.3% in pooled safety population, 3.9% in MCL safety population), herpesvirus infection (1.7% in the pooled safety population, 2.3% in MCL safety population)
- **Eye disorders:** vision changes (3.4% in the pooled safety population, 7% in MCL safety population)
- **Blood and lymphatic disorders**: febrile neutropenia (2.9% in the pooled safety population, 2.3% in MCL safety population)
- **Cardiac disorders:** atrial fibrillation or flutter (2.7% in the pooled safety population, 3.9% in MCL safety population)
- **Metabolism and nutrition disorders:** tumor lysis syndrome (0.5% in the pooled safety population, 0.8% in the MCL safety population)

Laboratory Findings

The Applicant's Position:

Analyses of data from clinical laboratory evaluations were consistent with the analyses of AEs reported in OMTSAS for Study 18001. Hematology (neutrophils, hemoglobin, platelets, lymphocytes) laboratory abnormalities were present at baseline; while some worsened while on treatment, these changes were transient with most returning to baseline or better as of the last postbaseline value recorded. No additional significant safety signals were identified from clinical laboratory evaluations.

Hematology

At baseline, it is notable that patients in the OMTSAS had abnormal (Grade ≥ 2) hematology values in platelets (19.9% [low]), neutrophils (13.7% [low]), and lymphocytes (36.9% [high]).

Analysis of hematology lab values were consistent with analyses of the hematological AEs and did not reveal any additional safety findings. Overall, on-treatment hematologic laboratory abnormalities shared a common trend of transient decrease with recovery at the last postbaseline value recorded for neutrophils, hemoglobin and platelets, and transient increase with a recovery at last post baseline recorded for lymphocytes.

Reported events of this nature did not generally impact overall study drug tolerability and were most commonly managed with supportive care and brief study drug interruption.

Lab shift analysis tables for abnormal hematologic laboratory tests for lymphocyte count, hemoglobin count, leukocyte count, neutrophil count, and platelet count are presented in Table 67 through Table 71.

Table 67: Hematology Shifts from Baseline According to CTCAE Toxicity Grade: Lymphocyte Count

	OMTSAS (N = 725), Baseline grade					
Worst postbaseline grade, n (%)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Lymphocytes count increase (n = 696)						
Grade 0	310 (44.5)	0	2 (0.3)	0	0	312 (44.8)
Grade 1	0	0	0	0	0	0
Grade 2	89 (12.8)	0	32 (4.6)	1 (0.1)	0	122 (17.5)
Grade 3	40 (5.7)	0	75 (10.8)	147 (21.1)	0	262 (37.6)
Grade 4	0	0	0	0	0	0
Total	439 (63.1)	0	109 (15.7)	148 (21.3)	0	696 (100.0)
Lymphocytes count decreased (n = 696)						
Grade 0	396 (56.9)	2 (0.3)	14 (2.0)	2 (0.3)	1 (0.1)	415 (59.6)
Grade 1	36 (5.2)	12 (1.7)	5 (0.7)	3 (0.4)	0	56 (8.0)
Grade 2	41 (5.9)	20 (2.9)	27 (3.9)	12 (1.7)	0	100 (14.4)
Grade 3	17 (2.4)	8 (1.1)	22 (3.2)	30 (4.3)	7 (1.0)	84 (12.1)
Grade 4	16 (2.3)	2 (0.3)	5 (0.7)	9 (1.3)	9 (1.3)	41 (5.9)
Total	506 (72.7)	44 (6.3)	73 (10.5)	56 (8.0)	17 (2.4)	696 (100.0)
	MSAS (N = 164), Baseline grade					
Worst postbaseline grade, n (%)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Lymphocytes count increase (n = 155)						
Grade 0	91 (58.7)	0	0	0	0	91 (58.7)

Grade 1	0	0	0	0	0	0
Grade 2	26 (16.8)	0	6 (3.9)	0	0	32 (20.6)
Grade 3	14 (9.0)	0	13 (8.4)	5 (3.2)	0	32 (20.6)
Grade 4	0	0	0	0	0	0
Total	131 (84.5)	0	19 (12.3)	5 (3.2)	0	155 (100.0)
Lymphocytes count decreased (n = 155)						
Grade 0	70 (45.2)	2 (1.3)	3 (1.9)	0	0	75 (48.4)
Grade 1	9 (5.8)	4 (2.6)	0	3 (1.9)	0	16 (10.3)
Grade 2	10 (6.5)	8 (5.2)	7 (4.5)	6 (3.9)	0	31 (20.0)
Grade 3	4 (2.6)	6 (3.9)	6 (3.9)	9 (5.8)	0	25 (16.1)
Grade 4	3 (1.9)	0	3 (1.9)	1 (0.6)	1 (0.6)	8 (5.2)
Total	96 (61.9)	0 (12.9)	19 (12.3)	19 (12.3)	1 (0.6)	155 (100.0)
	MSAS-200 (N = 148), Baseline grade					
Worst postbaseline grade, n (%)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Lymphocytes count increase (n = 139)						
Grade 0	78 (56.1)	0	0	0	0	78 (56.1)
Grade 1	0	0	0	0	0	0
Grade 2	24 (17.3)	0	6 (4.3)	0	0	30 (21.6)
Grade 3	13 (9.4)	0	13 (9.4)	5 (3.6)	0	31 (22.3)
Grade 4	0	0	0	0	0	0
Total	115 (82.7)	0	19 (13.7)	5 (3.6)	0	139 (100.0)
Lymphocytes count decreased (n = 139)						
Grade 0	65 (46.8)	2 (1.4)	2 (1.4)	0	0	69 (49.6)
Grade 1	9 (6.5)	3 (2.2)	0	3 (2.2)	0	15 (10.8)
Grade 2	7 (5.0)	6 (4.3)	6 (4.3)	6 (4.3)	0	25 (18.0)
Grade 3	4 (2.9)	6 (4.3)	5 (3.6)	7 (5.0)	0	22 (15.8)
Grade 4	3 (2.2)	0	3 (2.2)	1 (0.7)	1 (0.7)	8 (5.8)
Total	88 (63.3)	17 (12.2)	16 (11.5)	17 (12.2)	1 (0.7)	139 (100.0)

Table 68: Hematology Shifts from Baseline According to CTCAE Toxicity Grade: Hemoglobin Count

Worst postbaseline grade, n (%)	OMTSAS (N = 725), Baseline grade					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hemoglobin count decreased (n = 714)						
Grade 0	118 (16.5)	6 (0.8)	0	0	0	124 (17.4)
Grade 1	103 (14.4)	187 (26.2)	8 (1.1)	0	0	298 (41.7)
Grade 2	23 (3.2)	74 (10.4)	80 (11.2)	12 (1.7)	0	189 (26.5)
Grade 3	5 (0.7)	28 (3.9)	47 (6.6)	23 (3.2)	0	103 (14.4)
Grade 4	0	0	0	0	0	0
Total	249 (34.9)	295 (41.3)	135 (18.9)	35 (4.9)	0	714 (100.0)
Worst postbaseline grade, n (%)	**MSAS (N = 164), Baseline grade**					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Hemoglobin count decreased (n = 163)						
Grade 0	27 (16.6)	2 (1.2)	0	0	0	29 (17.8)
Grade 1	24 (14.7)	57 (35.0)	1 (0.6)	0	0	82 (50.3)
Grade 2	4 (2.5)	25 (15.3)	8 (4.9)	0	0	37 (22.7)
Grade 3	2 (1.2)	5 (3.1)	6 (3.7)	2 (1.2)	0	15 (9.2)
Grade 4	0	0	0	0	0	0
Total	57 (35.0)	89 (54.6)	15 (9.2)	2 (1.2)	0	163 (100.0)
Worst postbaseline grade, n (%)	**MSAS-200 (N = 148), Baseline grade**					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Hemoglobin count decreased (n = 147)						
Grade 0	23 (15.6)	2 (1.4)	0	0	0	25 (17.0)
Grade 1	19 (12.9)	52 (35.4)	1 (0.7)	0	0	72 (49.0)
Grade 2	4 (2.7)	25 (17.0)	8 (5.4)	0	0	37 (25.2)
Grade 3	1 (0.7)	4 (2.7)	6 (4.1)	2 (1.4)	0	13 (8.8)
Grade 4	0	0	0	0	0	0
Total	47 (32.0)	83 (56.5)	15 (10.2)	2 (1.4)	0	147 (100.0)

Table 69: Hematology Shifts from Baseline According to CTCAE Toxicity Grade: Leukocyte Count

Worst postbaseline grade, n (%)	OMTSAS (N = 725), Baseline grade					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Leukocyte count increase (n = 714)						
Grade 0	593 (83.1)	0	0	3 (0.4)	0	596 (83.5)
Grade 1	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0
Grade 3	62 (8.7)	0	0	56 (7.8)	0	118 (16.5)
Grade 4	0	0	0	0	0	0
Total	655 (91.7)	0	0	59 (8.3)	0	714 (100.0)
Leukocyte count decreased (n = 714)						
Grade 0	430 (60.2)	9 (1.3)	6 (0.8)	3 (0.4)	0	448 (62.7)
Grade 1	80 (11.2)	16 (2.2)	6 (0.8)	0	0	102 (14.3)
Grade 2	54 (7.6)	23 (3.2)	21 (2.9)	4 (0.6)	0	102 (14.3)
Grade 3	21 (2.9)	8 (1.1)	6 (0.8)	11 (1.5)	0	46 (6.4)
Grade 4	8 (1.1)	2 (0.3)	1 (0.1)	3 (0.4)	2 (0.3)	16 (2.2)
Total	593 (83.1)	58 (8.1)	40 (5.6)	21 (2.9)	2 (0.3)	714 (100.0)
Worst postbaseline grade, n (%)	**MSAS (N = 164), Baseline grade**					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Leukocyte count increase (n = 163)						
Grade 0	153 (93.9)	0	0	0	0	153 (93.9)
Grade 1	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0
Grade 3	6 (3.7)	0	0	4 (2.5)	0	10 (6.1)
Grade 4	0	0	0	0	0	0
Total	159 (97.5)	0	0	4 (2.5)	0	163 (100.0)
Leukocyte count decreased (n = 163)						
Grade 0	104 (63.8)	1 (0.6)	1 (0.6)	0	0	106 (65.0)
Grade 1	16 (9.8)	4 (2.5)	2 (1.2)	0	0	22 (13.5)
Grade 2	10 (6.1)	9 (5.5)	6 (3.7)	1 (0.6)	0	26 (16.0)

	OMTSAS (N = 725), Baseline grade					
Grade 3	3 (1.8)	3 (1.8)	1 (0.6)	0	0	7 (4.3)
Grade 4	0	1 (0.6)	1 (0.6)	0	0	2 (1.2)
Total	133 (81.6)	18 (11.0)	11 (6.7)	1 (0.6)	0	163 (100.0)
	MSAS-200 (N = 148), Baseline grade					
Worst postbaseline grade, n (%)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Leukocyte count increase (n = 147)						
Grade 0	137 (93.2)	0	0	0	0	137 (93.2)
Grade 1	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0
Grade 3	6 (4.1)	0	0	4 (2.7)	0	10 (6.8)
Grade 4	0	0	0	0	0	0
Total	143 (97.3)	0	0	4 (2.7)	0	147 (100.0)
Leukocyte count decreased (n = 147)						
Grade 0	98 (66.7)	0	1 (0.7)	0	0	99 (67.3)
Grade 1	12 (8.2)	4 (2.7)	1 (0.7)	0	0	17 (11.6)
Grade 2	9 (6.1)	8 (5.4)	6 (4.1)	1 (0.7)	0	24 (16.3)
Grade 3	2 (1.4)	3 (2.0)	1 (0.7)	0	0	6 (4.1)
Grade 4	0	1 (0.7)	0	0	0	1 (0.7)
Total	121 (82.3)	16 (10.9)	9 (6.1)	1 (0.7)	0	147 (100.0)

Table 70: Hematology Shifts from Baseline According to CTCAE Toxicity Grade: Neutrophil Count

Worst postbaseline grade, n (%)	OMTSAS (N = 725), Baseline grade					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Neutrophil count decreased (n = 708)						
Grade 0	345 (48.7)	7 (1.0)	6 (0.8)	1 (0.1)	0	359 (50.7)
Grade 1	41 (5.8)	7 (1.0)	1 (0.1)	1 (0.1)	0	50 (7.1)
Grade 2	68 (9.6)	12 (1.7)	10 (1.4)	1 (0.1)	2 (0.3)	93 (13.1)
Grade 3	65 (9.2)	4 (0.6)	14 (2.0)	15 (2.1)	5 (0.7)	103 (14.5)
Grade 4	58 (8.2)	4 (0.6)	19 (2.7)	13 (1.8)	9 (1.3)	103 (14.5)
Total	577 (81.5)	34 (4.8)	50 (7.1)	31 (4.4)	16 (2.3)	708 (100.0)
Worst postbaseline grade, n (%)	**MSAS (N = 164), Baseline grade**					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Neutrophil count decreased (n = 161)						
Grade 0	96 (59.6)	3 (1.9)	0	0	0	99 (61.5)
Grade 1	12 (7.5)	3 (1.9)	0	0	0	15 (9.3)
Grade 2	13 (8.1)	5 (3.1)	1 (0.6)	0	0	19 (11.8)
Grade 3	9 (5.6)	0	2 (1.2)	1 (0.6)	1 (0.6)	13 (8.1)
Grade 4	13 (8.1)	0	1 (0.6)	1 (0.6)	0	15 (9.3)
Total	143 (88.8)	11 (6.8)	4 (2.5)	2 (1.2)	1 (0.6)	161 (100.0)
Worst postbaseline grade, n (%)	**MSAS-200 (N = 148), Baseline grade**					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Neutrophil count decreased (n = 145)						
Grade 0	86 (59.3)	3 (2.1)	0	0	0	89 (61.4)
Grade 1	11 (7.6)	3 (2.1)	0	0	0	14 (9.7)
Grade 2	13 (9.0)	5 (3.4)	1 (0.7)	0	0	19 (13.1)
Grade 3	7 (4.8)	0	2 (1.4)	1 (0.7)	1 (0.7)	11 (7.6)
Grade 4	11 (7.6)	0	0	1 (0.7)	0	12 (8.3)
Total	128 (88.3)	11 (7.6)	3 (2.1)	2 (1.4)	1 (0.7)	145 (100.0)

Table 71: Hematology Shifts from Baseline According to CTCAE Toxicity Grade: Platelet Count

	OMTSAS (N = 725), Baseline grade					
Worst postbaseline grade, n (%)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Platelet count decreased (n = 703)						
Grade 0	219 (31.2)	19 (2.7)	0	0	0	238 (33.9)
Grade 1	97 (13.8)	156 (22.2)	16 (2.3)	1 (0.1)	0	270 (38.4)
Grade 2	6 (0.9)	30 (4.3)	26 (3.7)	12 (1.7)	0	74 (10.5)
Grade 3	4 (0.6)	15 (2.1)	20 (2.8)	17 (2.4)	4 (0.6)	60 (8.5)
Grade 4	9 (1.3)	8 (1.1)	6 (0.9)	14 (2.0)	24 (3.4)	61 (8.7)
Total	335 (47.7)	228 (32.4)	68 (9.7)	44 (6.3)	28 (4.0)	703 (100.0)
	MSAS (N = 164), Baseline grade					
Worst postbaseline grade, n (%)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Platelet count decreased (n = 157)						
Grade 0	55 (35.0)	4 (2.5)	0	0	0	59 (37.6)
Grade 1	34 (21.7)	23 (14.6)	4 (2.5)	0	0	61 (38.9)
Grade 2	2 (1.3)	5 (3.2)	2 (1.3)	1 (0.6)	0	10 (6.4)
Grade 3	0	7 (4.5)	2 (1.3)	5 (3.2)	0	14 (8.9)
Grade 4	4 (2.5)	1 (0.6)	3 (1.9)	4 (2.5)	1 (0.6)	13 (8.3)
Total	95 (60.5)	40 (25.5)	11 (7.0)	10 (6.4)	1 (0.6)	157 (100.0)
	MSAS-200 (N = 148), Baseline grade					
Worst postbaseline grade, n (%)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Platelet count decreased (n = 141)						
Grade 0	48 (34.0)	4 (2.8)	0	0	0	52 (36.9)
Grade 1	31 (22.0)	22 (15.6)	4 (2.8)	0	0	57 (40.4)
Grade 2	2 (1.4)	3 (2.1)	2 (1.4)	1 (0.7)	0	8 (5.7)
Grade 3	0	7 (5.0)	2 (1.4)	5 (3.5)	0	14 (9.9)
Grade 4	1 (0.7)	1 (0.7)	3 (2.1)	4 (2.8)	1 (0.7)	10 (7.1)
Total	82 (58.2)	37 (26.2)	11 (7.8)	10 (7.1)	1 (0.7)	141 (100.0)

Liver Function Tests

The majority of patients maintained their baseline levels across all LFT parameters (ALT [84.9%], AST [80.8%], ALP [85.6%], total bilirubin [90.2%]), and shifts were predominantly low grade (shift in 1 severity grade) for all parameters. Analysis of laboratory parameters did not reveal any additional safety findings.

Lipase

According to laboratory tests, while there were some patients (18.4%) who experienced an increased lipase of any grade, approximately a third of those patients (5.9%) had shifts that were Grade 3 or 4 (Table 72).

Shift analysis of worst postbaseline values found that the majority of patients (81.6%) had maintained their baseline grade or better lipase throughout the study, while few (8.4%) had a significant upward shift of 2 grades or more. At the time of the last postbaseline assessment, 94.7% of patients had returned to their baseline grade or better for lipase.

While transient increases in lipase were noted in patients on study, clinically significant increases (as indicated by AE reporting) in lipase were uncommon, and these events were not significantly impactful to patients' ability to tolerate therapy. Thus, this was not identified as a clinically significant safety concern.

Table 72: Summary of Selected Abnormal Serum Chemistry Laboratory Tests in Order of Decreasing Incidence

Abnormal laboratory test	n	Any grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 – 4 n (%)
OMTSAS (N = 725)							
ALT increased	710	107 (15.1)	85 (12.0)	10 (1.4)	12 (1.7)	0	12 (1.7)
Alkaline phosphatase increased	710	102 (14.4)	86 (12.1)	14 (2.0)	2 (0.3)	0	2 (0.3)
AST increased	713	137 (19.2)	114 (16.0)	17 (2.4)	6 (0.8)	0	6 (0.8)
Bilirubin increased	713	70 (9.8)	55 (7.7)	12 (1.7)	3 (0.4)	0	3 (0.4)
Creatinine increased	713	189 (26.5)	112 (15.7)	72 (10.1)	2 (0.3)	3 (0.4)	5 (0.7)
Lipase increased	490	90 (18.4)	43 (8.8)	18 (3.7)	23 (4.7)	6 (1.2)	29 (5.9)
MSAS (N = 164)							
ALT increased	162	20 (12.3)	16 (9.9)	1 (0.6)	3 (1.9)	0	3 (1.9)
Alkaline phosphatase increased	163	21 (12.9)	20 (12.3)	1 (0.6)	0	0	0
AST increased	163	31 (19.0)	25 (15.3)	4 (2.5)	2 (1.2)	0	2 (1.2)

Abnormal laboratory test	n	Any grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 – 4 n (%)
Bilirubin increased	163	12 (7.4)	9 (5.5)	2 (1.2)	1 (0.6)	0	1 (0.6)
Creatinine increased	163	49 (30.1)	29 (17.8)	17 (10.4)	0	3 (1.8)	3 (1.8)
Lipase increased	110	14 (12.7)	7 (6.4)	1 (0.9)	4 (3.6)	2 (1.8)	6 (5.5)

Source/Program: SCS Table 14.4.25

Hy's Law

Liver function laboratory data were assessed to identify any patients who might meet criteria for Hy's Law. This yielded a single patient who was then clinically reviewed.

This patient is a 74-year-old White male with Stage IV MCL who developed liver function test abnormalities on 2 occasions (at Cycle 3 Day 1 and on Cycle 7 Day 1; the latter of which is the event meeting criteria for consideration of Hy's Law). These events were considered unrelated to study treatment. Preceding both occurrences, the patient had noted increased acetaminophen use. On both occasions, he was instructed to discontinue the acetaminophen and his liver function recovered. This patient remains on study (Cycle 18) and his liver function has been normal throughout the duration of pirtobrutinib therapy apart from these cited adverse events. Although these laboratory abnormalities meet criteria for possibly representing hepatotoxicity consistent with Hy's Law, upon further review, the identified alternative etiology prohibits all criteria from being met. Thus, this case does not meet Hy's Law criteria.

Safety data as of the cut-off date did not identify any risk of drug-induced livery injury for pirtobrutinib.

The FDA's Assessment:
Analysis of lab-shift data was used for laboratory AE reporting. Table 73 and Table 74 summarize new or worsening laboratory abnormalities in the MCL and pooled safety populations, respectively, with the 'n' for each AE corresponding to the number of patients who had a baseline and at least one post-treatment assessment for that parameter.

Hematologic laboratory AEs occurred in ≥25% of patients in the pooled safety population and in ≥30% of patients in the MCL safety population.

In the pooled safety population, Grade 3-4 laboratory abnormalities in ≥10% of patients were neutropenia, lymphocytosis, anemia, thrombocytopenia, and lymphopenia. Grade 3-4 laboratory abnormalities in ≥10% of patients in the MCL safety population were lymphocytosis, neutropenia, lymphopenia, and thrombocytopenia. Grade 4 laboratory abnormalities in > 5% of patients in the MCL safety population included decreased neutrophils (10%), platelets (7%), and lymphocytes (6%).

Table 73: Common (≥ 10%) TE Laboratory Abnormalities in FDA's MCL Safety Population

Parameter	N evaluable from 128 [a]	Any grade		Grade 3-4		Grade 4	
		N	%	N	%	N	%
Hematologic [b]							
Anemia	127	53	**42%**	11	**9%**	0	**0%**
Thrombocytopenia	122	47	**39%**	17	**14%**	9	**7%**
Neutropenia	125	45	**36%**	20	**16%**	12	**10%**
Lymphocytosis [c]	120	41	**34%**	22	**18%**	0	**0%**
Lymphopenia	120	38	**32%**	18	**15%**	7	**6%**
Chemistry							
Creatinine increase	127	38	**30%**	2	**1.6%**	2	**1.6%**
LDH increase [c]	126	30	**24%**	0	**0%**	0	**0%**
Calcium decrease	127	24	**19%**	2	**1.6%**	1	**0.8%**
Sodium decrease	127	17	**13%**	0	**0%**	0	**0%**
Potassium decrease	127	16	**13%**	2	**1.6%**	0	**0%**
Lipase increase	90	11	**12%**	4	**4.4%**	1	**1.1%**
Potassium increase	127	14	**11%**	1	**0.8%**	0	**0%**
Hepatic							
AST increase	127	22	**17%**	2	**1.6%**	0	**0%**
Albumin decrease [c]	127	21	**17%**	1	**0.8%**	0	**0%**
ALT increase	126	15	**12%**	3	**2.4%**	0	**0%**
Alk phos increase	127	15	**12%**	0	**0%**	0	**0%**

[a] Denominator used to calculate incidence varies from 90 to 127 based on number of patients with a baseline and at least one post-treatment value.
[b] Leukopenia also met the threshold for inclusion, but is represented by neutropenia and lymphopenia.
[c] Not considered an adverse reaction.
Source: FDA analysis based on ADLB.xpt and ADLB2.xpt datasets and based on CTCAE version 5.0.

Table 74: Common (≥ 10%) TE Laboratory Abnormalities in FDA's Pooled Safety Population

Parameter	N evaluable, from 583 [a]	Any grade		Grade 3-4		Grade 4	
		N	%	N	%	N	%
Hematologic [b]							
Neutropenia	566	231	**41%**	133	**23%**	71	**13%**
Anemia	572	212	**37%**	64	**11%**	0	**0%**
Lymphocytosis [c]	554	163	**29%**	92	**17%**	0	**0%**
Thrombocytopenia	561	149	**27%**	60	**11%**	28	**5%**
Lymphopenia	554	131	**24%**	57	**10%**	22	**4%**
Chemistry							
Creatinine increase	572	145	**25%**	3	**0.5%**	2	**0.3%**
Calcium decrease	572	135	**24%**	10	**1.7%**	5	**0.9%**
Sodium decrease	572	121	**21%**	2	**0.3%**	0	**0%**
LDH increase [c]	570	570	**19%**	0	**0%**	0	**0%**
Lipase increase	445	84	**19%**	26	**5.8%**	5	**1.1%**
Potassium increase	572	70	**12%**	6	**1.0%**	1	**0.2%**
Potassium decrease	572	68	**12%**	7	**1.2%**	0	**0%**
Magnesium decrease	560	62	**11%**	1	**0.2%**	0	**0%**
Hepatic							
AST increase	572	102	**18%**	5	**0.9%**	0	**0%**
Albumin decrease [c]	572	93	**16%**	3	**0.5%**	0	**0%**
ALT increase	569	86	**15%**	12	**2.1%**	0	**0%**
Alk phos increase	569	76	**13%**	3	**0.5%**	0	**0%**
Bilirubin increase	572	62	**11%**	4	**0.7%**	0	**0%**

[a] Denominator used to calculate incidence varies from 445 to 572 based on number of patients with a baseline and at least one post-treatment value.
[b] Leukopenia also met the threshold for inclusion, but is represented by neutropenia and lymphopenia.
[c] Not considered an adverse reaction.
Source: FDA analysis based on ADLB.xpt and ADLB2.xpt datasets and based on CTCAE version 5.0.

