26 April 2023
EMA/308908/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jaypirca

International non-proprietary name: pirtobrutinib

Procedure No. EMEA/H/C/005863/0000

Note

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

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List of abbreviations

API	Active pharmaceutical ingredient
AUC	Area under the plasma concentration-time curve
BID	Twice a day (bis in die)
BTK	Bruton's tyrosine kinase
C0	Extrapolated plasma concentration at time 0
Cl	Clearance
Cmax	Maximum observed plasma concentration
CQA	Critical quality attribute
CMR	Carcinogenic, mutagenic, or toxic for reproduction
CNS	Central nervous system
CV	Cardiovascular
DoE	Design of experiment
DLBCL	Diffuse large B-cell lymphoma
DSC	Differential Scanning Calorimetry
DT	Dissipation time
ECG	Electrocardiogram
ERA	Environmental risk assessment
FISH	Fluorescent in situ hybridisation
FOB	Functional observation battery
Fpen	Percentage of market penetration
FTIR	Fourrier transform infrared spectroscopy
GC	Gas chromatography
GLP	Good laboratory practice
hERG	Human ether-à-go-go-related gene
HPBL	Human peripheral blood lymphocytes
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
IC50	Concentration causing 50% inhibition
Kd	Dissociation rate constant (s-1)
KLH	Keyhole limpet haemocyanin
Koc	Adsorption/desorption coefficient based on organic carbon content
Kow	Partition coefficient octanol/water (= Pow)

LD50	Concentration causing lethality of 50% in animals
LLDPE	Low-density polyethylene
LOEL	Lowest observed effect level
MCL	Mantle cell lymphoma
MTD	Maximum tolerated dose
NIRS	Near infrared spectroscopy
NMR	Nuclear magnetic resonance
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
NOEL	No observed effect level
N/A	Not applicable
NHP	Non-human primate
OECD	Organization for Economic Co-operation and Development
PAR	Proven acceptable ranges
PBMC	Peripheral blood mononuclear cells
PBT	Persistence, bioaccumulation and toxicity
PEC	Predicted environmental concentration
PK	Pharmacokinetics
PNEC	Predicted no effect concentration
QD	Once a day (quaque die)
QbD	Quality by design
QTc	Corrected QT interval
QTTP	Quality target product profile
RP	Reverse phase
SD	Standard deviation
SDD	Spray dried dispersion
SEM	Scanning electron microscopy
t1/2	Half-life (hours) = ln 2 / kd
TDAR	T-cell antibody response
Tmax	Time to Cmax
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 25 May 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Jaypirca, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2021.

Jaypirca, was designated as an orphan medicinal product EU/3/21/2450 on 21 June 2021 in the following condition: Treatment of mantle cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 30 October 2023. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/jaypirca.

The applicant applied for the following indication: as monotherapy for the treatment of adult patients with mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0197/2021 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active substance status

The applicant requested the active substance pirtobrutinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
17 September 2020	EMEA/H/SA/4588/1/2020/II	Larissa Higgins and Ole Weis Bjerrum
29 January 2021	EMA/SA/0000046065	Kolbeinn Gudmundsson and Larissa Higgins

The Scientific Advice pertained to the following quality and clinical aspects:

- The planned starting material designation and control strategy;
- Whether the CHMP agree on the unmet medical need and that the patient population with MCL is adequately represented by the eligibility criteria of the MCL cohort of study LOXOBTK-18001;
- The design of the ongoing study LOXO-BTK-18001 to allow the evaluation of the benefit-risk balance of LOXO-305 for a CMA in previously treated MCL patients who have received at least one prior regimen that included a BTKi, in particular, the use of ORR as the primary endpoint and DOR as a secondary endpoint;
- The design of the Phase 3 study of LOXO-305 versus investigator's choice in patients with MCL previously treated but BTKi naïve to confirm a positive benefit-risk in patients with relapsed MCL;
- The patient population and study design, including treatment regimen, primary endpoint, interim analysis and statistical analyses, of the pivotal Phase 3 study for the treatment of patients with previously treated CLL or SLL who have received at least one prior regimen that included a BTKi.

1.7. Steps taken for the assessment of the product

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

Rapporteur : Alexandre Moreau Co-Rapporteur: Edward Laane

The application was received by the EMA on	25 May 2022
The procedure started on	16 June 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 September 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 September 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	9 September 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	13 October 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	31 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 February 2023
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 April 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Jaypirca on	26 April 2023
The CHMP adopted a report on similarity of Jaypirca with Tecartus on (see Appendix on similarity)	26 April 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 April 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for pirtobrutinib is: monotherapy for the treatment of adult patients with mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

2.1.2. Epidemiology

MCL is a rare and aggressive subtype of B-cell NHL and is incurable with current therapies. MCL accounts for 3% to 10% of all new NHL cases per year with a typical incidence of approximately 1 to 2 per 100,000 in Europe and the US (Dreyling et al. 2017; Jain and Wang 2019). Prognosis for patients with MCL is poor, with OS of 3 to 5 years at diagnosis (Dreylinget al. 2018). MCL is more common in men (3:1; male:female) and patients are typically aged 60 to 70 years old at diagnosis.

2.1.3. Biologic features

The majority of MCL cases have an immunophenotype which is positive for B cell antigens (CD5, BCL-2, and cyclinD1), and negative for CD23 and follicular centre cell-associated antigens, such as CD10 and BCL-6.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Patients diagnosed with MCL can be categorised as low risk, intermediate risk, or high risk using the MCL International Prognostic Index (MIPI), which incorporates clinical features (Hoster et al. 2008) with tumour cell proliferation and blastoid histology as additional prognostic factors. Generally, MIPI classification of intermediate or high risk is associated with poor prognosis.

While the indolent presentation of MCL is reported in a minority of patients with smoldering or leukaemic histology, the typical clinical presentation of MCL is aggressive and includes classic, blastoid, or pleomorphic histology with treatment at diagnosis required for most patients.

2.1.5. Management

Frontline treatment selection is based on patient characteristics and candidacy for intensive chemoimmunotherapy approaches, which yield high response rates including CRs but few long-term remissions (Lenz et al. 2005; Flinn et al. 2014). Young and fit patients typically receive intensive chemoimmunotherapy with autologous stem cell transplantation in the first-line setting (NCCN 2021b; Flinn et al. 2014; Lenz et al. 2005). Cure with this approach is rare and relapse is nearly universal.

Treatment benefits become progressively shorter with each subsequent line of therapy after relapse (Kumar et al. 2019). Prior to the development of BTK inhibitors, salvage therapies such as bortezomib, lenalidomide, or temsirolimus were approved, yielding ORRs 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). Covalent BTK inhibitors (for example, ibrutinib) are the most established therapy for relapsed MCL based on efficacy data that are clearly superior to other approved salvage therapies with

ORRs of 70% to 84% and a median PFS of 12 to 22 months (Rule et al. 2019; Wang et al. 2019; Song et al. 2020).

While there are