An assessment of laboratory abnormalities warranting additional evaluation is provided below.

A. Lymphocytosis

Lymphocytosis, defined as an elevation in ALC of ≥50% from baseline and a post-baseline assessment ≥5,000/µL, is a known effect of treatment with BTK inhibitors and occurred in 34% of patients in the MCL safety population and 42% of patients in the pooled safety population (Source: response to IRs sent on 11/14/2022). In the MCL safety population, the median time to onset was 1.1 weeks and 75% of cases occurred within 2.1 weeks (Source: response to IRs sent on 11/14/2022). Lymphocytosis resolved in 54% of patients and median duration was 11.0 weeks (Source: response to IRs sent on 11/14/2022). BTK inhibitor-related lymphocytosis is related to the redistribution of lymphocytes from the nodal component to the peripheral blood and is not considered an adverse reaction to the drug (Herman et al. 2014).

Reviewer's Comments:

- ***Given the mechanism of action of lymphocytosis seen with BTK inhibitor treatment, lymphocytosis was not included in the laboratory AR table but was described (with incidence and descriptors of time course) in text below the table.***

B. Hyponatremia

A higher-than-expected incidence of hyponatremia was seen in both the MCL safety population (13%) and the pooled safety population (21%). The majority of cases were Grade 1-2, with a 0.3% incidence of Grade 3 hyponatremia in the pooled safety population and no Grade 4 events occurred. The median time to onset was 8.3 weeks (Q1, Q3: 2.3, 23.6) and the median time to resolution was 4.1 weeks (Q1, Q3: 3.0, 4.4). The majority of cases resolved without supportive care. Two patients with Grade 3 hyponatremia required supportive care, each receiving normal saline infusions for management of hyponatremia (Source: response to IRs sent on 10/12/2022 and 12/12/2022).

There was no identified plausible mechanism for hyponatremia and no suggestive findings in non-clinical or clinical pharmacology studies (Source: response to IRs sent on 10/12/2022). It is possible that hyponatremia was precipitated in this population of patients with hematologic malignancies by fluid shifts related to dehydration, vomiting, or diarrhea.

Reviewer's Comments:

- ***Based on the incidence of hyponatremia in the MCL safety population, it met the threshold for inclusion in the common laboratory AR table.***

C. Hy's Law

One patient with MCL who was treated at the 200mg dose of pirtobrutinib was noted to develop liver function test abnormalities on C3D1 and C7D1 and met Hy's law laboratory criteria on C7D1. On C7D1, he developed Grade 3 bilirubin, AST, and ALT increase and Grade 2 lipase increase, requiring study drug interruption (Source: response to IR sent 11/1/2022). He was found to have increased acetaminophen use prior to both occurrences and was instructed to discontinue acetaminophen. Following resolution of laboratory abnormalities 26 days later, he resumed study drug at the previous dose and has remained on treatment since then (up to Cycle 18 as of the data cut-off) without recurrence of liver function test abnormalities (Source: response to IR sent 11/1/2022). Given the time course of laboratory abnormalities in relation to increased acetaminophen use, it is likely that acetaminophen use precipitated the findings, and it is unlikely that this potential Hy's law case was related to pirtobrutinib treatment.

Vital Signs

The Applicant's Position:

Summary statistics for diastolic and systolic blood pressure, pulse rate, respiration rate, and temperature in Study 18001 are summarized in the CSR (Module 5.3.5.2). Analysis of vital signs in Study 18001 did not reveal any new safety concerns relative to overall assessment of AEs for the OMTSAS. No notable changes were observed between the medians of baseline and last measured systolic blood pressure, diastolic blood pressure, and pulse rate.

The FDA's Assessment:
FDA did not verify this analysis.

Electrocardiograms

The Applicant's Position:

During the clinical trial, the QT interval was corrected using the Fridericia method as specified by the Study 18001 protocol. If the QTcF was not provided, the value was derived using the heart rate, QT interval, and RR interval values provided, as outlined in the SCS SAP.

Overall, the median baseline QTcF value was 393.3 ms and the median maximum value on treatment was 420.0 ms with a median maximum increase from baseline of 27.7 ms. At the time of the last measurement, the median QTcF value was slightly elevated above baseline at 400.0 ms.

Shift analysis of QTcF is described in detail in the CSR for Study 18001. There were no notable findings. Adverse events of QTcF prolongation were infrequent, all were ≤ Grade 2 in severity, and none were reported to be serious.

Of note, a thorough QT study was conducted in healthy participants in Study LOXO-BTK-20011 and findings constitute a negative result of the thorough QT study.

Overall, no safety signals were identified.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. The FDA QT review team reported that no significant QTcF prolongation was detected in the thorough QT study.

Immunogenicity

The Applicant's Position:
No safety issues related to immunogenicity were identified for pirtobrutinib.

The FDA's Assessment:
Not applicable.

8.2.5 Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Adverse events of special interest are discussed in the section titled "Significant Adverse Events".

The FDA's Assessment:
Specific AESIs warranting additional exploration (hemorrhage, infections, arrhythmias, and SPMs) and select laboratory findings are discussed in the "Adverse Events of Special Interest" and "Laboratory Findings" sections above. Additional safety issues which warranted a more thorough evaluation are described below.

8.2.5.1 Analyses of Additional Safety Findings

8.2.5.1.1 *Peripheral Neuropathy*

There was a 10.5% incidence of any-grade peripheral neuropathy (PN) in the pooled safety population and a 13.3% incidence in the MCL safety population. FDA performed narrow and broad MedDRA queries for peripheral neuropathy; at that time, the safety populations being evaluated included patients who underwent dose escalation. In the pooled safety population of patients who received the 200mg starting dose (n=640), incidence by broad SMQ was 10.9% and by narrow SMQ was 4.5%.

To further characterize the peripheral neuropathy events, a query was sent to the Applicant regarding a plausible mechanism, the incidence of baseline PN, the time course, manifestations, and incidence of resolution. The Applicant has not identified a plausible mechanism, by which pirtobrutinib could cause PN, based on non-clinical findings, and considers confounding factors such as pretreatment with chemotherapeutic agents known to cause PN and medical conditions such as diabetes mellitus, to contribute to the incidence of PN seen in the BRUIN trial (Source: response to IRs sent on 10/12/2022). Based on the pooled safety population (n=640) and using the broad SMQ approach, 33.8% of patients with treatment-emergent PN had peripheral neuropathy at baseline and 43.7% had been previously treated with agents known to incidence peripheral neuropathy (regimens containing vincristine, platinum agents, thalidomide, and bortezomib) (Source: response to IRs sent on 10/12/2022). The median time to onset was 9.6 weeks (Q1, Q3: 2.1, 33.0); 29.6% of patients had PN that resolved at a median of 3.1 weeks (Q1, Q3: 1.4, 4.6) (Source: response to IRs sent on 10/12/2022).

Reviewer's Comments:

- ***The incidence of peripheral neuropathy based on final FDA-grouping (as described in Appendix 19.5) most closely aligns with the broad SMQ approach. FDA grouping includes terms such as paresthesia, hypoesthesia, and numbness and tingling, when occurring in areas consistent with peripheral neuropathy. Any reports of these terms in locations such as the lip, scalp, or other inconsistent locations, were not included. Based on the incidence per FDA grouping of preferred terms in the pooled safety population of patients with the 200mg starting dose who did not undergo dose escalation, 10.5%, the threshold was met for inclusion in the table of common ARs in the label.***

8.2.5.1.2 Ocular Toxicity

In non-clinical studies, two high-dose male dogs were found to have corneal lesions. To further evaluate for ocular effects in human subjects, a query was sent to the Applicant regarding a plausible mechanism of visual changes, the incidence of baseline visual disorders, the time course to onset, incidence of resolution, and time course to resolution.

At that time, the analysis was based on a safety population which included those who underwent dose escalation. In the pooled safety population (n=640), the incidence of vision disorder using the HLGT was 3.3%, 0.5% of which had baseline vision disorder. One of the 21 cases identified was a case of double vision which was found to be related to a known pituitary mass. The median time to onset was 12 weeks (Q1, Q3: 1.3, 30.1) and vision changes resolved in 57.1% of patients at a median of 1.9 weeks (Q1, Q3: 1.2, 10.4). Treatment for vision disorder occurred in only one patient, in whom double vision was related to a pituitary mass and treatment with dexamethasone was administered. The Applicant has not identified a plausible mechanism for vision changes seen with pirtobrutinib. While there is a higher incidence of vision changes identified with ibrutinib, the mechanism has not been defined, though it has been proposed to be related to the Th1-based immune response (Bohn et al. 2022). The applicant does not consider the proposed mechanism of ocular toxicity with ibrutinib to be relevant to pirtobrutinib, given the differences between the two drugs in off-target kinase inhibition and the variable safety profiles between the two drugs.

Reviewer's Comments:

- ***Overall, the incidence of all-grade vision changes is 3.4% in the pooled safety population (n=583). Other than the case of double vision related to a pituitary mass which led to Grade 3 vision loss, all other cases were Grade 1-2 in severity. The majority of AEs categorized as vision changes were blurred vision. Vision changes did not meet the threshold for inclusion in the table of common ARs in the label, but given the clinical relevance of visual changes including blurred vision, it is included in the list of clinically relevant ARs in <10% of patients.***

8.2.5.1.3 Neurologic Changes

The FDA evaluated the incidence of neurologic changes by grouping terms including memory changes, memory impairment, depressed consciousness, and dementia. The incidence of neurologic changes was 7% in the pooled safety population and 9% in the MCL safety population. The majority of neurologic changes reported in the MCL safety population were memory changes (81%), followed by dementia and depressed consciousness (9% each).

Reviewer's Comments:

- ***Given the clinical relevance of neurologic changes, these were considered for inclusion as clinically relevant ARs in <10% of patients. However, given the breakdown of the reported terms in the MCL safety population, as noted above, the decision was made to restrict the term reported in the list of clinically relevant ARs to 'memory changes.'***

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable. This application did not include COA analyses informing the safety or tolerability of pirtobrutinib.

The FDA's Assessment:
FDA agrees that COA analyses were not included in this submission.

8.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Position:

Age

In the OMTSAS, there were 254 (35.0%) patients who were ≤ 65 years of age, 294 (40.6%) patients were 65 to < 75 years of age, 153 (21.1%) patients were 75 to < 85 years of age, and there were 24 (3.3%) patients 85 years of age or older. There were no notable differences in the incidence of total AEs between subgroups defined by age cut-offs/thresholds. Relative to younger patients, patients ≥ 85 years of age had higher incidences of AEs leading to dose reduction (12.5% [≥ 85] vs. 4.9% [< 85]) and discontinuation (12.5% [≥ 85] vs. 6.0% [< 85]), although this may be reflective of the limited number of patients ≥ 85 years of age (n = 24) in Study 18001. Otherwise, there were no notable differences in severity of AEs, seriousness of AEs, or actions taken due to AEs between subgroups defined by age cut-offs/thresholds.

There were no notable differences in incidences of AEs between subgroups defined by age cut-offs/thresholds.

Sex

There were more males (66.5%) than females in the OMTSAS, reflecting the increased prevalence of MCL and CLL/SLL in males. The incidence of fatal AEs was 7.1% for males and 4.5% for females. There were no notable differences in AE severity, seriousness, or actions taken due to AEs between males and females.

Other than contusion (15.8% [male] vs. 25.5% [female]) and nausea (11.8% [male] vs. 21.0% [female]), there were no notable differences in incidences of AEs based on sex.

Race

Of the OMTSAS, 86.6% of patients were White, 5.8% were Asian, 3.0% were Black or African American, and 3.6% were Other. In general, there were no notable differences in the incidences of AEs, AE severity, seriousness, or actions taken due to AEs between racial subgroups.

The FDA's Assessment:
The FDA disagrees that there were no differences in the safety of pirtobrutinib by age. In the pooled safety population, 392 (67%) were 65 years of age and older, while 153 (26%) were 75 years of age and older. As shown in Table 75, there were numerically higher rates of Grade ≥3 AEs and SAEs in patients 65 years of age and older.

Table 75: Summary of Safety by Age Group

	Age <65 (n=191), n (%)	**Age ≥65 (n=392), n (%)**
Deaths	26 (14%)	88 (22%)
Death due to AE	11 (6%)	26 (7%)
Grade ≥3 AE	83 (43%)	219 (56%)
SAE	46 (24%)	153 (39%)
AE leading to dose reduction	3 (1.6%)	21 (5%)
AE leading to dose interruption	49 (26%)	145 (37%)
AE leading to discontinuation	12 (6%)	23 (6%)

Source: FDA analysis based on ADAE.xpt

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:

There were no additional studies performed to evaluate any specific safety concerns.

The FDA's Assessment:
Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Carcinogenicity studies were not conducted or required to support the use of pirtobrutinib in the proposed indication.

The FDA's Assessment:
Not Applicable.

Human Reproduction and Pregnancy

The Applicant's Position:

Women who were known to be pregnant or breastfeeding were excluded from studies with pirtobrutinib; birth control measures during treatment and ongoing pregnancy screening were enforced to ensure that no fetus was exposed to pirtobrutinib. Additionally, no pregnancies occurred during the development of the program and there was no known drug exposure of breastfed infants of lactating women.

The FDA's Assessment:
The FDA agrees with the Applicant's statement. The USPI includes a Warning and Precaution on embryo-fetal toxicity.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

There were no children enrolled in any of the studies submitted with this application. The safety of pirtobrutinib in pediatric patients has not been established.

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose

The highest planned dose of pirtobrutinib in Study 18001 was a total daily dose of 300 mg QD. In a healthy participant PK study, a single dose of 900 mg was administered.

To the Applicant's knowledge, no overdoses, defined as a daily exposure which exceeded the maximum daily assigned dose, have resulted in any AEs to date in the pirtobrutinib program.

To date, no known antidote exists for pirtobrutinib overdose. Standard supportive measures were to be followed in the event of an acute overdose. No evidence exists to date of adverse cumulative effects with long-term chronic dosing with pirtobrutinib.

Drug Abuse

No information is available at this time on pirtobrutinib abuse or misuse, nor is there evidence that pirtobrutinib would be a candidate for such.

Withdrawal and Rebound

No studies or analyses specifically addressed clinical issues related to pirtobrutinib withdrawal and/or rebound. In the OMTSAS, 51.7% of patents had their treatment interrupted either for AE or other reasons. In all cases of treatment interruption, treatment was reinstated successfully without known sequelae due to the reinstatement of treatment.

The FDA's Assessment:
The FDA agrees with the Applicant's statements.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

To date, pirtobrutinib has not been granted market authorization.

The FDA's Assessment:
Not applicable.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety of pirtobrutinib in the postmarket setting is not expected to differ significantly from that observed in Study LOXO-BTK-18001 as assessed during the safety review of this NDA submission.

The FDA's Assessment:
With larger numbers of patients exposed and with longer duration of exposure over time, new safety signals may emerge, or existing safety signals may occur at higher than expected incidences. Two safety PMRs will be issued to address the potential for additional safety findings in the postmarket setting (Section 13.0).

8.2.11 Integrated Assessment of Safety

The Applicant's Position:

The primary safety analysis set is based on all 725 patients irrespective of B-cell malignancy, who received at least one dose of pirtobrutinib as monotherapy (OMTSAS). A separate analysis for the patient population with MCL (MSAS; n = 164) and the subgroup of MCL patients receiving the 200 mg QD starting dose (MSAS-200; n = 148) was also performed. No notable differences in the safety profile of pirtobrutinib between the OMTSAS, MSAS, and the MSAS-200 subgroup were identified.

As of the data cut-off date, 31 January 2022, in the OMTSAS, 360 (49.7%) patients were continuing to receive pirtobrutinib. The median time on treatment was 8.05 months (range: 0, 34.0); 655 (90.3%) patients had received at least one dose of pirtobrutinib at the proposed dose of 200 mg QD and 699 (96.4%) patients received 200 QD or higher. The median age of patients receiving pirtobrutinib was 68.0 years (range: 27, 95) and the population was heavily pretreated, having received a median of 3 prior lines of therapy (range: 0, 13). Most patients (566 [78.1%]) had received previous BTK inhibitor therapy, including 95 (13.1%) patients who had discontinued prior BTK inhibitor therapy due to intolerance/toxicity.

Safety data, across safety analysis sets, demonstrate that pirtobrutinib is well tolerated with a safety profile that is consistent with the BTK inhibitor drug class and/or the underlying disease setting and reflects the high degree of selectivity of pirtobrutinib. Toxicities were manageable per protocol guidance, which form the basis of proposed labeling. Overall, 681 patients (93.9%) experienced a TEAE; 296 (40.8%) patients experienced Grade 1 or 2, and 340 (46.9%) experienced Grade 3 or 4 events as the worst severity. The most common TEAEs (occurring in ≥ 15% of patients) included fatigue (190 [26.3%] patients), diarrhoea (160 [22.1%] patients), and contusion (138 [19.0%] patients). The most common Grade 3 or 4 TEAEs (occurring in ≥ 5%

of patients) included neutrophil count decreased (77 [10.6%] patients), neutropenia (62 [8.6%] patients), and anaemia (56 [7.7%] patients).

In conclusion, the overall tolerability of pirtobrutinib in patients with B-cell hematologic malignancies, such as MCL and CLL/SLL, was favorable and characterized by toxicities common to the drug class and/or the underlying disease setting. AEs were manageable with dose omission/modification and/or supportive care routine to hematologic practice and suitable for label guidance. The Sponsor considers the data sufficient to characterize the safety profile of pirtobrutinib.

The FDA's Assessment:

Given the differences in the safety populations identified by the Applicant and the FDA's safety populations, the FDA's assessment of safety differs from that of the Applicant and is described below.

The evaluation of safety of pirtobrutinib is based on 583 patients with hematologic malignancies, including 128 patients with MCL, who received the 200mg dose of pirtobrutinib without subsequent dose escalation. The study required an ANC ≥ 750/µL, platelet count ≥50,000/µL, transaminases ≤2.5x ULN (≤5x ULN in the presence of liver metastases), and bilirubin ≤1.5x ULN (≤3x ULN in the presence of liver metastases). All patients included in the MCL safety population received a prior BTK inhibitor. The majority of patients were refractory or relapsed to prior BTK inhibitor therapy; only a minority of patients (13% in the MCL safety population) discontinued any prior BTK inhibitor due to intolerance or toxicity. Based on the characteristics of the patients in the safety population, the ability to characterize the tolerability of pirtobrutinib in patients who were intolerant to a prior BTK inhibitor is limited. The median duration of treatment with pirtobrutinib was 3.8 months in the MCL safety population and 7.5 months in the pooled safety population.

In the MCL safety population, serious adverse reactions occurred in 38% of patients, most frequently due to infections (including pneumonia, sepsis, and COVID-19). Nine percent of patients permanently discontinued treatment due to adverse reactions, again most commonly due to infections (pneumonia and sepsis). Adverse reactions led to dose interruptions in 32% of patients and dose reductions in 5% of patients, most commonly due to infections (pneumonia and COVID-19) and cytopenias (neutropenia and anemia).

The most common AEs in the MCL safety population, with incidence ≥15% were fatigue, musculoskeletal pain, diarrhea, edema, dyspnea, pneumonia, and bruising. Clinically relevant AEs that occurred at a lower incidence include arthritis or arthralgia (14%), peripheral neuropathy (10%), memory changes (9%), vision changes (7%), sepsis (4.3%), atrial fibrillation or flutter (3.9%), herpesvirus infection (2.3%), and tumor lysis syndrome (0.8%). Grade 3-4 laboratory abnormalities with incidence ≥10% were lymphocytosis, neutropenia, lymphopenia, and thrombocytopenia. Other adverse events of special interest, defined based on the known

safety profile of BTK inhibitors, included infection (Any Grade: 39%, Grade 3-4: 19%), hemorrhage (Any Grade: 13%, Grade 3-4: 3%), and second primary malignancies (Any Grade 3%).

The safety data are limited by the relatively short duration of exposure, particularly in the MCL safety population, however there are an adequate number of patients in the safety populations to perform a current assessment of safety, which will be supported by longer-term safety data requested in a PMR. In summary, pirtobrutinib has an acceptable safety profile; it was tolerable in the majority of patients, with adverse events that were generally manageable.

SUMMARY AND CONCLUSIONS – Section 8

8.3 Statistical Issues

The FDA's Assessment:
As described above in 'Patient Disposition', the FDA does not agree with the analysis sets identified by the Applicant. For efficacy, the FDA's analysis sets are the PAS subpopulation (n=74) and PAS + SAS1 subpopulation (n=120). There were no other statistical issues.

8.4 Conclusions and Recommendations- Section 8

The FDA's Assessment:
The results of the LOXO-BTK-18001 study, a multicenter single-arm study of pirtobrutinib in patients with B-cell malignancies, support accelerated approval of pirtobrutinib for the treatment of adult patients with relapsed or refractory MCL after at least 2 lines of systemic therapy, including a BTK inhibitor. In the primary efficacy population of 120 patients (PAS + SAS1), ORR by IRC per Lugano was 50% (95% CI: 40.7%, 59.3%) and the KM estimate of median DOR by IRC was 8.3 months (95% CI: 5.7, NE) with 24 events observed at a median duration of follow-up of 7.3 months. The KM estimates of DOR rate at 6 months and 9 months were 65.3% (95% CI: 49.8%, 77.1%) and 46.4% (95% CI: 28.7%, 62.4%), respectively.

In the efficacy population of 74 patients (PAS), which represents a population with longer duration of follow-up, the KM estimate of median DOR by IRC was 11.9 months (95% CI: 6.5, NE) with 18 events observed at a median duration of follow-up of 8.2 months. The KM estimates of DOR rate at 6 months and 9 months were 70.9% (95%CI: 53.4%, 82.9%) and 50.3% (95% CI: 30.7%, 67.1%), respectively. Taken together, the efficacy data including response rates and durability of response, support the determination of substantial evidence of effectiveness with pirtobrutinib.

The safety profile was acceptable, based on analysis of the MCL-only and pooled safety populations. Pirtobrutinib was generally well-tolerated with an AE profile that was manageable in the majority of patients.

Pirtobrutinib demonstrates an advantage in efficacy over available therapies for a refractory, BTK inhibitor-pretreated patient population of MCL patients, and thus, the totality of data supports accelerated approval of pirtobrutinib for the treatment of adults with relapsed or refractory MCL after at least 2 lines of systemic therapy, including a BTK inhibitor.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9.0 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The application was not presented to the Oncologic Drug Advisory Committee or other external consultants, as it did not raise significant efficacy concerns or new safety concerns for the proposed indication.

10.0 Pediatrics

The Applicant's Position:

Patients less than 18 years of age were excluded from the clinical studies of pirtobrutinib. The proposed indication, mantle cell lymphoma, is not reported to occur in the pediatric population. The Sponsor has requested and been granted a waiver for pediatric studies. The efficacy and safety of pirtobrutinib in pediatric patients has not been studied.

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

11.0 Labeling Recommendations

The FDA's assessment:
The table below provides the FDA's high-level summary of the significant changes made to the USPI for Jaypirca (pirtobrutinib) NDA 216059. See the USPI attached to the approval letter for final labeling.

Table 76: FDA's Description of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
1 Indications and Usage	The proposed indication is for the (b) (4)	The revised indication is for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a BTK inhibitor.
2 Dosage and Administration	(b) (4)	Severe renal impairment: Add dose reduction or discontinuation guidelines, based on current dose. Strong CYP3A inhibitor or strong or moderate CYP3A inducer: Add guidance to avoid concomitant use, with dose modification guidelines for strong inhibitors and moderate inducers, if unavoidable.
5 Warnings and Precautions (W&P)	(b) (4)	Revised based on pooled safety population who received the 200 mg dose without dose escalation (n=583).
6 Adverse Reactions	• (b) (4) • (b) (4)	• Revised population includes BTK inhibitor-pretreated patients who received the 200 mg dose (n=128). • Laboratory abnormality table expanded to include non-hematologic lab abnormalities
7 Drug Interactions	(b) (4)	Revised to describe the effect of concomitant use and cross

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	(b) (4)	reference to dosage modification guidelines in Section 2.
8.5 Geriatric Use	(b) (4)	Revised to describe numerically higher rates of grade ≥ 3 ARs and serious ARs in patients age ≥ 65 and state that there were not sufficient numbers of patients <65 to determine whether efficacy differed between age groups.
8.6 Renal Impairment	(b) (4)	Revised to state that severe renal impairment increases pirtobrutinib exposure with recommendations to dose-reduce, with cross reference to Section 2.
14.1 Clinical Studies	• (b) (4) • (b) (4) • (b) (4)	• Revised efficacy population includes BTK inhibitor-pretreated patients with MCL who received the 200 mg dose (n=120). • Includes Lugano-based ORR in the efficacy table with CT-only based ORR as a footnote. Includes the percentage of patients who had PET scans utilized in response assessments. • Includes DOR rate at 6 months (by K-M method)

The Applicant's Position:

Labeling recommendations have been submitted with the initial NDA; no changes from the Sponsor are recommended at this time.

The FDA's Assessment:

FDA modified sections of the USPI as described in the table above. The following sections provides additional rationale for the recommended regulatory action.

Rationale for indication statement: The MCL efficacy population from Study LOXO-BTK-18001 included BTK inhibitor-pretreated patients with 1 or more prior lines of therapy, however there were few patients with only 1 prior line of therapy (8% in the primary efficacy population of 120 patients). Thirty-four percent had 2 prior lines, 20% had 3 prior lines, and 38% had 4 or more prior lines. Taken together, 92% of the efficacy population received 2 or more prior lines of therapy. Ninety-seven percent of patients had relapse or refractoriness to the prior BTK inhibitor, while 3% were intolerant to the prior BTK inhibitor.

Given the population in which the demonstration of efficacy with pirtobrutinib is based, the recommended indication is for patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor.

Rationale for accelerated approval: The currently approved treatment options for relapsed/refractory MCL include BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), brexucabtagene autoleucel, bortezomib, and lenalidomide, of which only bortezomib and lenalidomide have regular approval and are considered currently available therapies. Lenalidomide and bortezomib have demonstrated modest response rates in patients with R/R MCL (ranging from 26-31% in the pivotal studies) and data are not available with these agents for patients who are relapsed or refractory following a prior BTK inhibitor. Thus, based on the response rates and sufficient durability of response demonstrated by pirtobrutinib in a relapsed/refractory, BTK inhibitor pre-treated MCL patient population, the study demonstrates an advantage over available therapies.

12.0 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The clinical review team does not recommend a REMS. Based on the observed safety profile of pirtobrutinib, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13.0 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends three PMRs. The first is a safety PMR; given the limited duration of exposure in the safety populations in Study 18001 (3.8 months in the MCL safety population and 7.5 months in the pooled safety population), this PMR is being issued to characterize the longer-term safety of pirtobrutinib with at least 24 months of follow-up. The second is an additional safety PMR. Given that treatment with BTK inhibitors has been shown to be associated with increased SPM risk, a PMR is being issued to characterize this risk with extended follow up of at least 5 years. The third is an accelerated approval PMR to verify clinical benefit, given that accelerated approval is being recommended based on a single-arm trial. The confirmatory trial intended to verify clinical benefit is the BRUIN MCL-321 trial (NCT04662255), a Phase 3 randomized study of pirtobrutinib vs. investigator's choice of BTK inhibitor (ibrutinib, acalabrutinib, or zanubrutinib) in patients with previously treated, BTK inhibitor-naïve MCL. As of 07/15/2022, 26% of patients have been enrolled. This trial is considered to be well underway. Refer to action letter for milestone dates.

PMR #1: Conduct a study to characterize the longer-term safety of pirtobrutinib monotherapy, at a planned dose of 200 mg daily, in patients with hematologic malignancies treated in Study 18001. Characterize safety and exposure with a minimum of 24 months of follow-up. Include evaluations, supplemented by narratives, of deaths in the absence of treated progressive disease, serious adverse reactions, adverse reactions of special interest (including but not limited to serious infections, cardiac arrhythmias, bleeding, cytopenias, and second primary malignancies), and treatment discontinuations for reasons other than progressive disease.

PMR #2: Conduct an integrated safety analysis of patients with hematologic malignancies treated with pirtobrutinib monotherapy at the 200 mg daily dose in clinical trials and from post-marketing reports to further characterize the risk of second primary malignancies with extended follow-up. Patients enrolled in clinical trials should have 5 years minimum follow-up for development of second primary malignancies. Include evaluations of incidence rates, types, severity, time to onset, potential predisposing factors, and outcomes.

PMR #3: Complete a randomized clinical trial to obtain data on the clinical efficacy and safety of pirtobrutinib in patients with mantle cell lymphoma. The trial should compare pirtobrutinib monotherapy to an investigator's choice of approved BTK inhibitors in patients with mantle cell lymphoma. The primary endpoint should be progression-free survival as assessed by an independent review committee, with secondary endpoints that include overall survival and objective response rate. The trial should enroll a sufficiently representative study population to reflect the racial and ethnic diversity of the U.S. patient population with mantle cell lymphoma and allow for interpretation of the results in these patient populations.

14.0 Division Director (DHOT)

X

15.0 Division Director (OCP)

X

16.0 Division Director (OB)

X

17.0 Division Director (Clinical)

X _____

18.0 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19.0 Appendices

19.1 References

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19.2 Financial Disclosure

The Applicant's Position:

Financial disclosure information was collected for all 922 Investigators and Sub-Investigators participating in Study 18001.

The FDA's Assessment:
FDA agrees with the Applicant's statement and the table below.

Covered Clinical Study (Name and/or Number):* LOXO-BTK-18001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 922		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant and confirmed/edited by the FDA.

19.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees.

19.4 OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1 Bioanalytical Methods Section

Data:
In the Study 18001 and the clinical pharmacology package two validated HPLC/MS/MS methods were used to quantitate pirtobrutinib. The two methods are outlined in Table 77 and Table 78 and their cross validation in Table 79. A method was developed to measure the M1 metabolite of pirtobrutinib.

Table 77: Summary of Bioanalytical Validation Used for Quantification of Pirtobrutinib in Human Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	LOXO-305-DMPK-026 (original validation) LOXO-305-DMPK-045 (change of mobile phases, and solution and long-term plasma stability)		
Method description	HPLC/MS/MS Assay Validation for the Determination of LOXO-305 from Human Plasma		
Materials used for standard calibration curve and concentration	Pirtobrutinib Lot N170232 Pirtobrutinib $^{13}C,D_3$ Lot A0005995-1R (b) (4)		
Validated assay range	1.00 to 1000 ng/mL		
Material used for QCs and concentration	Pirtobrutinib Lot N170232 Pirtobrutinib $^{13}C,D_3$ Lot A0005995-1R (b) (4)		
MRDs	NA		
Source and lot of reagents	NA		
Regression model and weighting	Linear $1/x^2$ regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	LOXO-305-DMPK-026 LOXO-305-DMPK-045 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.0% to 2.3%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 8.7%	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 3 QCs**	-11.7% to 0.4%	
	Interbatch %CV	≤ 6.8%	

	TE	NA	
Selectivity & matrix effect	6 batches of blank plasma were tested and met criteria. No matrix effects were observed.		
Interference & specificity	6 batches of blank plasma were tested and no significant interference was observed between LOXO-305 and LOXO-305 $^{13}C,D_3$.		
Hemolysis effect	One lot of 10% hemolyzed plasma was tested. No significant interference was observed.		
Lipemic effect	One lot of lipemic plasma was tested. No significant interference was observed.		
Dilution linearity & hook effect	51-fold dilution validated. Hook effect not applicable.		
Bench-top/process stability	Plasma: 72 hours at room temperature.		
Freeze-thaw stability	4 freeze/thaw cycles at -70°C		
Long-term frozen storage stability	210 days at -20°C and 215 days at -70°C		
Parallelism	Not determined.		
Carry over	There was no significant carry over.		
Method performance in Studies			
Assay passing rate	52 out of 55 batches passed (95%)		LOXO-BTK-18001
Standard curve performance	• Cumulative bias range: -3.3% to 3.0% • Cumulative precision: ≤ 8.7% CV		
QC performance	• Cumulative bias range: -2.0% to 3.0% • Cumulative precision: ≤ 7.6% CV		
Method reproducibility	See LOXO-305-DMPK-042[a]		
Study sample analysis/ stability	Samples were stored up to 588 days at -70°C. Stability was established for 534 days at -70°C. One sample was analyzed outside of validated stability.		

Abbreviations: CV = coefficient of variation; HPLC/MS/MS = high-performance liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; MRD = minimum required dilutions; NA = not applicable; QC = quality control; TE = total error; ULOQ = upper limit of quantitation.

- Study LOXO-BTK-18001 was analyzed for pirtobrutinib using both LOXO-305-DMPK-026 (64 batches) and LOXO-305-DMPK-042 (79 batches). Because these methods were cross-validated, the method reproducibility for this study is reported with LOXO-305-DMPK-042.

Table 78: Summary of Bioanalytical Validation Used for Quantification of Pirtobrutinib in Human Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	LOXO-305-DMPK-042 (original validation) LOXO-305-DMPK-044 (interference with multiple comedications) LOXO-305-DMPK-054 (interference with repaglinide) LOXO-305-DMPK-055 (interference with multiple comedications) LOXO-305-DMPK-071 (interference with LSN3828720) LOXO-305-DMPK-080 (plasma long-term stability) LOXO-305-DMPK-085 (plasma long-term stability)

Method description	HPLC/MS/MS Assay Validation for the Determination of LOXO-305 from Human Plasma		
Materials used for standard calibration curve and concentration	Pirtobrutinib Lot N170232 Midazolam Lot FE01221602 α-hydroxymidazolam Lot FN09021601 Rifampin Lot LRAA9622 Itraconazole Lot MKCD8090 Repaglinide Lot R038K0 Caffeine Lot FN05101901 Warfarin Lot 1385525 Omeprazole Lot R065N0 Digoxin Lot BCCD4453 LSN3828720 Lot 00041-18-18 Pirtobrutinib $^{13}C,D_3$ Lot A0005995-1R (b) (4)		
Validated assay range	20.0 to 20000 ng/mL		
Material used for QCs and concentration	Pirtobrutinib Lot N170232 Midazolam Lot FE01221602 α-hydroxymidazolam Lot FN09021601 Rifampin Lot LRAA9622 Itraconazole Lot MKCD8090 Repaglinide Lot R038K0 Caffeine Lot FN05101901 Warfarin Lot 1385525 Omeprazole Lot R065N0 Digoxin Lot BCCD4453 LSN3828720 Lot 00041-18-18 Pirtobrutinib $^{13}C,D_3$ Lot A0005995-1R (b) (4)		
MRDs	NA		
Source and lot of reagents	NA		
Regression model and weighting	Quadradic $1/x^2$ regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	LOXO-305-DMPK-042 LOXO-305-DMPK-080 LOXO-305-DMPK-085 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.0% to 5.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.5%	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 3 QCs**	0.0% to 3.0%	
	Interbatch %CV	≤ 6.4%	
	TE	NA	
Selectivity & matrix effect	6 lots of blank plasma were tested and met criteria. No matrix effects were observed.		

Interference & specificity	No significant interference in the quantification of pirtobrutinib was observed in the presence of midazolam, α-hydroxymidazolam, rifampin, itraconazole, repaglinide, caffeine, omeprazole, warfarin, digoxin, LSN3828720.	
Hemolysis effect	One lot of 10% hemolyzed plasma was tested. No significant interference was observed.	
Lipemic effect	One lot of lipemic plasma was tested. No significant interference was observed.	
Dilution linearity & hook effect	5-fold dilution validated. Hook effect not applicable.	
Bench-top/process stability	Plasma: 72 hours at room temperature.	
Freeze-thaw stability	4 freeze/thaw cycles at -70°C	
Long-term storage	425 days at -20°C and 534 days at -70°C	
Parallelism	Not determined.	
Carry over	There was no significant carry over.	
Method performance in Studies		
Assay passing rate	20006: 23 out of 23 batches passed (100%) 20008: 22 out of 24 batches passed (92%) 20010: 9 out of 10 batches passed (90%) 20014: 14 out of 14 batches passed (100%) 20011: 14 out of 14 batches passed (100%) 20009: 22 out of 22 batches passed (100%) 20016: 10 out of 12 batches passed (83%) 20017: 15 out of 15 batches passed (100%) 20007: 5 out of 5 batches passed (100%) 20013: 9 out of 9 batches passed (100%) 20021: 16 out of 16 batches passed (100%) 18001: 77 out of 79 batches passed (97%)	LOXO-BTK-20006 LOXO-BTK-20008 LOXO-BTK-20010 LOXO-BTK-20014 LOXO-BTK-20011 LOXO-BTK-20009 LOXO-BTK-20016 LOXO-BTK-20017 LOXO-BTK-20007 LOXO-BTK-20013 LOXO-BTK-20021 LOXO-BTK-18001

Standard curve performance	20006: • Cumulative bias range: -3.0% to 2.5% • Cumulative precision: ≤ 4.6% CV 20008: • Cumulative bias range: -2.4% to 2.5% • Cumulative precision: ≤ 7.6% CV 20010: • Cumulative bias range: -2.3% to 3.3% • Cumulative precision: ≤ 6.1% CV 20014 • Cumulative bias range: -3.3% to 8.0% • Cumulative precision: ≤ 6.4% CV 20011: • Cumulative bias range: -3.7% to 2.5% • Cumulative precision: ≤ 6.2% CV 20009: • Cumulative bias range: -3.3% to 2.0% • Cumulative precision: ≤ 7.1% CV 20016: • Cumulative bias range: -3.5% to 4.0% • Cumulative precision: ≤ 5.1% CV 20017: • Cumulative bias range: -2.6% to 2.80% • Cumulative precision: ≤ 5.9% CV 20007: • Cumulative bias range: -6.6% to 8.3% • Cumulative precision: ≤ 4.2% CV 20013 • Cumulative bias range: -3.0% to 2.3% • Cumulative precision: ≤ 6.3% CV 20021 • Cumulative bias range: -2.0% to 2.3% • Cumulative precision: ≤ 6.0% CV 18001 • Cumulative bias range: -2.2% to 1.0% • Cumulative precision: ≤ 5.8% CV	

QC performance	20006: • Cumulative bias range: 0.6% to 4.0% • Cumulative precision: ≤ 4.8% CV 20008: • Cumulative bias range: 2.5% to 5.0% • Cumulative precision: ≤ 6.4% CV 20010: • Cumulative bias range: -2.5% to 3.7% • Cumulative precision: ≤ 6.5% CV 20014: • Cumulative bias range: 0.2% to 2.8% • Cumulative precision: ≤ 7.8% CV 20011: • Cumulative bias range: 0.0% to 2.5% • Cumulative precision: ≤ 7.0% CV 20009: • Cumulative bias range: -3.8% to 2.8% • Cumulative precision: ≤ 4.6% CV 20016: • Cumulative bias range: 1.2% to 1.7% • Cumulative precision: ≤ 4.5% CV 20017: • Cumulative bias range: 1.9% to 5.27% • Cumulative precision: ≤ 6.9% CV 20007: • Cumulative bias range: 2.5% to 5.8% • Cumulative precision: ≤ 8.8% CV 20013 • Cumulative bias range: 0.0% to 2.8% • Cumulative precision: ≤ 5.0% CV 20021 • Cumulative bias range: 0.0% to 1.7% • Cumulative precision: ≤ 5.9% CV 18001 • Cumulative bias range: 0.0% to 3.5% • Cumulative precision: ≤ 6.6% CV	

Method reproducibility	20006: 11% of samples were run in the ISR and 96% passed criteria. 20008: 5% of the samples were run in the ISR and 97% passed criteria. 20010: 12% of samples were run in the ISR and 95% passed criteria. 20014: 10% of samples were run in the ISR and 97% passed criteria. 20011: 10% of samples were run in the ISR and 98% passed criteria. 20009: 13% of samples were run in the ISR and 100% passed criteria. 20016: 11% of samples were run in the ISR and 98% passed criteria. 20017: 12% of samples were run in the ISR and 100% passed criteria. 20007: 11% of samples were run in the ISR and 100% passed criteria. 20013: 12% of samples were run in the ISR and 100% passed criteria. 20021: 10% of samples were run in the ISR and 98% passed criteria. 18001: 4% of samples were run in the ISR and 93% passed criteria.	
Study sample analysis/ stability	Samples were stored up to 588 days at -70°C. Stability was established for 534 days at -70°C.	

Abbreviations: CV = coefficient of variation; HPLC/MS/MS = high-performance liquid chromatography with tandem mass spectrometry; ISR = incurred sample reanalysis; LLOQ = lower limit of quantitation; MRD = minimum required dilutions; NA = not applicable; QC = quality control; TE = total error; ULOQ = upper limit of quantitation.

Table 79: Summary of Method Modifications and Cross-Validation Results

Bioanalytical method validation report name and hyperlink	LOXO-305-DMPK-087 AV21-LY3527727-01 Cross Validation
Reason for cross-validation	Two HPLC-MS/MS methods were developed to determine concentrations of pirtobrutinib in human K_2EDTA plasma, one at a low range (1.00 to 1000 ng/mL) and one at a high range (20.0 to 20000 ng/mL). The methods were cross validated to compare the analysis of spiked human samples prepared and analyzed using both methods.
Experiment summary	49 spiked samples were analyzed for pirtobrutinib using both methods. 85.7% of the results fell within the ±20% acceptance range, and the Lin's concordance correlation coefficient was 0.97720, with the 95% confidence limits of 0.96520 to 0.98510.

The FDA's Assessment:

The Applicant's bioanalytical methods validation to quantify pirtobrutinib plasma

concentrations and cross-validation appear acceptable.

19.4.2 Pharmacometrics Review

The current pharmacometrics review evaluates the following:

a. The adequacy of the population PK (PPK) model in describing pirtobrutinib PK in adults with hematological malignancies, evaluating and quantifying the effect of intrinsic and extrinsic factors on PK exposure and predicting pirtobrutinib exposure for exposure-efficacy and safety analyses.
b. The relationship between pirtobrutinib exposure and the overall response rate (ORR).
c. The relationship between pirtobrutinib exposure and the incidence of Grade 3 and above anemia, neutropenia and infection or any grade hypertension.
d. The relationship between pirtobrutinib exposure and the change from baseline of any grade in neutrophile counts, platelet counts, hemoglobin levels, systolic and diastolic blood pressure.

The Applicant's PPK was considered acceptable in describing pirtobrutinib PK. No dose adjustment is required based on the PPK model-estimated effect of the identified statistically significant covariates on clearance (CL), such body weight, hypoalbuminemia and mild to moderate renal impairment. The PPK model was considerate adequate to perform simulations and predict various pirtobrutinib exposure metrics (average concentration [Cavg], Cmax and Ctrough) for the exposure-response analyses.

The exposure-efficacy relationships showed non-significant trends of lower response under a pirtobrutinib dose of 50 mg (estimated average response of about 30% compared to a 200 mg dose with an average response of about 60%). However, the non-significant trends should be interpreted with caution due to few observations under pirtobrutinib doses below 200 mg, rendering the assessment of an exposure-response relationship challenging.

The exposure-safety analyses were considered flat or shallow across pirtobrutinib exposure and dose levels, including for the maximum increase in systolic blood pressure (about 20 mmHg) and the maximum decrease in platelet count (about 30 x 10^9/L). However, most of the observations are from the 200 mg dose and therefore these relationships should be interpreted with caution, as relationships from multiple dose levels are more informative (particularly when patient factors may confound the analyses).

19.4.2.1 PPK Assessment Summary

The Applicant's Assessment:

General Information		
Objectives of PPK Analysis		• Characterize the PK of pirtobrutinib in patients with hematological malignancies. • Identify patient factors, laboratory parameters, and disease characteristics that may influence pirtobrutinib disposition in this patient population. • Consider the clinical impact of the findings of these analyses on recommendations for dose(s) and/or dosing regimens in the patient population and subpopulations.
Study Included		Study LOXO-BTK-18001 (BRUIN; J2N OX-JZNA). (data cutoff date of 31 January 2022)
Dose(s) Included		Phase 1: Starting doses of 25 to 300mg QD Phase 2: 200mg QD
Population Included		Patients with hematological malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL)
Population Characteristics (**Table 80**)	General	Age – median 68 yr (range 27-95 yr) Weight – median 76.6 kg (range 35.7-152.5 kg) Sex – Female N = 201 (34%), Male N = 395 (66%) Race: White N = 509 (86%) Black or African American N = 17 (3%) Asian N = 39 (7%) Other N = 29 (5%) Not reported N=1 (<1%)
	Organ Impairment	Renal function: Normal N = 121 (20%) Mild impairment N=304 (51%) Moderate impairment N = 166 (28%) Severe impairment N = 4 (1%) Hepatic function: Normal N = 474 (80%) Mild impairment N = 106 (18%) Moderate impairment N = 13 (2%) Severe impairment N = 1 (<1%) Not reported N = 1 (<1%)
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ		Total 595 patients with 4487 evaluable observations 213 BLQ samples obtained pre-dose 17 BLQ samples obtained post-dose
Sampling Schedule	Rich Sampling	Table 81
	In ITT Population	Table 81
Covariates Evaluated	Static	Age, sex, race/ethnicity, body weight, cancer type, formulation
	Time-varying	albumin, renal function, hepatic function

Final Model	Summary	Acceptability [FDA's comments]
Software and Version	• NONMEM (Version 7.4.2) • R (Version 4.1.2) • PsN (Version 4.8.1)	Acceptable
Model Structure	2-compartment model with 4 transit compartments for absorption.	Acceptable
Model Parameter Estimates	Table 82	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Model parameter estimation was performed with overall high precision and interindividual variability was generally low to moderate. Shrinkage for interindividual ETA parameters on CL/F and MTT were 3% and 57%, respectively	Acceptable
BLQ for Parameter Accuracy	17 post-dose BLQ samples were excluded (<1%). Parameter accuracy assessment for BLQ was not carried out.	Acceptable
GOF, VPC	Figure 15 and Figure 16	Acceptable
Significant Covariates and Clinical Relevance	a total of 3 patient factors were found to meet the criteria for inclusion in the final popPK model: • body weight on CL/F, Q/F, Vc/F, Vp/F, • serum albumin on CL/F and Vc/F • eGFR on CL/F	Acceptable
Analysis Based on Simulation (optional)	Figure 17, Figure 18, and Figure 19	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	Steady state was achieved within 5 days of once daily dosing. The mean (CV%) steady-state AUC and Cmax were 91300 h*ng/mL (41%) and 6460 ng/mL (26%), respectively, at the recommended dosage. • *Age, Race and Body Weight:* Based on a population pharmacokinetic analysis in patients with cancer, age (range 27-95 years), gender (394 males and 201 females), and body weight (range 35.7-152.5 kg) had no clinically meaningful effect on the exposure of pirtobrutinib.	Acceptable. Based on the PPK model the estimated terminal half-life for pirtobrutinib is 18.5 hours.

Table 80: Summary of Baseline Patient Characteristics for the Population Pharmacokinetic and Exposure-Response Analyses in Study 18001

	Study Population	
	Population PK/ Exposure-Safety	Exposure-Efficacy (MCL)
	(N = 595)	(N = 73)
Age (years)		
Range	27 – 95	50 – 87
Median	68.0	71.0
Mean (%CV)	67.6 (14.7)	69.6 (12.3)
Weight (kg)[a]		
Range	35.7 – 152.5	46.6 – 149.5
Median	76.6	78.0
Mean (%CV)	78.3 (22.5)	80.2 (23.8)
Body mass index (kg/m^2)[b]		
Range	14.1 – 47.2	18.9 – 45.4
Median	26.4	27.4
Mean (%CV)	26.8 (18.0)	27.7 (18.8)
Serum Albumin (g/L)		
Range	19.0 – 56.5	27.0 – 51.0
Median	41.0	42.0
Mean (%CV)	40.1 (13.2)	41.1 (10)
Estimated glomerular filtration rate[c] (mL/min/1.73 m^2)		
Range	22.3 – 131.8	25.7 – 105
Median	72.2	69.7
Mean (%CV)	72.0 (26.8)	68.1 (26.7)
Sex (N, %)		
Female	201 (34)	15 (21)
Male	394 (66)	58 (79)
Race (N, %)		
White	509 (86)	60 (82)
Black or African American	17 (3)	1 (1)
Asian	39 (7)	6 (8)
Others[d]	29 (5)	6 (8)
Not reported	1 (< 1)	---
Ethnic origin (N, %)		
Non-Hispanic	548 (92)	67 (92)
Hispanic	23 (4)	3 (4)
Not reported	24 (4)	3 (4)
Renal function[e] (N, %)		
Normal	121 (20)	7 (10)
Mild impairment	304 (51)	39 (53)
Moderate impairment	166 (28)	26 (36)
Severe impairment	4 (1)	1 (1)
Hepatic function[f] (N, %)		
Normal	474 (80)	60 (82)
Mild impairment	106 (18)	11 (15)
Moderate impairment	13 (2)	2 (3)
Severe impairment	1 (< 1)	---
Not reported	1 (< 1)	---

	Study Population	
	Population PK/ Exposure-Safety	Exposure-Efficacy (MCL)
	(N = 595)	(N = 73)
Cancer type (N, %)		
MCL	140 (23)	73 (100)
CLL/SLL	263 (44)	---
All other NHL patients	192 (32)	---
Formulation of first dose (N, %)		
T1	210 (35)	33 (46)
T2	385 (65)	38 (54)

Abbreviations: AST = aspartate aminotransferase; CLL = chronic lymphocytic leukemia; %CV = percent coefficient of variation; eGFR = estimated glomerular filtration rate; MCL = mantle cell lymphoma; MDRD = Modification of Diet in Renal Disease; N = number of patients; PK = pharmacokinetics; SLL = small lymphocytic lymphoma; TBI = total bilirubin; ULN = upper limit of normal.

[a] Baseline body weight missing for 2 patients (N= 593).

[b] Height missing for 31 participants (N = 564).

[c] eGFR as calculated by the Modification of Diet in Renal Disease Study Group equation (MDRD-6) = 170 • [serum creatinine (mg/dL)]^-0.999 • [age]^-0.176 • [serum urea nitrogen (mg/dL)]^-0.17 • [serum albumin (g/dL)]^0.318• [0.762 if patient is female] • [1.18 if patient is black] (Levey et al. 1999).

[d] Includes American Indian or Alaska native, Native Hawaiian or other Pacific Islander, or Other.

[e] Classified as normal (eGFR ≥ 90 mL/minute/1.73 m^2), mild impairment (60 mL/minute/1.73 m^2 ≤ eGFR < 90 mL/minute/1.73 m^2), moderate impairment (30 mL/minute/1.73 m^2 ≤ eGFR < 60 mL/minute/1.73 m^2), and severe impairment (15 mL/minute/1.73 m^2 ≤ eGFR < 30 mL/minute/1.73 m^2).

[f] As determined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction (Patel et al. 2004). Classified as normal (TBI ≤ ULN and AST ≤ ULN), mild impairment (TBI ≤ 1.5 • ULN and AST > ULN) or (ULN < TBI ≤ 1.5 • ULN), moderate impairment (1.5 • ULN < TBI ≤ 3 • ULN), or severe impairment (TBI > 3 • ULN).

Source: Applicant's Pharmacometric Modelling Report, Table 9.1, page 35.

Table 81: **Pharmacokinetic Collection Schedule in Study 18001**

Study Phase	Measurement Schedule	PK Timepoints
Phase 1 Dose Escalation	C1D1	Intense sampling:
	C1D8 (±2 days)	Predose, 1, 2, 4, 8 hours
	C2D1 (±3 days)	
	C4D1 (±3 days)	
Phase 1 Dose Expansion and Phase 2	C1D8 (±2 days)	Sparse sampling:
	C4D1 (±3 days)	Predose only

Abbreviations: C1D1 = Cycle 1 Day 1; C1D8 = Cycle 1 Day 8; C2D1 = Cycle 2 Day 1; C4D1 = Cycle 4 Day 1; PK = pharmacokinetics.

Note: Additional PK sampling was conducted when patients underwent a dose escalation and/or when considered necessary by the Sponsor/Investigator, irrespective of study phase.

Source: Applicant's Pharmacometric Modelling Report, Table 7.2, page 26.

Table 82: **Pharmacokinetic and Covariate Parameters in Population Model**

Parameter	Parameter Estimates (%SEE)		Final Model Bootstrap
	Base Model	**Final Model**	**95% CI**
Bioavailability (F, fraction, Θ1)	1 fixed	1 fixed	1 fixed
Mean transit time (MTT, h, Θ2)	1.08 (2.89)	1.08 (2.97)	(1.02, 1.14)
Clearance (CL, L/h, Θ3)	2.07 (1.93)	2.02 (1.66)	(1.96, 2.10)
Intercompartmental clearance (Q, L/h, Θ5)	8.65 (10.3)	8.38 (10.5)	(6.60, 10.7)
Central volume of distribution (Vc, L, Θ4)	33.2 (3.49)	32.8 (3.60)	(30.0, 35.4)
Peripheral volume of distribution (Vp, L, Θ6)	19.8 (5.40)	19.5 (5.49)	(17.4, 22.2)
Covariate Effects			
Allometry on CL and Q			
Body Weight (kg; Θ9)[a]	0.444 (17.7)	0.524 (11.5)	(0.386, 0.653)
Allometry on Vc and Vp			
Body Weight (kg; Θ10)[b]	0.760 (6.95)	0.785 (6.31)	(0.685, 0.881)
Covariate effects on CL			
eGFR (mL/min/1.73 m^2; Θ12)[c]	NA	0.00329 (31.0)	(0.00118, 0.00525)
Albumin (g/L; Θ11)[d]	NA	-0.677 (16.7)	(-0.915, -0.457)
Covariate effect on Vc			
Albumin (g/L; Θ13)[e]	NA	-0.513 (22.0)	(-0.759, -0.259)
Interindividual variability CV%			
MTT (Ω_2)	25.1% (29.6)	25.0% (30.7)	(17.4, 33.1%)
CL (Ω_3)	39.5% (7.10)	37.9% (7.61)	(34.8, 41.0%)
Interoccasion variability CV%			
MTT	45.9% (13.4)	45.9% (13.4)	(39.1, 52.7%)
Residual variability			
Proportional	0.208 (2.46)	0.205 (2.37)	(0.195, 0.214)

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

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

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

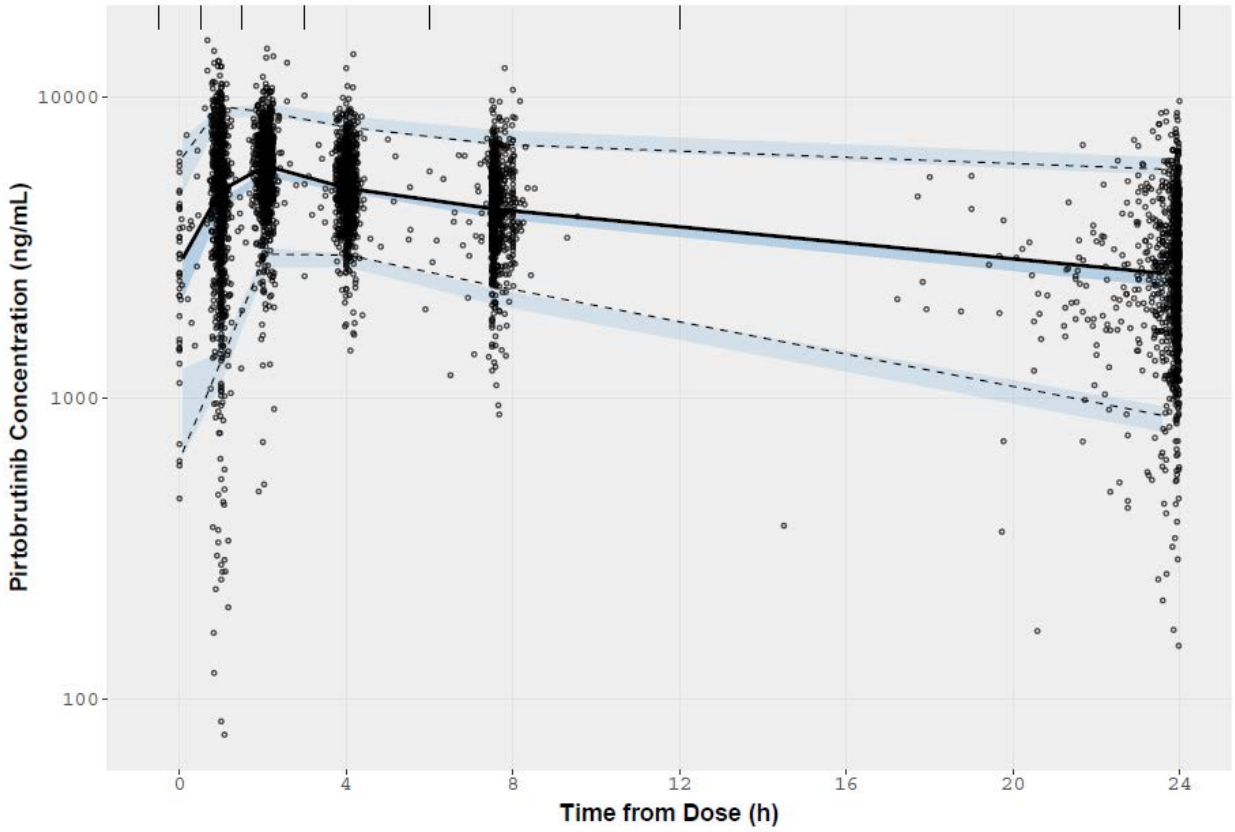
[c] CL/F = Population estimate of CL*(exp(Θ12*(eGFR-74.96)).

[d] CL/F = Population estimate of CL*((ALB/41.6)**Θ11).

[e] V_c/F = Population estimate of Vc* ((ALB/41.6)**Θ13).

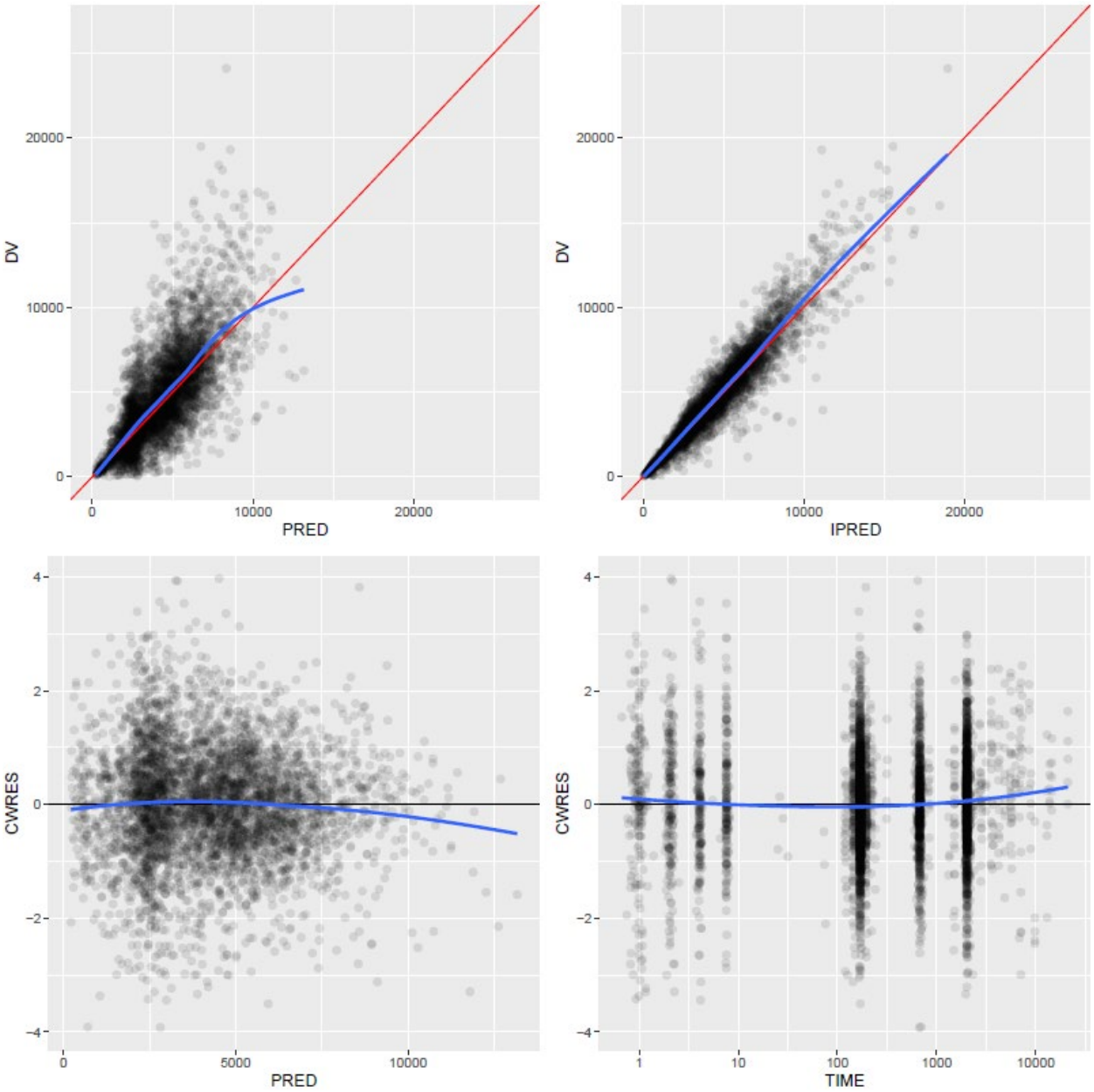
Source: Applicant's Pharmacometric Modelling Report, Table 9.2, page 40.

Figure 15: Visual Predictive Check of the Population Pharmacokinetic Model For Pirtobrutinib



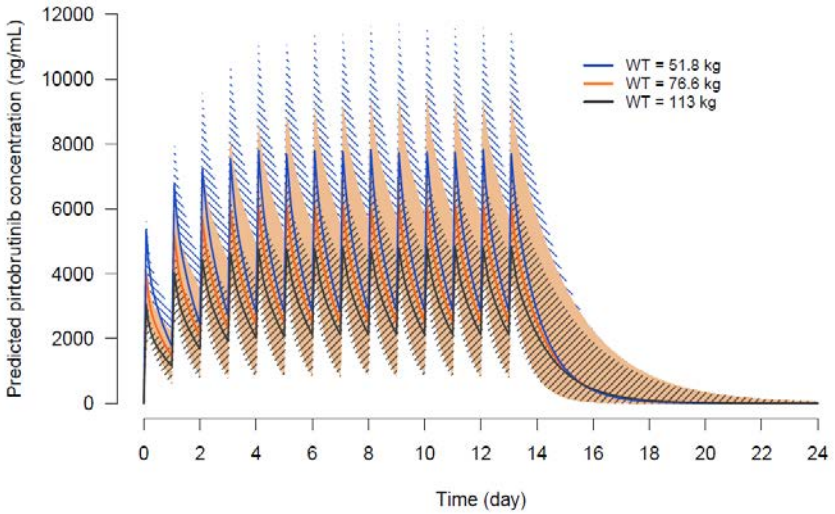
Solid black line represents median of observed data, dotted black lines represent the 5th and 95th percentiles of observed data. Shaded blue area depicts the model-predicted 95% confidence interval for 5th, 50th (median), and 95th percentiles.
Source: Applicant's Pharmacometric Modelling Report, Figure 9.2, page 41.

Figure 16: Pirtobrutinib Final Population PK Model Goodness-Of-Fit Plots



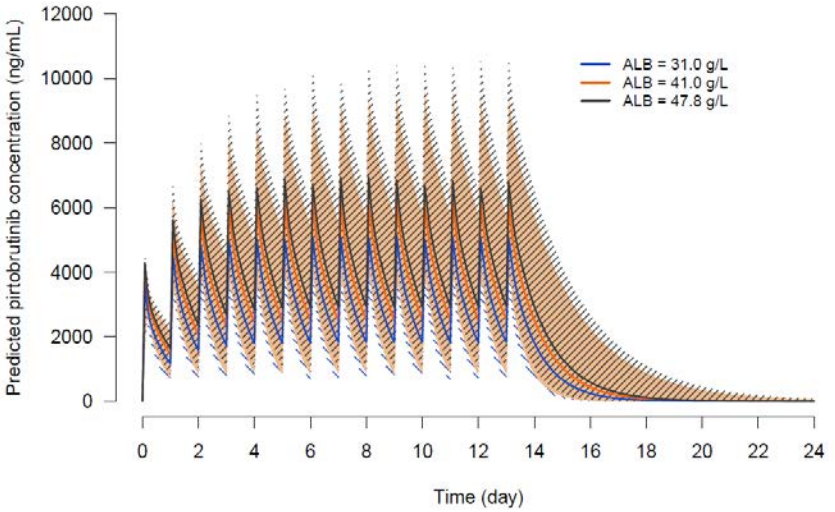
Abbreviations: CWRES = conditional weighted residual; DV = dependent variable (pirtobrutinib concentration, ng/mL); IPRED = individual predicted; PK = pharmacokinetic; PRED = population predicted; TIME = time from first dose (hr). Blue lines represent loess fits to data.
Source: Applicant's Pharmacometric Modelling Report, Figure ATT.4.2, page 122.

Figure 17: Simulated PK Profiles at 200 mg QD for Patients with Body Weights Which Are 5th, 50th, and 95th Percentiles of Observed Patient Characteristics in Study 18001



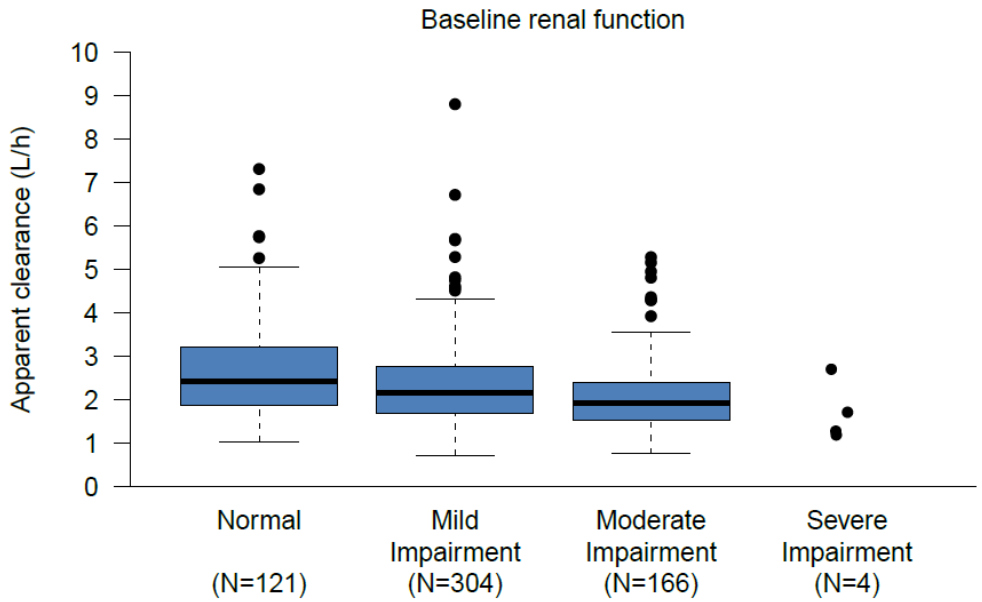
Abbreviations: PK = pharmacokinetic; QD = once daily; WT = body weight.
Solid lines represent the median prediction, with shaded areas corresponding to 90th prediction intervals based on interindividual variability.
Source: Applicant's Pharmacometric Modelling Report, Figure 10.2, page 48.

Figure 18: Simulated PK Profiles at 200 mg QD for Patients with Serum Albumin Values Which Are 5th, 50th, and 95th Percentiles of Observed Patient Characteristics in Study 18001



Abbreviations: ALB = albumin; PK = pharmacokinetic; QD = once daily.
Solid lines represent the median prediction, with shaded areas corresponding to 90th prediction intervals based on interindividual variability.
Source: Applicant's Pharmacometric Modelling Report, Figure 10.8, page 54.

Figure 19: Box Plots of Apparent Clearance (L/h) Stratified by Baseline Renal Function



Box plots depict the 25th, 50th, and 75th percentiles.
Whiskers represent 1.5 times the inter-quartile range.
Normal = estimated glomerular filtration rate (eGFR) ≥ 90 mL/minute/1.73 m^2
Mild impairment = 60 mL/minute/1.73 m^2 ≤ eGFR < 90 mL/minute/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/minute/1.73 m^2 ≤ eGFR < 30 mL/minute/1.73 m^2
Source: Applicant's Pharmacometric Modelling Report, Figure 10.5, page 51.

The FDA's Assessment of the PPK model:

- The Applicant's PK model adequately describes the observed concentrations of pirtobrutinib in patients with different hematological malignancies. The PK model can be used to perform simulation and predict pirtobrutinib exposure metrics for exposure-response assessments.

- The PK parameter from the final model (**Table 82**) were estimated with a good precision (RSE ≤ 22%), except for a relatively lower precision for the effect of eGFR on CL (RSE of 31%), likely due to the lack of patients with severe renal impairment (n=4 [1% of patients]). The residual error (Epsilon) shrinkage was low (< 10%), indicating the informativeness of the goodness of fit (GOF) plots to diagnose structural and residual error model misspecifications.

- The PPK model GOF plots (**Figure 16**) and visual predict check (VPC) plot (**Figure 15**) were acceptable, indicating that the model is able to predict the observed data and to capture the observed variability in pirtobrutinib concentrations.

- The PK of pirtobrutinib was not affected by the type of hematological malignancy (MCL, CLL and SLL).

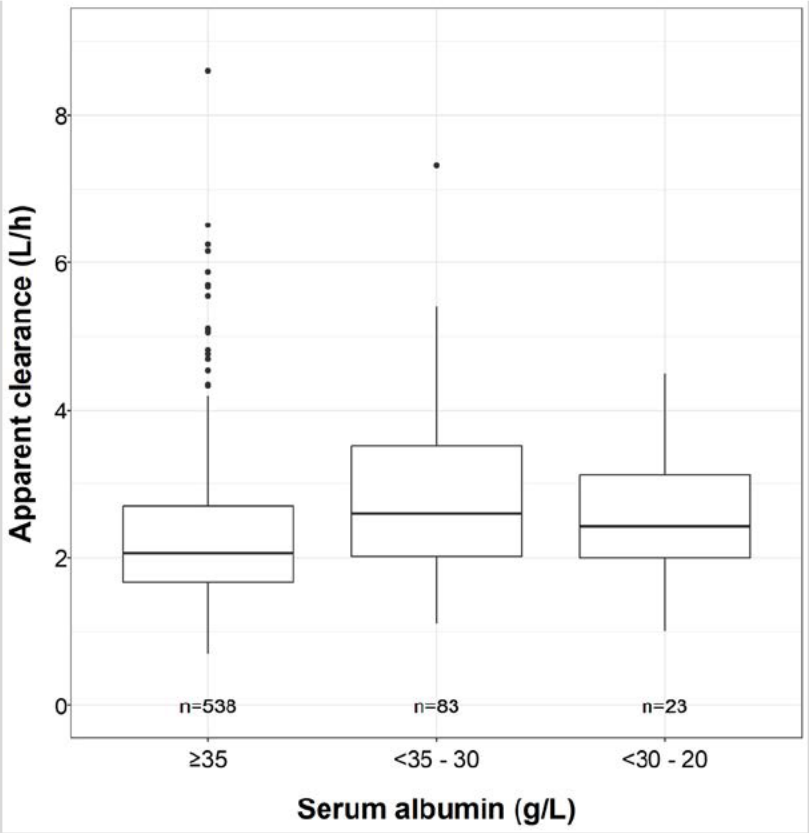
- Pirtobrutinib bioavailability (F1) and absorption rate constants (estimated by the MTT parameters) were not significantly affected by the tablet formulations (T1 and T2) used in the phase 1 and phase 2 trials. The T1 formulation was estimated to have 4% higher F1 and 6% lower MTT compared to the commercial tablet T2. The inclusion of tablet formulation on F1 or MTT decreased the objective function value (OFV) by 6.1 points for F1 (p value > 0.01, for 1 degree of freedom [df]) and by 2.5 points for MTT (p value > 0.01, for 1df).

- Serum albumin levels was found to be statistically significant covariate on CL, although no trend was observed from the exploratory plot of subject's individual CL versus serum albumin levels. In the PPK analysis dataset, 23 PK observations with a Grade 2 hypoalbuminemia (serum albumin = 20 - <30 g/L) were available. According to the PPK model, a subject with a serum albumin level of 25 g/L is predicted to have a 41% higher pirtobrutinib CL compared to a reference subject with normal albumin level of 41.6 g/L. In the PPK analysis dataset, no patient had a serum albumin levels < 20 g/L (Grade 3 severity). However, based on the estimated relationship a serum albumin level of 20 g/L is predicted to be associated with a 64% higher pirtobrutinib CL compared to a reference subject with an albumin level of 41.6 g/L.

  Although the PPK model estimated a statistically significant effect of serum albumin levels on CL (likely due to an increase in unbound drug), dose adjustment based on serum albumin level was not recommended based on the observed and predicted overlap in CL (**Figure 20**) and thus in exposure (**Figure 18**), as well as the shallow exposure-efficacy and safety relationships. In addition, the dedicated hepatic impairment study did show the need for dose adjustment.

- Renal function assessed by MDRD was a statistically significant covariate on pirtobrutinib CL. According to the PPK model, a subject with an eGFR of 20 mL/min/1.73m^2 (severe renal impairment) is predicted to have a 23% lower CL (23% higher steady-state AUC) compared to a reference subject with an eGFR of 100 mL/min/1.73 m^2. The model-estimated average increase in exposure in case of severe renal impairment was lower than the estimated 36% increase in AUC from the dedicated renal impairment study. This discrepancy is likely due to the fewer number of patients (n=4) with severe renal impairment in study 18001 (**Figure 19**).

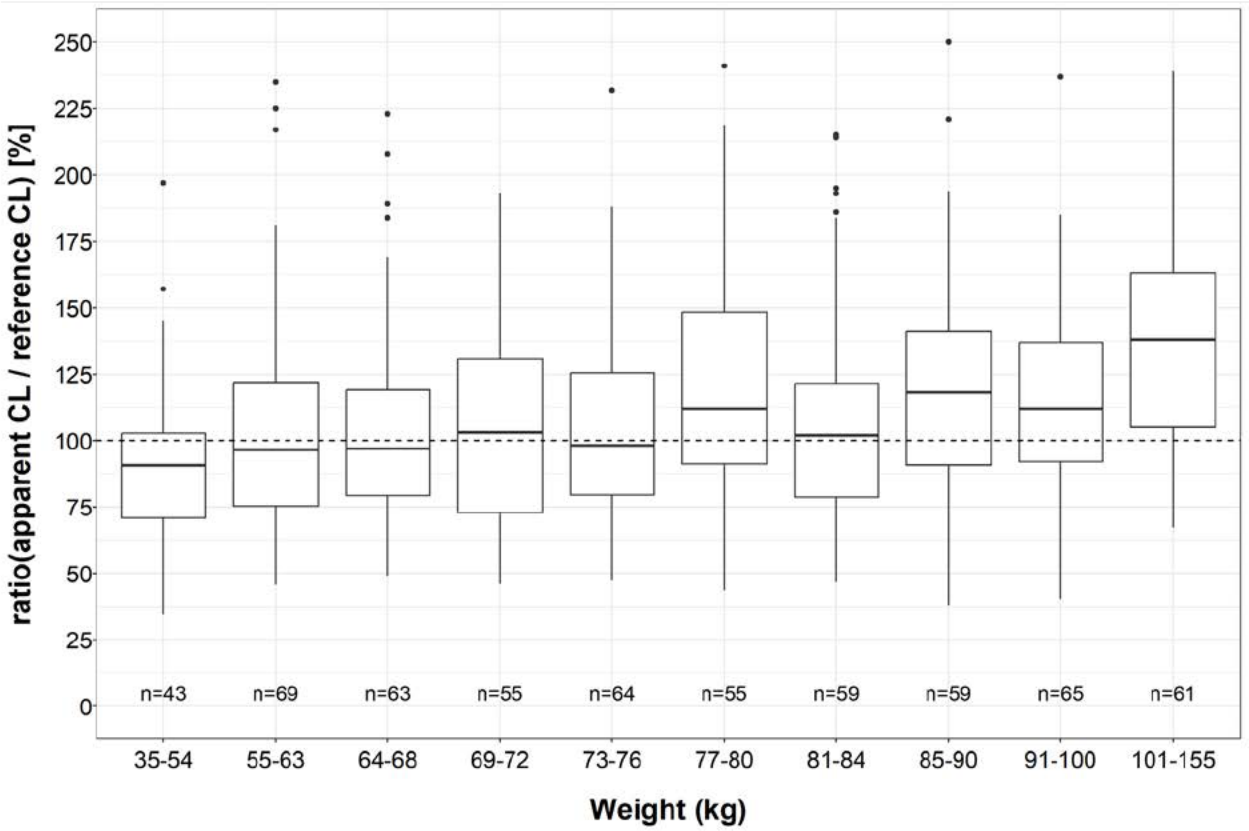
Figure 20: Distribution of Predicted Individual Clearances Stratified by Serum Albumin Levels



Source: FDA Reviewer

- Body weight was a significant covariate on CL. According to the PPK model, pirtobrutinib CL is predicted to decrease by 30% at the minimum recorded body weight in study 18001 (35 kg) and increase by 48% at the highest recorded body weight in study 18001 (150 kg). However, no dose adjustment based on body weight was recommended, due the overlap in exposure between body weight groups (**Figure 17** and
- **Figure 21**).
- **Figure 21** shows the distribution of the estimated pirtobrutinib individual CLs by weight groups from study 18001 relative to the estimated typical CL in a subject with a body weight of 70 kg. The distributions of CL values are overlapping with no clear trend in the different weight group.

Figure 21: Relative Change in Individual Clearances to a Reference 70 kg Subject, Stratified By Weight Groups



Note: The reference CL is the PPK model estimated apparent clearance (CL/F) of 2.02 L/h for a 70 kg subject.
Source: FDA Reviewer

19.4.2.2 Exposure-Response for Efficacy Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Characterize the relationship between pirtobrutinib systemic exposure and efficacy endpoints in patients with MCL and identify covariates that can influence these relationships.
Study Included		Study LOXO-BTK-18001 (BRUIN; J2N OX-JZNA). (data cutoff date of 31 January 2022)
Endpoint		Primary: Overall Response Rate (ORR), which includes patients with a best overall response (BOR) of partial response (PR) or complete response (CR).
No. of Patients (total, and with individual PK)		73 patients from the primary analysis set (PAS)
Population Characteristics (**Table 80**)	General	Age median 71 yr (50-87) Weight median 78.0 kg (46.6 – 149.5) Male N = 58 (79%) Female N = 15 (21%) White N = 60 (82%) Black or African American N = 1 (1%) Asian N = 6 (8%) Others N = 6 (8%)
	Pediatrics (if any)	Not applicable
Dose(s) Included		Phase 1: Starting doses 25 to 300mg QD Phase 2: 200mg QD
Exposure Metrics Explored (range)		Average concentration of pirtobrutinib from the start of treatment up to the time of event
Covariates Evaluated		Age, Body weight, Sex, Simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI)

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Logistic regression model	Acceptable
Model Parameter Estimates	Table 83	Acceptable
Model Evaluation	The base models for the efficacy exposure-response analysis consisted of a logistic regression model which estimated the incidence of the endpoint for the entire study population independent of drug exposure. The relationship between pirtobrutinib concentration and the efficacy endpoint was then tested using linear, log-linear, and Emax models. Exposure measures were tested for statistical significance (change in the MOF value, Δ3.841 points for 1 degree of freedom, $p<0.05$, based on $\chi 2$ distribution) to establish the final model.	See below
Covariates and Clinical Relevance	No statistically significant covariates were identified.	See below

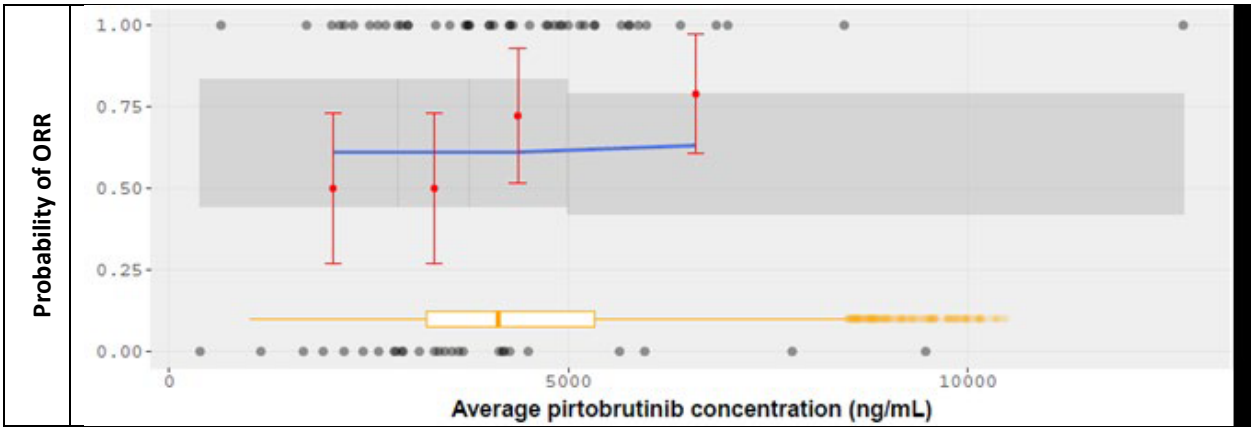
Simulation for Specific Population	Not applicable	Acceptable
Visualization of E-R relationships	Figure 22	Figure 24, **Error! Reference source not found.** APPEARS THIS WAY ON ORIGINAL
Overall Clinical Relevance for ER	The relationship between average concentration (Cavg) up to the time of the BOR event and ORR was not statistically significant. No statistically significant covariates were identified.	The Applicant's model-predicted probability of BOR versus Cavg (Figure 24) did not capture the observed average probability trend from the quartile plot. The FDA assessment of the BOR versus Cavg relationship found that a sigmoidal Emax model better fits and predicts the observed relationship, but the relationship did not reach the statistical significance of 0.05.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	At the recommended dosage, pirtobrutinib achieves pharmacokinetic exposures that can exceed the BTK IC96 at trough and thus deliver sustained BTK target inhibition throughout the once daily dosing period, regardless of the intrinsic rate of BTK turnover.	Acceptable

Table 83: **Parameter Estimates from Logistic Regression Model for Efficacy**

Parameter Description	Estimate (%SEE)	Probability of ORR
Parameter for LOGIT[a]	0.533 (45.4)	0.63

Abbreviations: L = likelihood of response; ORR = Objective Response Rate; SEE = standard error of the estimate.
[a] L = EXP(LOGIT)/(1+EXP(LOGIT)).
Source: Applicant's Pharmacometric Modelling Report, Table 9.3, page 42.

Figure 22: Visual Predictive Check of Logistic Regression Model for ORR



Abbreviations: CI = confidence interval; ORR = Objective Response Rate, which includes patients with a best overall response (BOR) of partial response (PR) or complete response (CR).
Solid blue lines and gray shaded areas are the logistic regressions and 95% CIs of the predicted probability of ORR. Black open circles reflect the observed ORR in pirtobrutinib treated patients. The observed response rate (red circles) and 95% CI (red error bars) of each exposure quartile are plotted versus concentration. Yellow box plots represent the 25th, 50th, and 75th percentiles of predicted average pirtobrutinib concentration for a 200 mg dose. Whiskers represent 1.5 times the inter-quartile range.
Source: Applicant's Pharmacometric Modelling Report, Figure 9.3, page 42.

The FDA's Assessment of the Exposure-Response Model for Efficacy:

The Applicant's model-predicted average probability of BOR versus Cavg (blue line in **Figure 22**) did not capture the observed average probabality trend from the quartile plot (red circles and error bars in **Figure 22**). The FDA assessement of the BOR versus Cavg relationship found that a sigmoidal Emax model better fits and predicts the observed relationship, but the relationship did not reach statistical significance for an alpha of 0.05. In contrast, the relationship between Ctrough as an exposure metric versus BOR was statistically significant, however the uncertainty around the parameter estimates was high, suggesting a week relationship that may be due to the lack of sufficient data at different dose levels.

The FDA assessment was based on 120 MCL patients from the PAS (n=74), SAS1 (n=37) and SAS2 (n=9) analysis datasets (**Table 84**), and was not limited to the PAS data used by the Applicant (n=73).

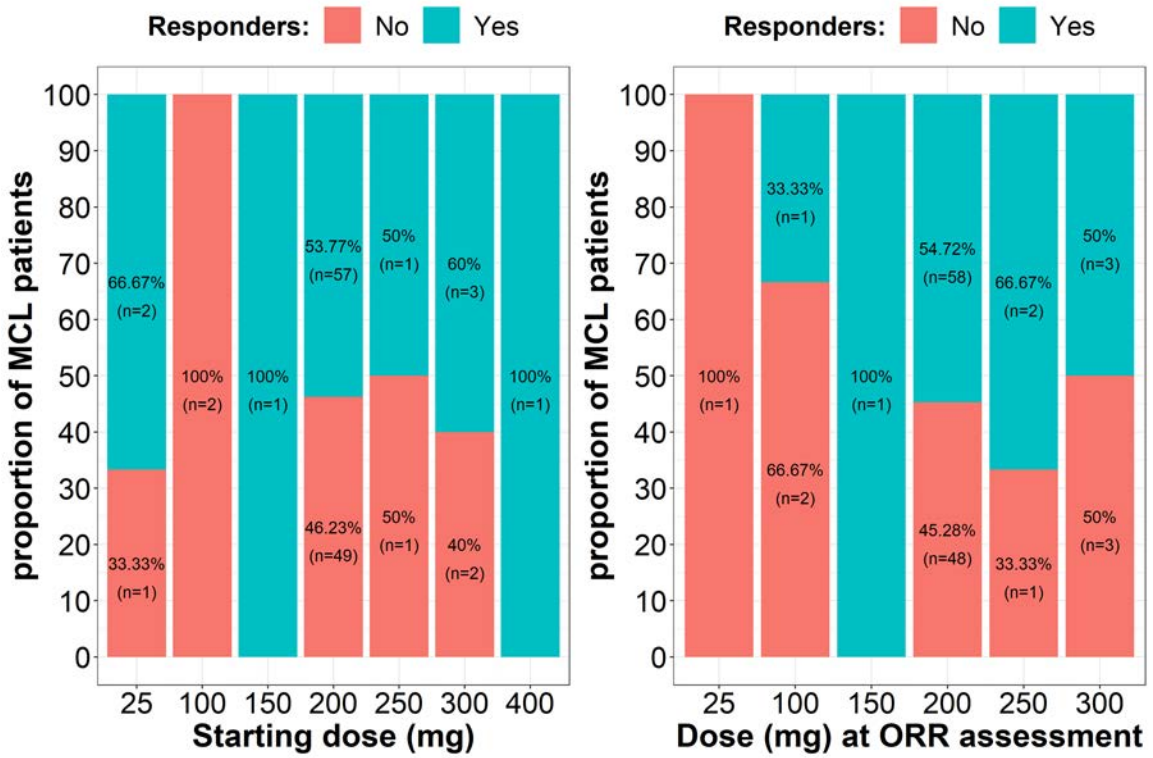
Most MCL patients (88%) were under a pirtobrutinib dose of 200 mg either at the initiation of treatment or at the time of BOR assessement. **Figure 23** shows the proportion of patients at each pirtobutinib dose level. No patient with MCL started treatment or were receiving a dose of 50 mg at the time of BOR assessment. 7 patients had dose reduction to 150 mg or 100 mg and 1 patient had a dose reduction to 50 mg during treatment.

Table 84: Analysis Sets for MCL

Analysis Set	Analysis Set Description
PAS	Confirmed diagnosis of MCL based on local pathology report obtained at time of Screening and with no known active CNS involvement.
	Treated with prior BTK inhibitor-containing regimen.
	At least 1 site of radiographically assessable disease as determined by Investigator, defined as LDi > 1.5 cm, or extra nodal site > 1.0 cm in LDi by CT.
	Received 1 or more doses of pirtobrutinib monotherapy.
SAS1	MCL patients who meet the PAS eligibility criteria but were enrolled after the 90th PAS patient by the data cut-off date.
SAS2	MCL patients who were treated with prior BTK inhibitor-containing regimen but do not meet at least 1 of the other PAS criteria.

Note: PAS = primary analysis set, SAS = supplementary analysis set.
Source: Adapted from Applicant's Clinical Overview, Table 3, page 24.

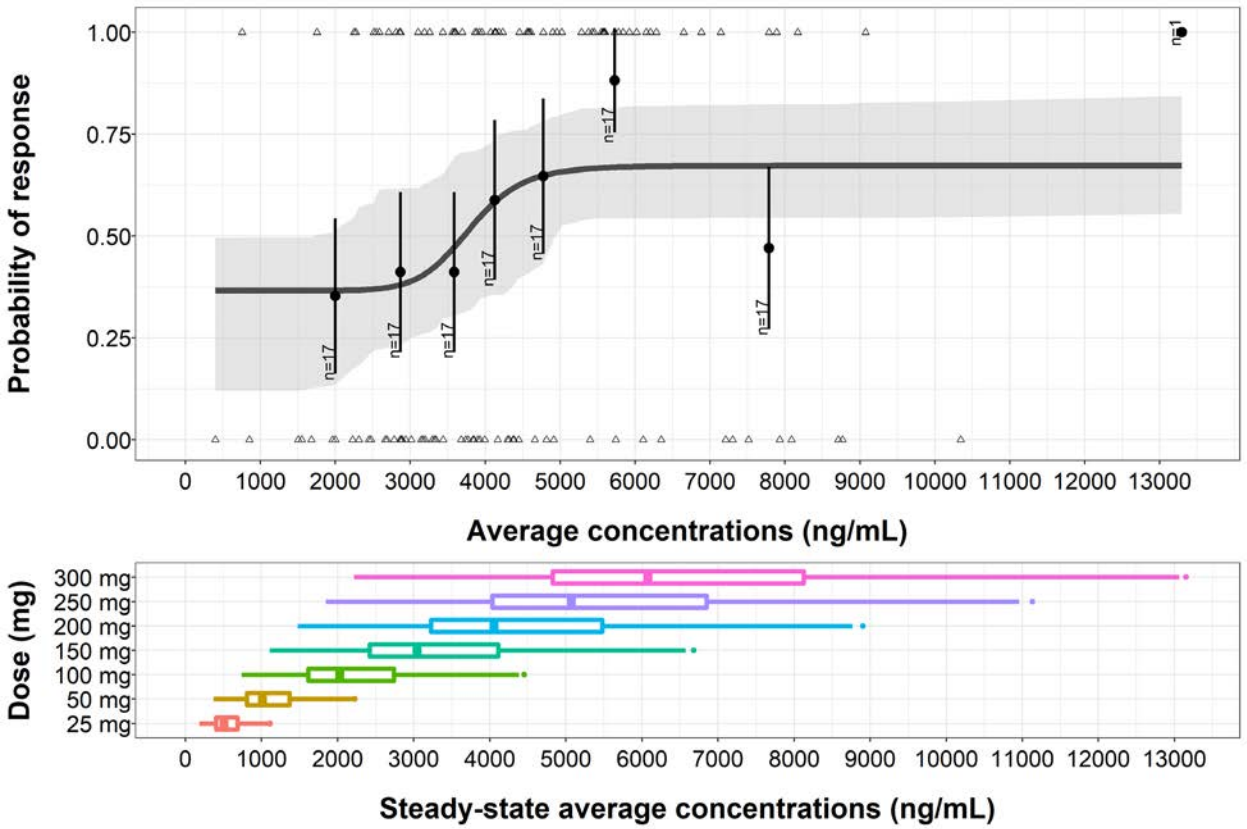
Figure 23: Proportion of Patients at Each Pirtobutinib Dose, Stratifid by Treatment Response



Source: FDA Reviewer

Figure 24 depicts the exposure-BOR relationship from 120 MCL patients, where the exposure metric was Cavg. The logistic regression using a sigmoidal Emax model to describe the realtionship between the probability of response and Cavg better fitted the observed data than the intercept only model. However the difference in OFV (-7.6 points) did not reach statistical significance (p value=0.055, for 3 degrees of freedom), likely due to the lack of observations at dose levels below 200 mg.

Figure 24: Model-Predicted Probability of Response Versus Average Pirtobrutinib Concentrations



Note: Upper panel: the shared area around the model-predicted response (solid black line) represents the 95%CI (buit from bootstrap analysis with 1000 replicates). The black solid circles and error bars represent the observed propotions and their 95% CI at each exposure quantile. The number of observations in each quantile is indicated near the error bar. Triangles are pirtobrutinib exposures among responders and non-responders. Lower panel: box-plots of pirtobrutinib steady-state average concentrations at each dose.
Source: FDA Reviewer

Table 85 summarizes the model parameter estimates. The 95%CI of the parameter estimates were large for Emax and the Hill coefficient and lacked precision, likely due to few observations at dose levels other than 200 mg (88% of patient received a dose of 200 mg). **Table 86** summarizes the model predicted response at different dose levels. The model-predicted proportion of responders at different dose levels were overlapping, as the exposure-response relationship was not statistically significant, although there was a trend of lower response rate under a 50 mg dose (33.7%) compared to a 200 mg dose (58.5%). The predicted proportion of responders at the 200 mg was in line with the overall response of 57.8% (95%CI: 46.9%, 68.1%) reported by the Applicant.

Table 85: Parameter Estimates from The Average Concentrations-Response Model

Parameter	Estimate	Bootstrap estimate (95%CI)
Intercept	-0.548	-0.614 (-1.78 - -0.015)
Emax	1.27	1.44 (0.651 - 2.49)
EC50 (ng/mL)	3810	3857 (2194 - 5020)
Hill coefficient	10.5	74.6 (4.64 - 77.8)

Note: Bootstrap estimates and 95% CI are reported as median and (2.5th - 97.5th percentiles) of the parameter estimates from 1000 replications.
Source: FDA Reviewer

Table 86: Model-Predicted Proportion of Response At Each Dose, Based on Average Pirtobrutinib Concentrations

Dose	Median Cavg,ss (25^{th} - 75^{th} percentile)	% Response (95%CI)
25 mg	501 (399 - 626)	33.7 (12.1 - 49.5)
50 mg	**1002 (798 - 1253)**	**33.7 (12.1 - 49.6)**
100 mg	**2004 (1596 - 2506)**	**34.6 (14.3 - 51.5)**
150 mg	3005 (2394 - 3758)	39.8 (25.4 - 61.7)
200 mg	**4007 (3193 - 5011)**	**58.5 (35.6 - 72.7)**
250 mg	5009 (3991 - 6264)	66.4 (53.5 - 80.2)
300 mg	6011 (4789 - 7517)	67.5 (54.4 - 81.9)

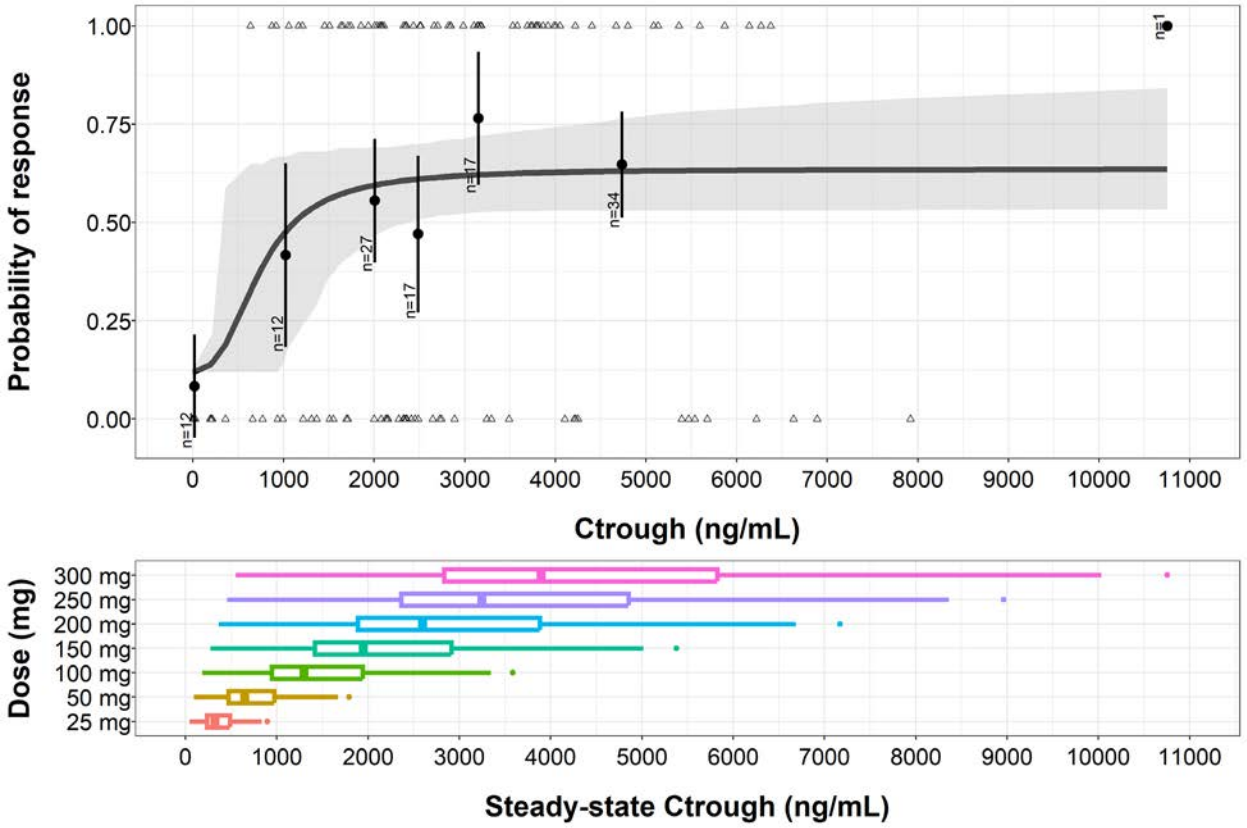
Note: Cavg,ss = steady-state average concentration. The 200 mg, 100 mg and 50 mg are the proporsed doses in the label.
Source: FDA Reviewer

Figure 25 depicts the exposure-BOR relationship from 120 MCL patients, where the exposure metric was Ctrough instead of Cavg. The logistic regression using a sigmoidal Emax model to describe the realtionship between the probability of response and Ctrough better fitted the observed data than the intercept only model, with a statistically significant difference in OFV of -16.6 (p value<0.001, for 3 degrees of freedom). However, the 95%CI of the parameter estimates were large for EC50 and the Hill coefficient and lacked precision, likely due to few observations at dose levels below 200 mg. **Table 87** summarizes the model parameter estimates, and **Table 88** summarizes the model predicted response at different dose levels.

The model-predicted proportion of responders at different dose levels were overlaping, likely due to the lack of precision of the estimated parameters, although there was a trend of lower response rate under a 50 mg dose (28.7%) compared to a 200 mg dose (60.9%). The predicted proportion of responders under 50 mg and 200 mg were consistent either Cavg or Ctrough as the exposure metric in the exposure-response analysis. The predicted proportion of responders at the 200 mg was in line with the overall response of 57.8% (95%CI: 46.9%, 68.1%) reported by the Applicant. The observed trend from the exposure-response relationship using Ctrough is also in agreement with the Applicant's predicted proportion of patients, at each dose level, with steady-

state Ctrough higher than the concentration responsible for 90% of maximum BTK inhibition (IC90) in-vitro (Figure 26), where about 30%, 79% and 96% of patients are predicted to exceed IC90 at doses of 50 mg, 100 mg and 200 mg, respectively.

Figure 25: Model-Predicted Probability of Response Versus Pirtobrutinib Trough Concentrations



Note: Upper panel:the shared ares around the model-predicted response (solid black line) represents the 95%CI (buit from bootstrap analysis with 1000 replicates). The black solid circles and error bars represent the observed propotions and their 95% CI at each Ctrough (minimum concentration) quantile. The number of observerations in each quantile is indicated near the error bar. Trianhgles are pirtobrutinib Ctrough among responders and non-responders. Lower panel: box-plots of pirtobrutinib steady-state Ctrough at each dose.
Source: FDA Reviewer

Table 87: Parameter Estimates from the Trough Concentrations-Response Model

Parameter	Estimate	Bootstrap estimate (95%CI)
Intercept	-1.98	-1.99 (-2 - -0.93)
Emax	2.54	2.41 (1.97 - 2.85)
EC50 (ng/mL)	644	501 (257 - 2508)
Hill coefficient	2.29	79 (12.5 - 80.5)

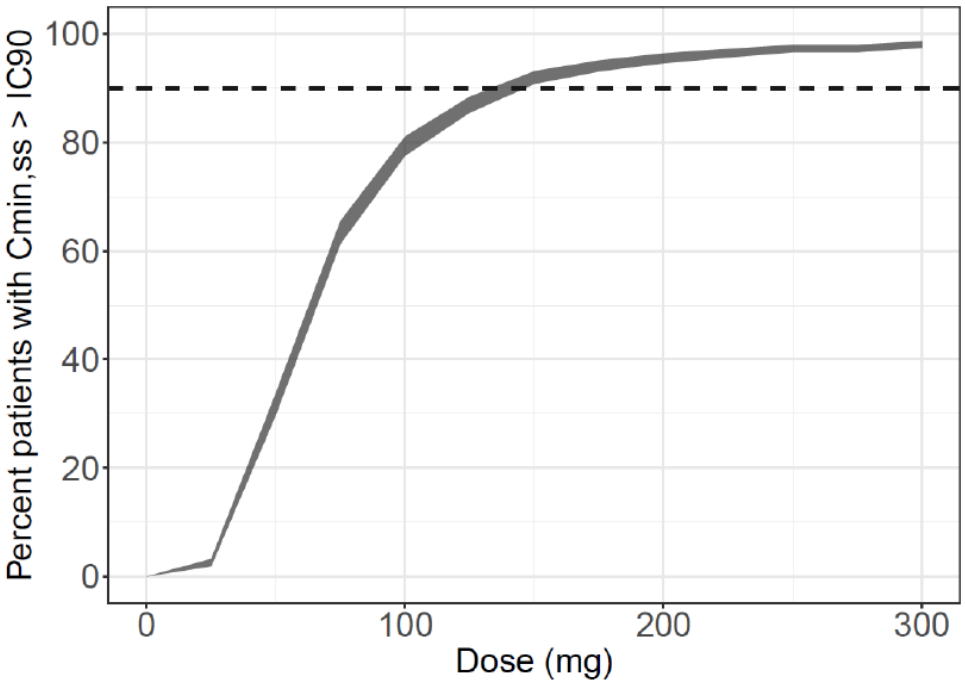
Note: bootstrap estimates and 95% CI are reported as median and (2.5th - 97.5th percentiles) of the parameter estimates from 1000 replications.
Source: FDA Reviewer

Table 88: Model-Predicted Proportion of Response at Each Dose, Based on Ctrough

Dose	Median Ctrough,ss (25^{th} - 75^{th} percentile)	% Response (95%CI)
25 mg	325 (236 - 485)	13.3 (11.9 - 48.5)
50 mg	**649 (472 - 970)**	**28.7 (11.9 - 64.9)**
100 mg	**1298 (944 - 1942)**	**53.7 (26.6 - 68)**
150 mg	1948 (1416 - 2912)	58.7 (45.5 - 69)
200 mg	**2597 (1889 - 3883)**	**60.9 (51.2 - 70.1)**
250 mg	3246 (2361 - 4854)	62.2 (52.7 - 72.3)
300 mg	3895 (2833 - 5825)	63.1 (53 - 73.9)

Note: Ctrough,ss = steady-state trough concentration. The 200 mg, 100 mg and 50 mg are the proporsed doses in the label.
Source: FDA Reviewer

Figure 26: Predicted Proportion of Patients Achieving Pirtobrutinib Minimum Concentrations Responsible for At Least 90% BTK Inhibition



Abbreviations: $C_{min,ss}$ = minimum concentration during a dosing interval at steady state, IC_{90} = drug concentration that produces 90% of maximum inhibitory effect (I_{max})
Dotted line represents 90% of patients, and the shaded areas correspond to the 95% confidence intervals.

Source: Applicant's Pharmacometric Modelling Report, Figure 10.1, page 46.

Conclusion: The exposure-efficacy relationships showed non-significant trends of lower response under a pirtobrutinib dose of 50 mg (estimated average response of 34% and 29% when considering Cavg and Ctrough as esposure metrics, respectively). However, the non-significant trends should interpreted with caution due to few observations under pirtobrutinib doses below 200 mg, rendering the assessment of an exposure-response realtionship challenging. Given the non-sigificant exposure-efficacy response relationships and the lack of alternative therapies in the intended treatment population, the proposed dose reduction of pirtobrutinib to 100 mg then 50 mg in case of Grade 3 to Grade 4 adverse event is acceptable.

19.4.2.3 Exposure-Response for Safety Assessment Summary

Data:

General Information		
Goal of ER analysis		Characterize the relationship between pirtobrutinib systemic exposure and safety endpoints in patients with hematological malignancies and identify covariates that can influence these relationships.
Study Included		Study LOXO-BTK-18001 (BRUIN; J2N-OX-JZNA) (data cutoff date of 31 January 2022)
Population Included		Patients with hematological malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL)
Endpoint		• Grade ≥3 anemia • Grade ≥ 3 neutropenia • Grade ≥ 3 infections/infestations • Hypertension.
No. of Patients (total, and with individual PK)		595
Population Characteristics (**Table 80**)	General	Age – median 68 yr (range 27-95 yr) Weight – median 76.6 kg (range 35.7-152.5 kg) Sex – Female N = 201 (34%), Male N = 395 (66%) Race: White N = 509 (86%) Black or African American N = 17 (3%) Asian N = 39 (7%) Other N = 29 (5%) Not reported N = 1 (< 1%)
	Organ impairment	Renal function: Normal N = 121 (20%) Mild impairment N = 304 (51%) Moderate impairment N = 166 (28%) Severe impairment N = 4 (1%) Hepatic function: Normal N = 474 (80%) Mild impairment N = 106 (18%) Moderate impairment N = 13 (2%) Severe impairment N = 1 (< 1%) Not reported N = 1 (< 1%)
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	Age – median 68 yr (range 27 – 95 yr, 64% of subjects >= 65 yr, 23% of subjects >= 75 yr)
Dose(s) Included		Phase 1: Starting doses 25 to 300mg QD Phase 2: 200mg QD
Exposure Metrics Explored (range)		Average concentration of pirtobrutinib from the start of treatment up to the time of event Maximum concentration of pirtobrutinib from the start of treatment up to the time of event.

Covariates Evaluated	Age, Body weight, BMI, Sex/Ethnicity, Cancer Type	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Logistic regression model	Acceptable
Model Parameter Estimates	Table 89	Acceptable
Model Evaluation	The base models for the safety exposure-response analysis consisted of a logistic regression model which estimated the incidence of the endpoint for the entire study population independent of drug exposure. The relationship between pirtobrutinib concentration and the safety endpoint was then tested using linear, log-linear, and Emax models. Exposure measures were tested for statistical significance (change in the MOF value, Δ3.841 points for 1 degree of freedom, $p < 0.05$, based on $\chi 2$ distribution) to establish the final model.	Acceptable.
Covariates and Clinical Relevance	No statistically significant covariates were identified.	Acceptable
Simulation for Specific Population	Not applicable	Acceptable
Visualization of E-R relationships	Figure 27	Acceptable
Overall Clinical Relevance for ER	No statistically significant relationship was identified between incidence of TEAE and the 2 measures of predicted exposure.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable	Acceptable

Table 89: Parameter Estimates from Logistic Regression Models for Safety

Parameter Description	Estimate (%SEE)	Probability of AE Incidence
Anemia Model		
Parameter for LOGIT[a]	-2.85 (6.39)	0.05
Neutropenia Model		
Parameter for LOGIT[a]	-1.50 (7.13)	0.18
Infection/Infestation Model		
Parameter for LOGIT[a]	-1.93 (6.58)	0.13
Hypertension Model		
Parameter for LOGIT[b]	-2.80 (8.43)	0.16[c]
Effect of CLL/SLL cancer type	1.12 (26.0)	

Abbreviations: AE = adverse event; CLL = chronic lymphocytic leukemia; I1 = binary indicator for cancer type (0 = MCL or NHL, 1 = CLL/SLL); L = the likelihood of Grade ≥ 3 anemia, Grade ≥ 3 neutropenia or Grade ≥ 3 infection/infestation, or any grade hypertension; SEE = standard error of the estimate; SLL = small lymphocytic lymphoma.

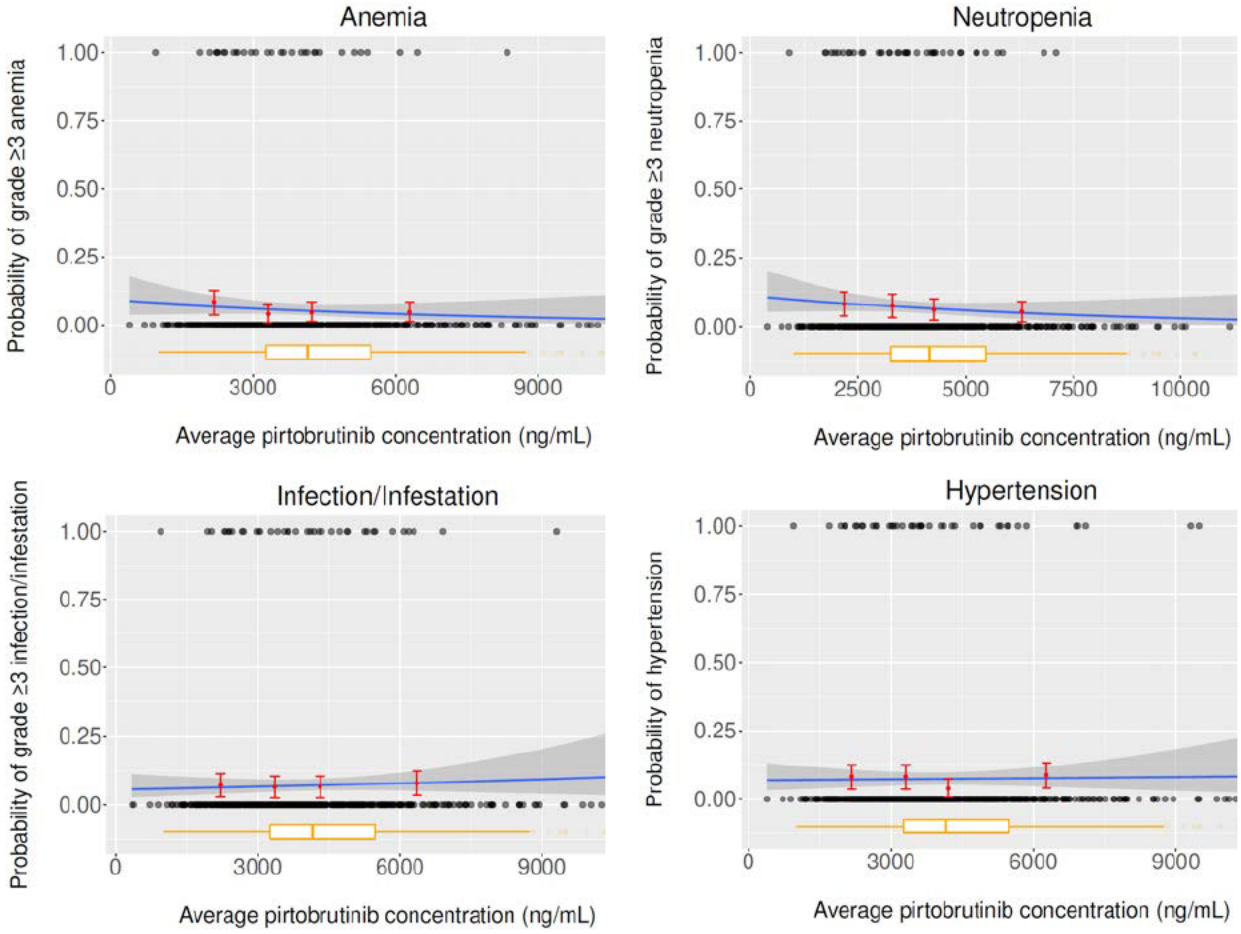
[a] L = EXP(LOGIT)/(1+EXP(LOGIT)).

[b] LOGIT = -2.80 + I1*1.12, where I1 is an indicator variable for CLL and SLL cancers.
L = EXP(LOGIT)/(1+EXP(LOGIT)).

[c] Calculation based on CLL/SLL cancer type.

Source: Applicant's Pharmacometric Modelling Report, Table 9.4, page 43.

Figure 27: Exposure-Response Relationships for Safety Endpoints Using the Average Concentration of pirtobrutinib up to the Day of TEAE for Participants in Study 18001



Abbreviations: CI = confidence interval; TEAE = treatment-emergent adverse event.
Solid blue lines and gray shaded areas are the logistic regressions and 95% CIs of the predicted probability of TEAE. Black open circles reflect the observed TEAEs in pirtobrutinib treated patients. The observed response rate (red circles) and 95% CI (red error bars) of each exposure quartile are plotted versus concentration. Yellow box plots represent the 25th, 50th, and 75th percentiles of predicted average pirtobrutinib concentration for a 200 mg dose. Whiskers represent 1.5 times the inter-quartile range.
Source: Applicant's Pharmacometric Modelling Report, Figure 9.4, page 44.

In addition to the logistic regression analyses to assess the relationship between pirtobrutinib Cmax or Cavg and the incidence of Grade 3 and above anemia, neutropenia and infection or any grade hypertension (**Figure 27**), the Applicant performed exposure-safety analyses for neutropenia, thrombocytopenia, anemia of any grade, as well as change in systolic and diastolic blood pressure, as continuous variables. Linear regressions were conducted to assess the

relationship between the maximum individual change from baseline (CFB) in the safety measure (neutrophile counts, platelet counts, hemoglobin levels, systolic and diastolic blood pressure) and pirtobrutinib Cavg (until the day of the event) or Cmax (at the day of the event). **Table 90** and **Table 91** summarizes the linear regression result for each continuous safety measure.

Table 90: Linear Regression Results of the Exposure-Safety Relationships for Neutrophils, Platelets and Hemoglobin of Any Grade

Linear Regression Model	p-value	Slope Parameter (95% CI)
Maximum change from baseline in neutrophil count vs Cav	0.74	0.0000272 (-0.000136, 0.00019)
Maximum change from baseline in neutrophil count vs C_{max}	0.78	0.0000176 (-0.000105, 0.00014)
Maximum change from baseline in platelet count vs Cav	0.16	-0.00196 (-.00468, 0.000771)
Maximum change from baseline in platelet count vs C_{max}	0.007	-0.00273 (-0.00473, -0.00073)
Maximum change from baseline in hemoglobin count vs Cav	0.51	-0.000235 (-0.000934, 0.000465)
Maximum change from baseline in hemoglobin count vs C_{max}	0.21	-0.000331 (-0.000849, 0.000187)

Source: Applicant's Clinical Information Amendment, Sequence 0039, Table 3, page 8.

Table 91: Linear Regression Results of the Exposure-Safety Relationships for Systolic and Diastolic Blood Pressure

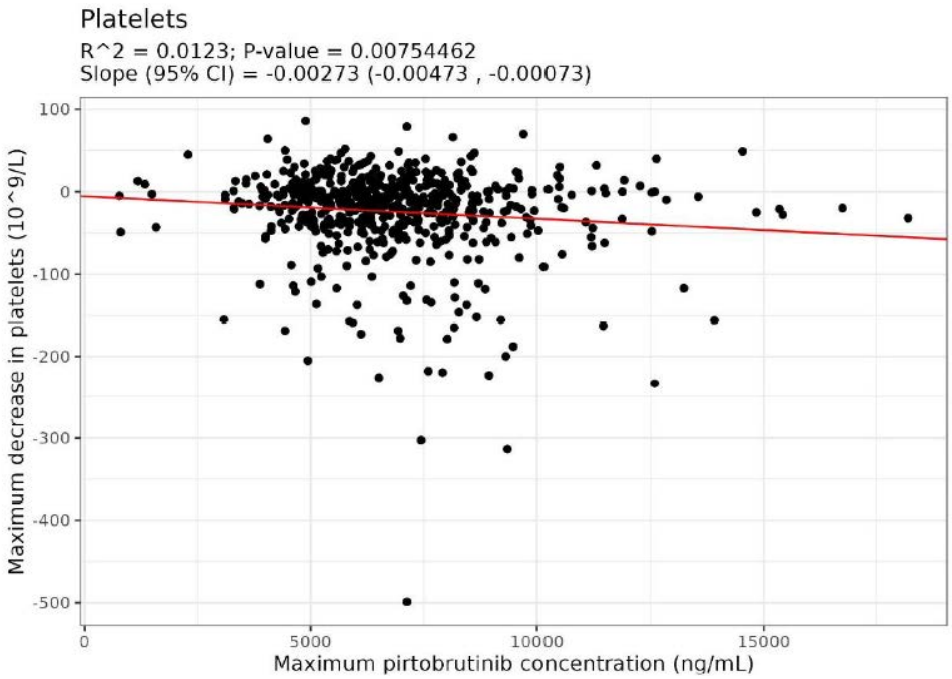
Linear Regression Model	p-value	Slope Parameter (95% CI)
Maximum change from baseline in systolic blood pressure vs Cav	0.045	0.000847 (0.0000209, 0.00167)
Maximum change from baseline in systolic blood pressure vs C_{max}	0.40	0.000276 (-0.000362, 0.000914)
Maximum change from baseline in diastolic blood pressure vs Cav	0.67	0.000102 (-0.000373, 0.000577)
Maximum change from baseline in diastolic blood pressure vs C_{max}	0.97	0.00000652 (-0.000361, 0.000374)

Source: Applicant's Clinical Information Amendment, Sequence 0039, Table 4, page 12.

The only significant relationships noted were between the maximum CFB in platelet count versus Cmax (p value = 0.007, **Figure 28**) and the maximum CFB in systolic blood pressure versus Cavg (p value = 0.045, **Figure 29**).

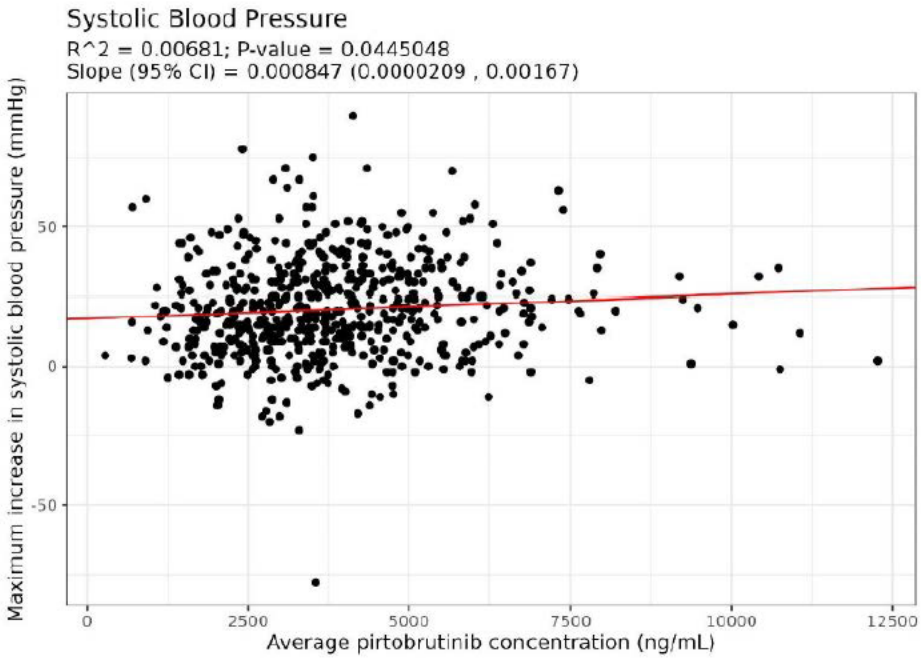
At the highest quartile of the observed Cmax, the predicted maximum decrease in platelet count was 32 ($x10^9$/L). Assuming a lower limit of normal (LLN) value of 150 ($x10^9$/L), this decrease in platelet count is equivalent to a Grade 1 toxicity according to CTCAE criteria (version 5). The predicted a maximum increase in systolic blood pressure was 22 mmHg, at the highest quartile of the observed Cavg. Assuming an upper limit of normal value of 120 mmHg, this increase is equivalent to a Grade 2 toxicity according to CTCAE criteria.

Figure 28: Maximum Decrease in Platelet Count Versus Pirtobrutinib Cmax



Source: Applicant's Clinical Information Amendment, Sequence 0039, Figure 4, page 10.

Figure 29: Maximum Increase in Systolic Blood Pressure Versus Pirtobrutinib Average Concentration



Source: Applicant's Clinical Information Amendment, Sequence 0039, Figure 6, page 13.

The FDA's Assessment of the Exposure-Response Model for Safety:

FDA agrees that no apparent relationships exist between pirtobrutinib exposure and key safety endpoints (Grade ≥3 anemia, Grade ≥3 neutropenia, Grade ≥3 infection/infestation, or any grade hypertension) within the range of exposures achieved at doses ranging from 25 mg to 300 mg QD (**Table 92**), although 86% of patients in the exposure-safety analysis dataset received a dose of 200 mg.

Table 92: Number of Patients Included in the PK and Exposure-Response Analyses by Study Phase and Planned Starting Dose in Study 18001

Study Phase	Starting Dose	PK/Exposure-Safety Population	Exposure-Efficacy Population
1	25 mg QD	5	3
	50 mg QD	6	0
	100 mg QD	9	2
	150 mg QD	20	1
	200 mg QD	112	20
	250 mg QD	25	2
	300 mg QD	20	5
2	200 mg QD	398	40
Total	---	595	73

Abbreviations: PK = pharmacokinetic; QD = once daily.

Source: Applicant's Pharmacometric Modelling Report, Table 7.1, page 24.

The only significant exposure-safety relationships found were between the maximum CFB in platelet count versus Cmax and the maximum CFB in systolic blood pressure versus Cavg, regardless of the severity grade. **Table 93** shows the predicted maximum CFB in platelet count and in systolic blood pressure under the average exposure from each pirtobrutinib dose. Although statistically significant, these exposure-safety relationships were shallow.

Table 93: Mean Predicted Change From Baseline in Systolic Blood Pressure and Platelets Count at Each Pirtobrutinib Dose Level

Dose	Mean (95%CI) increase in systolic blood pressure (mmHg)	Mean (95%CI) increase in platelets count (x10^9/L)
25 mg	17.4 (14.3, 20.4)	-11.8 (-23.5, -0.092)
50 mg	17.8 (15.1, 20.5)	-13.4 (-23.8, -2.91)
100 mg	18.7 (16.7, 20.7)	-17.2 (-24.7, -9.63)
150 mg	19.6 (18, 21.1)	-20 (-25.7, -14.3)
200 mg	20.5 (19.1, 21.9)	-24.4 (-28.8, -20)
250 mg	21.4 (19.7, 23.1)	-27.2 (-32.4, -22)
300 mg	22.2 (20, 24.5)	-31 (-38.6, -23.5)

Source: FDA Reviewer

Conclusion: Overall, the exposure-safety analyses were considered flat or shallow across pirtobrutinib exposure and dose levels, although most of the observation are from the 200 mg dose and therefore these relationship should be interpreted with caution.

19.4.3 Physiologically-Based Pharmacokinetic Modeling Review

The Applicant's position:

Pirtobrutinib (JAYPIRCA) is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy. The proposed dose for pirtobrutinib is 200 mg orally once daily with or without food. Applicant also proposed dose reduction based on adverse effects. Pirtobrutinib exposures (AUC, area under the curve and Cmax, maximum concentration) increased proportionally with increasing dose in the 25 mg to 300 mg QD dose range in patients. No maximum tolerated dose (MTD) was identified up to 300 mg. In the human ADME study (Study #20007), approximately 37.3% and 57.0% of the administered dose were recovered in the feces (18.2 % parent) and the urine (10% parent), respectively. The mean systemic clearance of pirtobrutinib after an IV dose is 1.63 L/h, and apparent oral clearance of pirtobrutinib is 2.02 L/h. Pirtobrutinib is highly permeable with 85% bioavailability. In-vitro studies showed that pirtobrutinib is metabolized by CYP3A4, glucuronosyltransferases (UGT)1A8, and UGT1A9. Pirtobrutinib also a substrate of P-gp and BCRP. In vitro, pirtobrutinib inhibited CYP2C8, CYP2C9, CYP3A4, P-gp and BCRP. Clinical DDI

studies has been conducted to evaluate the DDI potentials of pirtobrutinib as victim or perpetrator on metabolism pathways as summarized in Table 94. The Applicant also collected the PK of endogenous coproporphyrin I (CP-I) following a single oral dose of pirtobrutinib and steady-state pirtobrutinib. Pirtobrutinib did not increase the CP-I PK in healthy participants.

Table 94: DDI Potentials of Pirtobrutinib as Victim or Perpetrator on Enzyme- and Transporter-Mediated Pathways

Study	Target Pathway	Substrate	AUC	Cmax
LOXO-BTK-20006	Effect of strong 3A4 inhibitor	A single dose of pirtobrutinib 200 mg	↑1.49	↑1.04
	Effect of strong 3A4 inducer		↓0.71	↓0.43
LOXO-BTK-20008	Effect on 3A4 substrate	250 ug IV midazolam (SD)	↑1.12 (MDZ) ↓0.24 (1-OH-MDZ	↑↓0 (MDZ ↑↓0.08 (1-OH-MDZ
		500 ug oral midazolam (SD)	↑1.70 (MDZ) ↑1.12 (1-OH-MDZ	↑1.58 (MDZ ↑1.13 (1-OH-MDZ
LOXO-BTK-20010	Effect on CYP1A2 substrate	caffeine	↓0.09	↓0.04
	Effect on CYP2C9, substrate	S-warfarin	↑1.11	↑1.02
	Effect on 2C19 substrate	omeprazole	↑1.56	↑1.49
LOXO-BTK-20016	Effect on 2C8 substrate	repaglinide	↑2.3	↑1.98
LOXO-BTK-20021	Effect on P-gp substrate	digoxin	↑ 1.35	↑1.55

Source: Applicant's Clin Pharm Summary 17, 19, 22-25; 27, 29, 31, 35, 37

The applicant developed a PBPK model to predict the interactions with moderate and strong CYP3A4 inhibitors and moderate CYP3A4 inducers after single and multiple oral doses of 200 mg pirtobrutinib in healthy volunteers. DDI effects of CYP3A modulators on the PK of pirtobrutinib was used to inform the dosing recommendation in the United States Prescribing Information (USPI).

Applicant's PBPK modeling efforts

Pirtobrutinib PBPK model was built using Simcyp V19. The model was developed using clinical studies with full PK profiles. The model was initially developed using physiochemical properties, in vitro biological data, a human ADME study and clinical PK and DDI studies. The absorption of pirtobrutinib, was described using a first-order absorption model, and the drug is highly permeable with 85% absolute bioavailability. The systemic clearance (CL), volume of distribution at steady state (Vss), and renal clearance (CLR) for pirtobrutinib were obtained

from an IV study. The first-order absorption rate constant (ka) and lag time (tlag) were estimated to be 0.82 h-1 and 0.25 h, respectively, using sensitivity analysis to match clinically observed pirtobrutinib Cmax and AUC(0-∞) after a single dose of 200 mg pirtobrutinib. The fraction of systemic clearance attributed to CYP3A4 (fm,CYP3A4) for pirtobrutinib was estimated by fitted to the observed pirtobrutinib AUC(0-∞) and Cmax ratio in the presence of itraconazole and rifampin. The values for fm,CYP3A4 and Fg are 0.4 and 0.96. In vitro, pirtobrutinib is a reversible and time dependent CYP3A inhibitor (TDI), as well as a CYP3A inducer. The clinical DDI data with midazolam showed pirtobrutinib was a net CYP3A4 weak inhibitor (Table 94).

In-vitro studies showed that pirtobrutinib is metabolized by CYP3A4, glucuronosyltransferases (UGT)1A8, and UGT1A9. Pirtobrutinib also a substrate of P-gp and BCRP. In vitro, pirtobrutinib inhibited CYP2C8, CYP2C9, CYP3A4, P-gp and BCRP. Clinical DDI studies has been conducted to evaluate the DDI potentials of pirtobrutinib as victim or perpetrator on metabolism pathways as summarized in Table 93. The Applicant also collected the PK of endogenous coproporphyrin I (CP-I) following a single oral dose of pirtobrutinib and steady-state pirtobrutinib. Pirtobrutinib did not increase the CP-I PK in healthy participants.

The Applicant assumed that the inhibition effect was resulted from TDI. The irreversible inhibition parameters (KI and kinact) measured in-vitro overestimated the DDI effects, and the final kinact, 0.056, was fitted to the observed DDI data with midazolam and observed pirtobrutinib pharmacokinetics after 200 mg QD dosing of pirtobrutinib in LOXO-BTK-20008. The final model input parameters were summarized in Table 95:

Table 95: PBPK Input Parameters for Pirtobrutinib

Parameter	Value	Method/Reference
Molecular weight (g/mol)	479.43	
Log P	3.35	Predicted by ChemAxon
Compound type	Neutral	
B:P		Measured in-vitro
fup	0.046	
Fa	0.91	
ka (1/h)	0.82	fitted to match observed tmax and Cmax after a single dose of pirtobrutinib
Lag time (h)	0.25	
Fugut	1	Assumed
Qgut (L/h)	3.154	Estimated based on Fg of 0.96
Peff,man (10-4 cm/s)	4.49	Measured Papp of 48.8 ×10-6 cm/s scaled to Peff,man with in-house correlation: Log10(Peff,man $\times 10^{-4}$ cm/s) = 0.89 × Log10(Papp$\times 10^{-6}$ cm/s) - 0.85
Q (L/h)	3.56	Based on concentration-time profile following intravenous administration
VSAC (L/kg)	0.17	
Vss (L/kg)	0.54	
Kp scalar	0.145	Fitted to match clinically observed Vss
Enzyme Kinetics (Recombinant) CYP3A4 CLint (µL/min/pmol)	0.03	Calculated based on fm,CYP3A4 of 0.40 using the Simcyp retrograde calculator
Additional HLM CLint (µL/min/mg)	3.66	
CLR (L/h)	0.12	Measured from intravenous data
CLint,bile (µL/min/million cells)	0.47	To fit the fecal pirtobrutinib after intravenous administration
CYP3A KI (µM)	0.47	Measured
CYP3A kinact (h-1)	0.056	Fitted value to match clinical individual concentration-time profiles from Study LOXO-BTK-20008
fuinc	0.78	Measured value at 0.5 mg/mL human liver microsomes

Source: PBPK report Table 3.1

The Applicant evaluated the performance of pirtobrutinib PBPK model by comparing the simulated and observed clinical PK data following single and multiple dose administration of 200 mg as shown in Table 96 and Table 97 and Figure 30, respectively.

Table 96: Observed and Simulated Cmax and AUC of Pirtobrutinib Following a Single Dose of 200 mg in Healthy Subjects

Study		Predicted/Observed C_{max} ratio	Predicted/Observed $AUC_{(0-\infty)}$ ratio
Model building studies	LOXO-BTK-20006 2021, Part 1	1.06	1.37
	LOXO-BTK-20006 2021, Part 2	0.94	1.38
Model verification studies	LOXO-BTK-20007 2021, Part 2	0.94	1.06
	LOXO-BTK-20008 2021, Period 2	0.86	1.14[a]
	LOXO-BTK-20009 2021, Treatment A	1.01	1.30
	LOXO-BTK-20014 2020, Treatment A	0.77	1.23

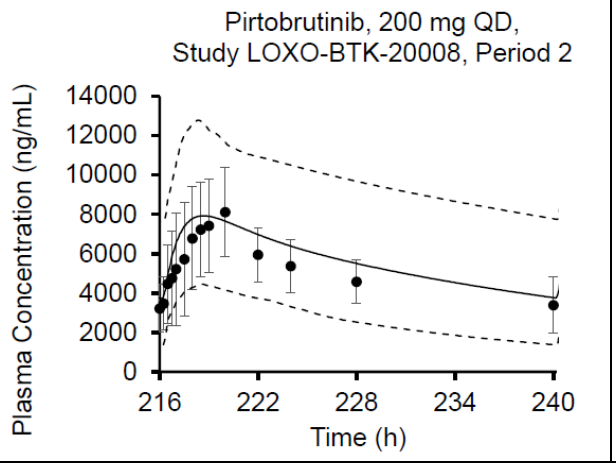
Source: PBPK report Table 4.2

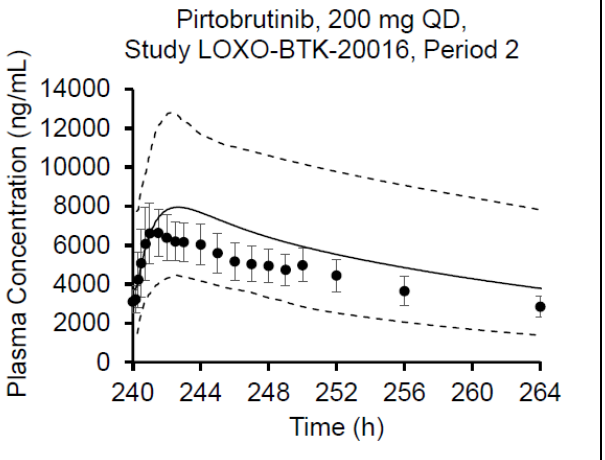
Table 97: Observed and Simulated Cmax and AUC of Pirtobrutinib Following Multiple Doses of 200 mg in Healthy Subjects

Study		Geometric mean (CV%)		Median (Range)
		C_{max} (ng/mL)	AUCτ (ng.h/mL)	t_{max} (h)
Predicted without TDI		6927 (29)	109965 (34)	2.72 (1.86 to 4.60)
Predicted with fitted k_{inact} of 0.056 h^{-1}		7707 (30)	127394 (36)	2.77(1.93 to 4.70)
Model building studies	LOXO-BTK-20008 2021, Period 2, alone[a]	8120 (28.0)	114000 (29.0)	3.00 (2.00 to 4.00)
	LOXO-BTK-20008 2021, Period 2, with IV midazolam[a]	8620 (24.3)	116000 (26.3)	3.00 (0.75 to 6.00)
	LOXO-BTK-20008 2021, Period 2, with oral midazolam[a]	8750 (26.5)	118000 (28.8)	3.00 (1.00 to 4.00)
Model verification studies	LOXO-BTK-20010 2021, Period 2, with oral cocktail[b]	9430 (24.3)	119000 (25.1)	2.50 (0.77 to 4.00)
	LOXO-BTK-20016 2021, Period 2, with oral repaglinide[c]	7220 (14.5)	105000 (16.9)	1.00 (0.50 to 5.00)

Source: PBPK report Table 4.5

Figure 30: Observed and Simulated Concentration-Time Profiles of Pirtobrutinib Following Multiple Doses of 200 mg in Healthy Subjects





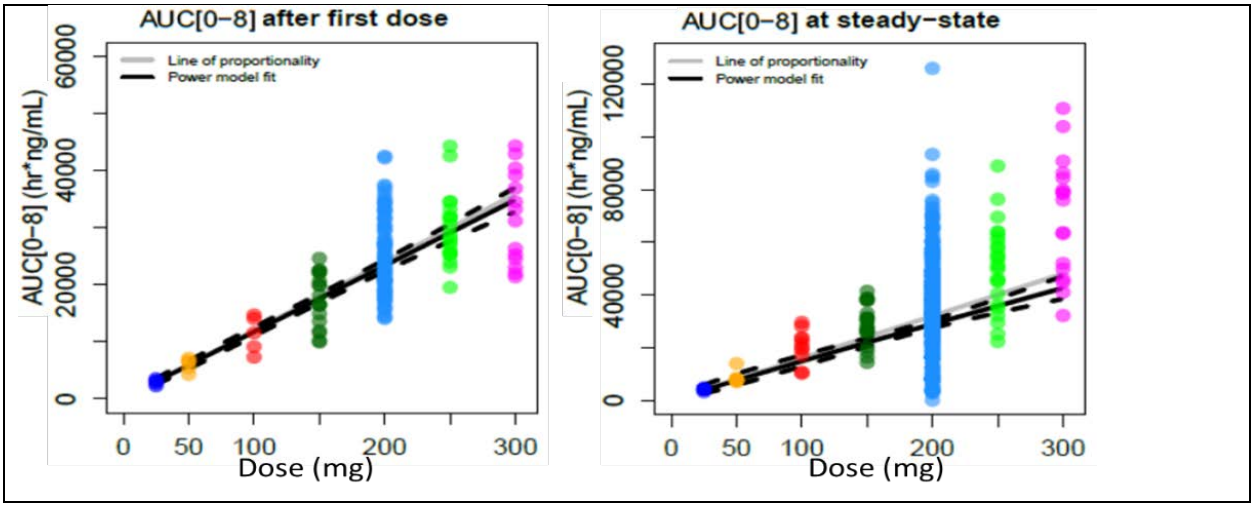
Observed data from Study 20008 Part I (circles) [left] and Study 20016 (circles)[right]. Solid black line: mean for the predicted population; grey lines: 5th-95th concentration-time percentiles.

Source: PBPK report Figure 4.4

The FDA's Assessment:

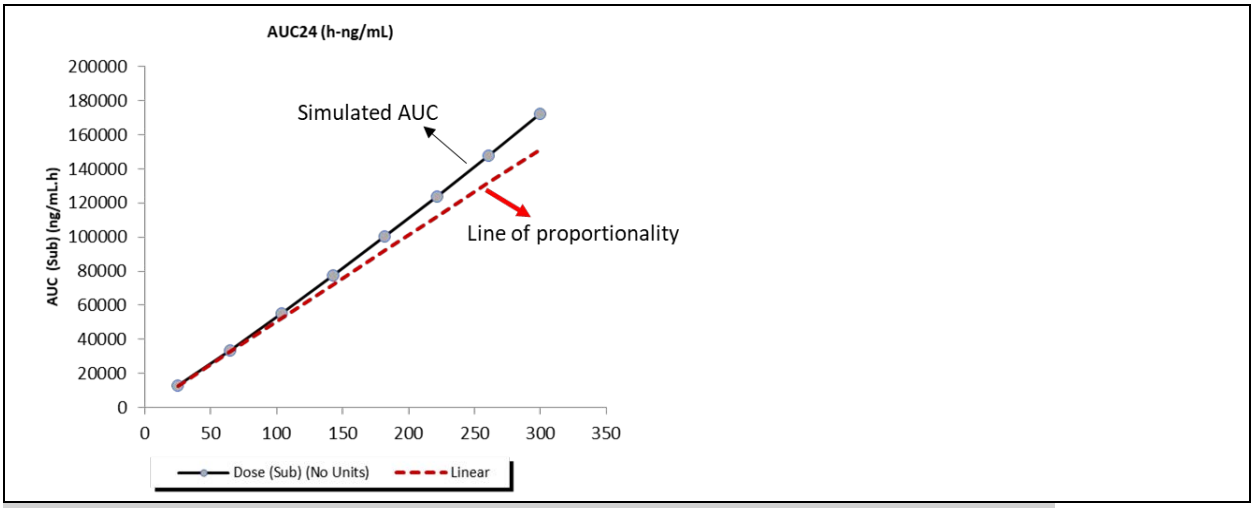
The Applicant did not compare the observed and simulated PK of pirtobrutinib in dose level other than 200 mg. Study 18001 showed that there is a slightly less than proportional increase in AUC0-8 of pirtobrutinib where pirtobrutinib was administered at 25-300 mg QD in patients (as shown in Figure 31). Pirtobrutinib is a weak CYP3A inhibitor and substrate of CYP3A. The Applicant's PBPK model predicted a more than proportional increase in AUCss following pirtobrutinib 25-300 mg QD (as shown in Figure 32). One possible reason is that the model may over-estimate the auto-inhibition effect on CYP3A pathway. However, the effect of such uncertainty in the predicted DDI effects up to 200 mg QD, the proposed therapeutical dose, is expected to be mild.

Figure 31: Observed AUC of Pirtobrutinib After a Single Dose or Multiple Doses of Pirtobrutinib from 25-300 mg in Study 18001



Source: LOXO-BTK-18001, Figure 20

Figure 32: Linearity Assessment of the Simulated AUC of Pirtobrutinib after Multiple Doses of Pirtobrutinib Ranging from 25 to 300 mg QD



Source: Simulated by the reviewer using the submitted Pirtobrutinib PBPK model

The Applicant's Position:

Model Application

The PBPK analysis was used to predict the PK of Pirtobrutinib following 200 mg single dose (SD) and/or 200 mg once daily dose (QD) in the presence of the following CYP3A modulators[1]:

- Strong CYP3A4 inhibitor, itraconazole capsule (200 mg QD)
- Strong CYP3A4 inhibitor, itraconazole solution (200 mg QD)
- Moderate CYP3A4 inhibitor Diltiazem (60 mg TID (three times daily))
- Moderate CYP3A4 inhibitor Fluconazole (600 mg QD)
- Moderate CYP3A4 inhibitor Verapamil (80 mg TID)
- Strong CYP3A4 inducer rifampin (600 mg QD)
- Moderate CYP3A inducer bosentan (125 mg BID (twice daily))

The default compound models (software's library, V19) for diltiazem, fluconazole, verapamil, and rifampin were used in the simulations for the respective DDIs. Applicant developed PBPK models for itraconazole and bosentan.

Itraconazole PBPK model for fed capsule -

The PBPK models for itraconazole and its metabolite hydroxyitraconazole (OH-itra) published by *Chen et al*. [2] were adapted and used in the current submission. The models were developed to describe the absorption behavior of a capsule formulation in the fed state as well as of a solution formulation in the fasted state. The input parameters for itraconazole and hydroxyitraconazole are listed in Table 98.

[1] (b) (4)

[2] Chen Y et al. Drug metabolism and disposition 39(11): 2085-2092

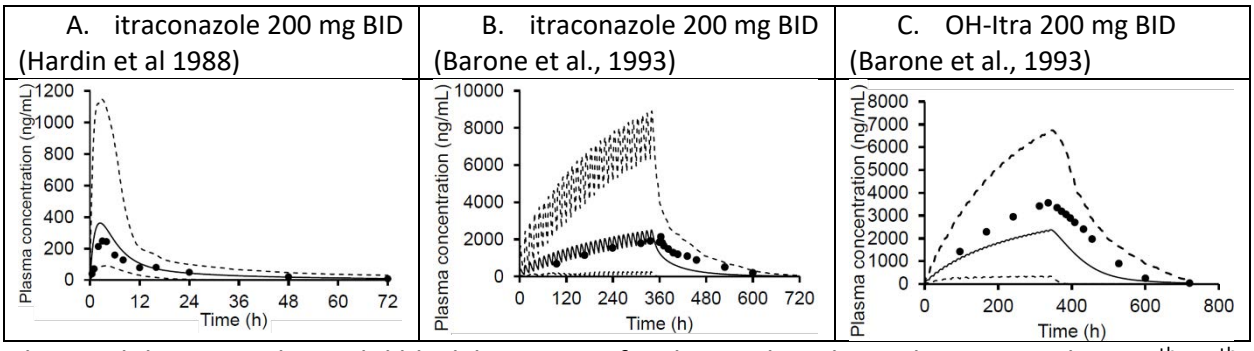
Table 98: PBPK Input Parameters for Itraconazole and Hydroxyitraconazole

Parameter	Itraconazole	Hydroxyitraconazole	Method/Reference
Molecular weight (g/mol)	705.6	721.7	Chen et al. 2019
Log P	4.9	4.1	
Compound type	Monoprotic base	Monoprotic base	
pKa	3.64	4.0	
B:P	0.6	0.55	
fu_p	0.0015	0.012	
Main plasma binding protein	Albumin		
Absorption	First Order		
Fa (capsule fed/solution fasted)	0.6/0.7	NA	Chen et al. 2019
ka (h^{-1}) (capsule fed/solution fasted)	0.25/0.45		
fu_{gut}	1		
Q_{gut}	13.7		
$P_{eff,man}$ (10^{-4} cm/s)	3.75		
Distribution	Minimal PBPK Model		
V_{ss} (L/kg)	4.75	4.72	Chen et al. 2019
V_{sac} (L/kg)	3	2.5	
k_{in} (h^{-1})	0.2	0.005	
k_{out} (h^{-1})	0.1	0	
Elimination			
CYP3A4 V_{max} pmol/min/mg protein	44.5	23	Chen et al. 2019
CYP3A4 $K_{m,u}$ (µM)	0.0233	0.0399	
Active uptake into hepatocyte	3.5	NA	
CL_R (L/h)	0	0	
CL_{bile} (L/h)	0	0	
Inhibition	CYP3A4		
$K_{i,u}$ (µM)	0.0010	0.0082	Chen et al. 2019

Source: PBPK report Table 3.2

The Applicant conducted internal validation of itraconazole model by comparing the observed and predicted PKs of itraconazole and its metabolite OH-itraconazole after a single or multiple oral doses of itraconazole capsule in published literatures. Figure 33 presents some validation results from the Applicant.

Figure 33: Observed and Predicted (Capsule Fed Model) Concentration-Time Profiles of Itraconazole and Hydroxyitraconazole (OH-itra) After Oral Dosing of 200 mg Itraconazole



Observed data in circles. Solid black line: mean for the predicted population; grey lines: 5th-95th concentration-time percentiles. Source: PBPK report Figure 4.5, 4.6 and 4.9

The inhibition of CYP3A4 by itraconazole (capsule fed model) was verified using CYP3A substrates, triazolam and zolpidem. Table 99 presented the comparison of observed and simulated DDI effects with triazolam. Reviewer also conducted additional simulations to compare the inhibition potential of itraconazole capsule on the PK of midazolam using the PBPK models of itraconazole capsule developed by Applicant and Simcyp and Simcyp's default midazolam model. The reviewer found that both models exhibited similar inhibition potential on the midazolam PK (results not shown).

Table 99: Observed and Predicted DDI Effect of Itraconazole (Capsule Fed Model) on the PKs of Triazolam

	Parameter	Observed Arithmetic mean	Predicted			V19 Predicted/Observed	
			V16[a]	V19			
				Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean
Triazolam 3 hours after itraconazole	$AUC_{(0-17)}$ ratio	2.83	4.20	3.05	2.89	1.08	1.02
	C_{max} ratio	1.76	2.20	1.95	1.92	1.11	1.09
Triazolam 12 hours after itraconazole	$AUC_{(0-17)}$ ratio	2.93	2.97	2.31	2.21	0.79	0.75
	C_{max} ratio	1.76	1.52	1.73	1.71	0.98	0.97
Triazolam 24 hours after itraconazole	$AUC_{(0-17)}$ ratio	2.57	2.18	1.83	1.77	0.71	0.69
	C_{max} ratio	1.71	1.71	1.55	1.52	0.91	0.89

Abbreviations: $AUC_{(0-17)}$ = area under the concentration–time curve from 0 to 17 hours after triazolam dosing, C_{max} = maximum plasma concentration, V = version.
[a] Source: Chen et al. 2019.

Source: PBPK report Table 4.5

Bosentan PBPK model

The bosentan PBPK model was developed according to Posada et al. (2020)[3]. The model included hepatic and non-hepatic clearance as observed at therapeutic bosentan plasma concentrations (Volz et al. 2017) and auto-induction of CYP3A4-mediated bosentan clearance. The input parameters of the bosentan model are listed in Table 100.

Table 100: PBPK Input Parameters for Bosentan

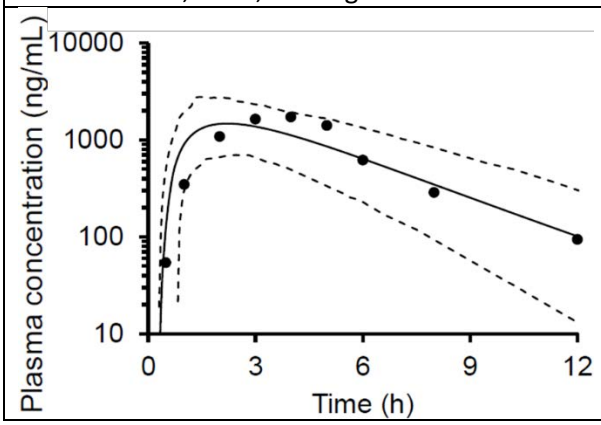
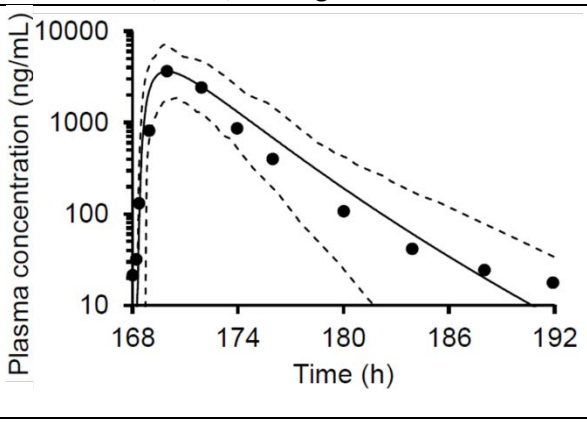
Parameter	Value	Method/Reference
Molecular weight (g/mol)	551.61	Krupa et al 2017
Log P	4.94	
Compound type	Monoprotic acid	
pKa	5.11	In-house measured
B:P	0.55	Simcyp default for acids
fup	0.029	In-house measured
Fa	0.68	Predicted using simcyp and comparing to recovery of bosentan in feces reported in Weber et al. 1999
ka (1/h)	0.37	Predicted using simcyp
Lag time (h)	0.5	Fitted based on observed data in Wrishko et al. 2008
Fugut	1	Assigned
Qgut (L/h)	5.7	Predicted using simcyp
Peff,man (10-4 cm/s)	0.85	Predicted from Papp in MDCK cells (Varma et al. 2015) using internal data for calibration
Vss (L/kg)	0.16	Weber et al. 1996
Microsomal CYP3A4 CLint,u (µL/min/mg)	20	Varma et al 2014
Active uptake into hepatocyte	2	fitted
Additional Clearance (L/h)	5.1	Calculated target-mediated (saturable) CL from dose-dependent intravenous data (total CL minus unsaturable CL;10.8 minus 5.7 L/h, Weber et al. 1996)
IndC50 (µM)	0.9	Sun et al. 2017
Indmax	13.7	

Source: PBPK report Table 3.4

The Applicant validated the bosentan PBPK model by comparing the observed and predicted bosentan PK following a single dose of 125 mg or 62.5 mg, as well as after single ascending doses of 100, 200 and 500 mg in healthy volunteers. The predicted versus observed Cmax and AUC ratios are within 0.66 to 1.02 and 0.80 to 1.05, respectively (The Applicant's PBPK report). Figure 34 presents the observed and predicted concentration-time profiles of bosentan.

[3] Posada et al, The Journal of Clinical Pharmacology 60(7): 915-930.

Figure 34: Observed and Predicted Concentration-Time Profiles of Bosentan After Single or Multiple Oral Dosing of Bosentan

Wrishko et al., 2008, 125 mg SD	Weber et al., 1999, 500 mg QD
	

Source: PBPK report Figure 4.25, 28. Observed data in circles. Solid black line: mean for the predicted population; grey lines: 5th-95th concentration-time percentiles.

The CYP3A4 induction potential by bosentan was validated with published clinical DDI results using CYP3A substrates midazolam and tadalafil. Information request was issued to request additional model validations using clinical data from DDI studies conducted with bosentan and the CYP3A substrates sildenafil and simvastatin. Table 101 presents the observed and predicted effect of bosentan with various CYP3A substrates.

Table 101: Observed and Predicted Effect of Bosentan with Various CYP3A Substrates

Substrate	Bosentan Dose	DDI effect on substrate's PK
Tadalafil	125 mg BID	Parameter / Geometric mean: Observed; Predicted V14; Predicted V19 AUCτ ratio: 0.585; 0.65; 0.66 C_{max} ratio: 0.734; 0.73; 0.73
Midazolam	125 mg BID	Parameter / Geometric mean: Observed; Predicted V14; Predicted V19 $AUC_{(2-4)}$ ratio: 0.31; 0.30; 0.29
Sildenafil	62.5 mg or 125 mg BID	Bosentan Dose / Parameter / Geometric mean: Observed; Predicted[a] 62.5 mg BID: $AUC_{(0-\infty)}$ ratio: 0.47; 0.43 C_{max} ratio: 0.55; 0.49 125 mg BID: $AUC_{(0-\infty)}$ ratio: 0.31; 0.32 Cmax ratio: 0.44; 0.39
Simvastatin	125 mg BID	Parameter / Geometric mean: Observed; Predicted AUCτ ratio: 0.66; 0.19 C_{max} ratio: 0.83; 0.21

Source PBPK report Table 41-42, Applicant's response to FDA's request

The FDA's Assessment:

The Applicant acknowledged that the model overpredicts the reported effect of bosentan on simvastatin. Applicant suggested that this reported simvastatin AUC ratio is an apparent outlier amongst clinical simvastatin drug interaction studies since simvastatin is considered as a sensitive index CYP3A substrate as midazolam.

Additional simulation to assess the effect of itraconazole capsule given under fasted condition

In the dedicated study LOXO-BTK-20006, itraconazole capsules were administered twice daily on Day 1, and once daily (QD) from Day 2 until Day 10. On Day 5, a single oral dose of 200 mg pirtobrutinib was administered. During the trial, itraconazole was administered with meals expect Day 5. On Day 5, a single oral dose of 200 mg pirtobrutinib and a single oral dose of 200 mg itraconazole was co-administered in the morning, following a fast of at least 10 hours prior to and 4 hours after dosing with pirtobrutinib and itraconazole. However, in the simulation, the PBPK model validated with itraconazole PK collected under fed condition was used to represent the DDI scenario in the study LOXO-BTK-20006.

Van Peer et al[4] reported that food would decrease the exposure of itraconazole in capsule formulation (See Table 102). In Chen et al[5], the fa (fraction absorbed) values of 0.3 and 0.9

[4] Van Peer et al. Journal of Clinical Pharmacology 36(4): 423-426.
[5] Chen Y et al. Drug metabolism and disposition 39(11): 2085-2092

were assigned to the PBPK model for itraconazole capsule when used in fasted or fed condition, respectively. Since the reversible inhibition mechanism was used in the PBPK models for itraconazole, the PK level of itraconazole would impact the inhibitory potential of itraconazole on CYP3A. Applicant's simulation which assumed that itraconazole capsules were always administered under fed condition could over-estimate itraconazole exposure on the day 5, when LOXO-305 was administered. Since fmCYP3A for pirtobrutinib was estimated using itraconazole DDI data (also with other supporting dataset), Reviewer conducted additional simulations to assess the effect of reduced itraconazole exposure on Day 5 on the estimated fmCYP3A for pirtobrutinib. The submitted PBPK model for itraconazole capsule did not account for the effect of food on the PK of itraconazole. To mimic the reduced itraconazole exposure on Day 5, the dose of itraconazole were reduced from 200 mg to 60 mg, a 3.5-fold reduction. The factor of 3.5 was derived based on the Cmax difference observed in itraconazole data when 100 mg itraconazole capsule was given in fasted or fed condition (see Table 102). The PK profile of itraconazole used in Reviewer's assessment is shown in Figure 35.

Table 102: Difference in Cmax and AUC of itraconazole follow the administration of itraconazole capsule in fed or fasted condition

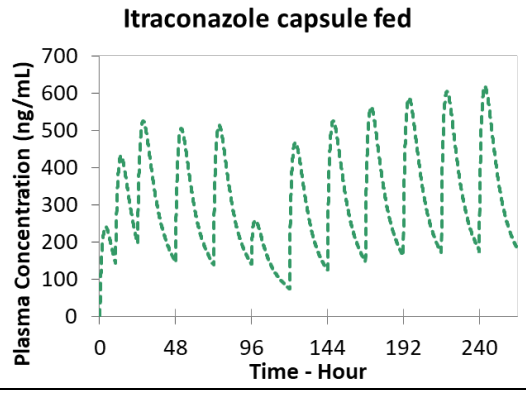
424 A. Van Peer et al.: Itraconazole availability

Table 1. Mean (SD) pharmacokinetic variables of a single oral itraconazole dose in 6 healthy subjects

	50 mg Capsules after a meal	100 mg Solution fasting	100 mg Capsules fasting	100 mg Capsules after a meal	200 mg Capsules after a meal
t_{max} (h)	3.2 (1.3)	1.7 (0.3)	3.3 (1.0)	4.0 (1.1)	4.7 (1.4)
C_{max} (ng·ml^{-1})	44.5 (16.4)	223 (84)	38.4 (19.9)	132 (67)	289 (100)
AUC (ng·h·ml^{-1})	567 (264)	1920 (679)	722 (289)	1900 (838)	5210 (2120)
f_{rel} (%)	-	100	39.8 (15.2)	102 (31)	-
$t_{1/2\lambda z}$ (h)	13 (2)	19 (4)	24 (9)	17 (3)	18 (4)

Source: Van Peer et al 1989

Figure 35: Simulation of Concentration-Time Profiles of Itraconazole in Study LOXO-BTK-20006



Dashed line: mean for the predicted concentration following customized dosing of itraconazole.
Day 1-4, 6-10: 200 mg
Day 5: 60 mg

Source: Reviewer's simulation using the submitted model and alternative dosing

The predicted effects of itraconazole on the AUC of pirtobrutinib (AUC ratio) using the Applicant's and reviewer's simulated PK profiles for itraconazole were 1.43 and 1.34, respectively, compared to the observed value of 1.49. Thus, the review re-optimized the CYP3A-mediatated clearance by fitting to the clinical PK and DDI dataset. Three model parameters were updated: CYP3A4 CLint increased from 0.03 to 0.034 (µL/min/pmol); additional hepatic clearance decreased from to 3.66 to 2.1 (µL/min/mg) and inhibition parameter kinact decreased from 0.053 to 0.051 (h-1). The resulted fmcyp3A for pirtobrutinib is approximately 0.49 compared to the value of 0.4 estimated by the Applicant. Table 103 presented the comparison of simulated PKs of pirtobrutinib following single or multiple doses of pirtobrutinib.

Table 103: Observed and Predicted Cmax and AUC of Pirtobrutinib Using the Applicant's and an Alternative PBPK Model for Pirtobrutinib

	Cmax (ng/mL) Geo. Mean			AUC (ug/mL*hr) Geo. Mean		
	Observed	Applicant's model	FDA's alternative model*	Observed	Applicant's model	FDA's alternative model*
Pirtobrutinib, 200 mg SD	1400	4605	4307.99	123	156.6	128.6
Pirtobrutinib, 200 mg steady state‡	7200-9430	7707	7578.88	105-114	127.4	124.7

Reference: PBPK table 4.3 and 4.5. *Review's simulation ‡ Simulated with final fitted kinact.

As presented in Table 104, the alternative PBPK model by the reviewer can reproduce the results from the clinical DDI data.

Table 104: Observed and Predicted DDI Effects of Pirtobrutinib on CYP3A Pathway Using the Applicant's and an Alternative PBPK Model

		Ratio of substrate's PK with and without a CYP3A modulator					
CYP3A modulators	CYP3A Substrate	Cmax ratio (90%CI)			AUCinf ratio (90%CI)		
		Obs	Pred A	Pred B	Obs	Pred A	Pred B
Pirtobrutinib As CYP3A substrate							
Itraconazole capsule, 200 mg	Pirtobrutinib, 200 mg SD	1.04 (0.95 to 1.1)	1.09 (1.08 to 1.09)	1.09 (1.08 to 1.09)	1.49 (1.40 to 1.58)	1.43 (1.41 to 1.46) 1.34*(1.32 to 1.36)	1.48* (1.45 to 1.50)
Rifampin, 600 mg		0.58 (0.54 to 0.62)	0.62 (0.6, 0.65)	0.61 (0.59 to 0.63)	0.29 (0.27 to 0.32)	0.27 (0.25 to 0.29)	0.24 (0.22 to 0.26)
Pirtobrutinib As CYP3A inhibitor							
200 mg pirtobrutinib QD	midazolam, 500 µg po, SD	1.58 (1.40 to 1.78)	1.46 (1.44 to 1.49)	1.47 (1.44 to 1.49)	1.70 (1.55 to 1.86)	1.74 (1.68 to 1.80)	1.73 (1.68 to 1.78)
	midazolam, 250 µg IV, SD	NA	1.06 (1.06 to 1.07)	1.06 (1.06 to 1.07)	1.12 (1.04 to 1.21)	1.30 (1.27 to 1.33)	1.31 (1.28 to 1.34)

Pred A: Simulated with Applicant's submitted model. Pred B: Simulated with FDA's alternative model. *Simulated with itraconazole dosing profiles are presented in Figure 35.

Upon validation of the alternative PBPK model for pirtobrutinib with clinical data, the reviewer used the alternative model to predict the DDI effects with fluconazole (moderate CYP3A inhibitor) and efavirenz (moderate CYP3A inducer). As shown the Table 105, the differences in the predicted DDI using two models were about 10%. The magnitude of difference is not expected to impact the dosing recommendation derived using different models. However, this modest difference was the result of a moderate contribution of the CYP3A pathway (fmCYP3A~0.4) on pirtobrutinib clearance. Nevertheless, the effect of food on itraconazole PK during the clinical DDI trials and the impact of interpretation biases in DDI assessment were evaluated by the reviewer.

Table 105: Comparison of the Predicted Effects of Moderate CYP3A Modulators on Pirtobrutinib PKs Following 200 mg QD Pirtobrutinib Using the Applicant's and Alternative PBPK Models

	Ratio of pirtobrutinib's PK with and without a CYP3A modulator			
	Applicant model* (fmCYP3A=0.4)		FDA model (fmCYP3A=0.49)	
	Cmax ratio	AUC ratio	Cmax ratio	AUC ratio
Fluconazole QD	1.20 (1.19 to 1.21)	1.29 (1.27 to 1.30)	1.29 (1.27 to 1.30)	1.40 (1.38 to 1.43)
Efavirenz QD	0.67 (0.65 to 0.69)	0.51 (0.48 to 0.54)	0.61 (0.59 to 0.63)	0.44 (0.42 to 0.47)

*Simulated using the Applicant's workspace files. Simcyp default models for Fluconazole and Efavirenz were used in the simulation

Results

Can the PBPK analyses predict the effects of CYP3A modulators on the PK of pirtobrutinib?

Yes. As shown in *Model Validation* section, the PBPK model could reasonably describe pirtobrutinib concentration- time profiles following administration of single or multiple doses of pirtobrutinib.

A fmCYP3A of 0.4 was obtained by fitting the observed itraconazole effects on pirtobrutinib PK. As shown in the Table 104, the Applicant's PBPK models can describe the observed DDI effects with itraconazole (strong CYP3A inhibitor), rifampin (strong CYP3A inducer) and midazolam (sensitive CYP3A substrate). Based on the estimated fmCYP3A, the Applicant conducted DDI simulations to evaluate the effects of moderate CYP3A inhibitors (diltiazem, fluconazole, and verapamil), and moderate CYP3A inducer (bosentan) on the PK of pirtobrutinib.

In the *Additional Simulation* section, the reviewer discussed the potential impact of the food on itraconazole exposure in DDI study LOXO-BTK-20006. Alternative PBPK model of pirtobrutinib was developed to predict the DDI effects of moderate CYP3A modulator on pirtobrutinib PK. The analyses showed a less than 15% difference in the predicted DDI effects with fluconazole (moderate CYP3A inhibitor) and efavirenz (moderate CYP3A inducer) using the two models. Thus, the Applicant's PBPK analyses were sufficient to predict the effects of CYP3A modulators on the PK of pirtobrutinib.

Table 106 presents the predicted effects of strong and moderate CYP3A modulators on the PK of pirtobrutinib following multiple doses of pirtobrutinib. To gain a broad understanding on the DDI effects with moderate CYP3A inducer, the Applicant conducted additional simulations to assess the effect of the moderate CYP3A inducer efavirenz on the PK of pirtobrutinib in response to FDA's information request. The reviewer also simulated the DDI effect of itraconazole using the Simcyp default PBPK model for itraconazole solution in the fasted condition.

Table 106: Predicted Effects of Multiple Doses of CYP3A Modulators on Cmax and AUC of Pirtobrutinib at Steady State

Multiple doses of CYP3A modulators + 200 mg pirtobrutinib QD for 10 days	Ratio of pirtobrutinib's PK with and without a CYP3A modulator	
	Cmax ratio (90%CI)	AUCinf ratio (90%CI)
CYP3A inhibitors		
Itraconazole capsule, 200 mg QD (fed, applicant's model) *	1.25, (1.23 to 1.26)	1.36, (1.34 to 1.38)
Itraconazole tablet, 200 mg QD (fasted, simcyp default) *	1.33 (1.31 to 1.35)	1.48 (1.45 to 1.51)
Diltiazem, 60 mg TID	1.14 (1.13 to 1.14)	1.20 (1.19 to 1.21)
Fluconazole, 200 mg QD	1.20 (1.19 to 1.21)	1.29 (1.27 to 1.30)
Verapamil, 80 mg TID	1.21 (1.20 to 1.22)	1.30 (1.29 to 1.32)
CYP3A inducers		
Rifampin, 600 mg QD*	0.47 (0.45-0.49)	0.29 (0.27-0.32)
Efavirenz, 600 mg QD[ǂ]	0.67 (0.65 to 0.69)	0.51 (0.48 to 0.54)
Bosentan, 125 mg BID	0.80 (0.79 to 0.81)	0.73 (0.72 to 0.75)

Source: PBPK report Table 5.2 and 5.4. *Reviewer's simulation. [ǂ]Applicant's response to FDA's IR

Conclusions

The PBPK analyses are adequate to evaluate the effects of moderate CYP3A modulators on the PK of pirtobrutinib.

- Verapamil, fluconazole, and diltiazem (moderate CYP3A inhibitors) are predicted to increase the Cmax of pirtobrutinib by 21%, 20% and 14%, respectively following multiple doses of 200 mg pirtobrutinib.
- Verapamil, fluconazole, and diltiazem (moderate CYP3A inhibitors) are predicted to increase the AUC of pirtobrutinib by 30%, 29% and 20%, respectively following multiple doses of 200 mg pirtobrutinib.
- Efavirenz and bosentan (moderate CYP3A inducers) are predicted to decrease the Cmax of pirtobrutinib by 33% and 20%, respectively following multiple doses of 200 mg pirtobrutinib.
- Efavirenz and bosentan (moderate CYP3A inducers) are predicted to decrease the AUC of pirtobrutinib by 49% and 27%, respectively following multiple doses of 200 mg pirtobrutinib.

19.5 FDA Grouping of Preferred Terms for Pirtobrutinib Safety Analysis

Note: Not all listed terms appear in the AE dataset.

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal ache, Abdominal cramp/cramping, Abdominal discomfort, Abdominal tenderness, Epigastric pain/soreness, Gastric/GI pain, RLQ discomfort, RLQ pain, Stomach pain	Abdominal bloating, abdominal distention, abdominal tightness, gastrointestinal discomfort
Anemia	All PTs containing "anemia", RBC count decreased, Decreased hemoglobin, decreased hematocrit	Pancytopenia, blood loss anemia
Arthritis or Arthralgia	All PTs containing "arthritis" or "arthralgia", except as noted, joint pain, joint stiffness, swelling in the joints, bilateral joint effusion, articular pain, pain in a shoulder, knee, or elbow, aches in hips and knees, articular rigidity	Pain of the hands, foot pain
Atrial fibrillation or flutter	Atrial fibrillation, Atrial fibrillation with rapid ventricular rate, Atrial flutter, Paroxysmal recurrent atrial fibrillation, Cardiac flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis", Bruises/bleeds easily, ecchymosis	Petechiae, Purpura
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias", All PTs containing "arrhythmia", PVCs, PACs	
Cardiac failure	All PTs containing "cardiac failure", Congestive heart failure, Left ventricular failure, Cardiopulmonary failure, Heart failure	Cardiovascular failure, cardiomyopathy
Chest pain	All PTs containing "chest pain", Chest discomfort, Angina pectoris, Angina NOS	Noncardiac chest pain, Chest muscle pain, Pleuritic chest pain
Chills	all PTs containing "chills", rigors,	Shaky and shivery
Colitis	Colitis, Colitis microscopic, Colitis ulcerative, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic	Enteritis
Constipation	All PTs containing "constipation"	
Cough	All PTs containing "Cough"	Postnasal drip
COVID-19	COVID-19 infection, SARS-COV-2 infection, narrow terms within COVID-19 SMQ * Cases of COVID-19 pneumonia are grouped as both pneumonia and as COVID-19	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Urgency with bowel movements, loose stools	Post procedural diarrhea, acute infectious diarrhea, diarrhea secondary to COVID-19
Dizziness	All PTs containing "Dizziness" or "Vertigo", Lightheadedness	

FDA Grouped PT	Included in Grouping	Not Included
Dyspnea	All PTs containing "Dyspnea", Shortness of breath, breathlessness	
Edema	Edema, Generalized edema, Face edema, Swelling face, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion, Bilateral LE edema, Edema- LUE, Edema- RUE, Edema- bilateral hands and feet, Ankle edema, Facial swelling	Edema blister, Localized sites of edema (e.g. Lip edema, Nasal edema, Periorbital edema, Eye swelling, mouth)
Eye Hemorrhage	Retinal hemorrhage, vitreous hemorrhage, subconjunctival hemorrhage	
Fatigue	Asthenia, Fatigue, Lethargy, ECOG performance status worsened, Chronic fatigue, extreme tiredness, no energy, low energy worsening of malaise, weakness, generalized weakness	Vaccination complication (sore arm and fatigue), weakness in a specific extremity
Febrile neutropenia	Febrile neutropenia, Neutropenic infection, Neutropenic sepsis* * Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs	Neutropenic enteritis
Fever	Fever, fever post-vaccination, fever of unknown origin, intermittent fever, non-neutropenic fever, pyrexia	
Gastroenteritis	Gastroenteritis and specific types (e.g. viral), Enteritis	Gastroenteritis radiation, Gastritis, Duodenitis
Gastrointestinal hemorrhage	All PTs containing "Gastrointestinal hemorrhage", Gastric hemorrhage, Gastric ulcer hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage, Acute gastrointestinal bleeding, Gastrointestinal disorder- blood in stool, Upper gastrointestinal bleed, Anal hemorrhage, colonic hemorrhage, GI bleed	Posthemorrhoidectomy hemorrhage
Headache	All PTs containing "headache", Migraine, Head pain, Forehead pain	Ocular migraine
Hematoma	All PTs containing "hematoma"	
Hemorrhage	All PTs containing "hemorrhage", "hemorrhagic", or "hematoma", all PTs contained in FDA's "Gastrointestinal hemorrhage" grouping, Menorrhagia, Hemarthrosis, Hemoptysis, Hematuria, Epistaxis, bleeding skin and subcutaneous tissue disorder	Petechiae, Purpura, FDA's grouping for "Bruising", conjunctival hemorrhage, gum bleeding, mouth bleeding, vaginal bleeding, bleeding at port site, mucosal bleeding, scrotal bleeding
Hemorrhage intracranial	Hemorrhage intracranial, Subdural hematoma, Subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	

FDA Grouped PT	Included in Grouping	Not Included
Hepatitis	All PTs containing "hepatitis", Hepatocellular injury, Hepatotoxicity, Drug-induced liver injury, Liver injury, Liver damage	FDA's "Transaminase elevation" grouping, PTs containing "Hepatic failure", Hepatic encephalopathy
Herpesvirus infection	High-level group term, "Herpes viral infection", Shingles infection	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia	Direct bilirubin increased
Hypertension	Hypertension, Essential hypertension, Blood pressure increased, Blood pressure systolic increased, hypertension-intermittent, hypertension-white coat syndrome intermittent	
Hypotension	Hypotension, Diastolic hypotension, Orthostatic hypotension, Blood pressure decreased	
Leukocytosis	Leukocytosis, White blood cell count increase	
Mucositis	All PTs containing mucositis, mouth pain, mouth sores, mouth ulcer, oropharyngeal pain	Parasthesia- mouth
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Noncardiac chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain, Bone pain, Back ache, Chest wall pain, Body aches, , Flank pain, Rib pain, Generalized pain, Myalgia (right wrist), Myalgia (left wrist), Myalgia (right hip)	Arthralgia, Arthritis Musculoskeletal stiffness, Back spasm, Bone marrow biopsy related iliac crest pain, myalgia at vaccine injection site, chest wall pain (chest tube insertion site), Groin pain, Disease related pain at tumor site, , Muscle cramps, back spasm, leg cramps
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion, Ischemic heart disease, cardiac arrest	Angina pectoris
Nausea	Nausea, Retching	
Neurological changes	Memory changes, amnesia, confusion, delirium, concentration impairment, dementia, seizure, tremor, including tremor of the hand, depressed level of consciousness, encephalopathy, altered mental status, hallucinations	Degenerative changes to the brain
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia/agranulocytosis	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma	
Palpitations	All PTs containing "palpitation"	

FDA Grouped PT	Included in Grouping	Not Included
Peripheral neuropathy	Peripheral neuropathy, neuralgia, peripheral sensory/motor neuropathy, peripheral polyneuropathy, numbness/tingling in hands, feet, etc., paresthesia, hypoesthesia, peripheral nerve paresis, facial palsy, Tingling in fingers and toes	Parasthesia, hypoesthesia, numbness, or tingling of the lip, scalp, or other areas not consistent with peripheral neuropathy
Petechiae and purpura	All PTs containing "petechiae" or "purpura"	
Pneumonia	All PTs containing "pneumonia", including within another word (e.g. bronchopneumonia), Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation, Bilateral pneumonia/lung infection, lung infection- COVID19 pneumonia, Lung infection * Cases of COVID-19 pneumonia will be grouped as both pneumonia and as COVID-19	
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease	
Pruritis	All PTs containing "itching" or "pruritis"	Pruritis (urticaria), itch R. ear
Rash	All PTs containing "rash", all PTs containing "dermatitis" except as noted, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Toxic skin eruption, Flat, scaly skin lesion, Skin reaction, Toxic epidermal necrolysis, Pustules, Blisters, acneiform rash, , single blister	All PTs containing "Eczema", Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes dermatitis, fungal skin rash, petechial rash, vaccination complication – rash at injection site, venous stasis dermatitis, hyperkeratotic plaque, seborrheic keratoses, skin hyperpigmentation, skin nodule, rash from cardioversion pads, single skin lesion, bug bites, Pruritis (urticaria), Hives, Welts, dermatitis atopic
Renal insufficiency	All PTs containing "renal failure" or "nephropathy", Acute kidney injury, Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal impairment, Hypercreatinemia, Chronic kidney disease, worsening kidney function	
Respiratory tract infection[a]	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection,	Upper respiratory tract infection, Lower respiratory tract

FDA Grouped PT	Included in Grouping	Not Included
	influenza, Haemophilus infection), Influenza like illness, flu-like symptoms, Sinobronchitis	infection, flu like symptoms post covid vaccine
Second primary malignancy	Breast cancer, anal SCC, high grade carcinoma, prostate adenocarcinoma, unspecified SCC, parotid SCC, DCIS, skin carcinoma, melanoma, bladder tumor, AML	Recurrent urothelial carcinoma
Sepsis	All PTs containing "Bacteremia" or "Sepsis", including within another word (e.g. urosepsis) Septic shock *** Note: Neutropenic sepsis is counted under both the "febrile neutropenia" and "sepsis" PTs**	
Supraventricular tachycardia	High-level term, "Supraventricular arrhythmias"	Sinus bradycardia
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Immune thrombocytopenic purpura
Thrombosis or thromboembolism	All PTs containing "thrombosis" except as noted, Peripheral embolism, Pulmonary embolism	Superficial thrombosis, Embolic cerebral infarction
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA's "Hepatitis" grouping, PTs containing "hepatic failure", Hepatic function abnormal
Upper respiratory tract infection	All PTs containing "upper respiratory tract infection," "sinusitis," "laryngitis," "tonsillitis," or "pharyngitis," including within another word (e.g. nasopharyngitis), all PTs containing "rhinitis" except as noted, Rhinovirus infection, Human rhinovirus test positive, infection of upper airway, common cold, cold symptoms	Rhinitis allergic, chronic vasomotor rhinitis, rhinorrhea, reflux laryngitis
Urinary tract infection	All PTs containing "cystitis" or "urinary tract infection", bladder infection	Cystitis, noninfective
Ventricular arrhythmia	High-level term, "Ventricular arrhythmias and cardiac arrest"-ventricular bigeminy	Supraventricular tachycardia
Vision Changes	Blurred vision, double vision, vision loss, visual aura, floaters	
Vomiting	Vomiting, emesis	

Source: FDA analysis

[a] This grouping defines respiratory tract infection (RTI) of unspecified localization. Where designated, FDA also evaluated all "RTI" including the "Upper RTI" and "Lower RTI" grouping.

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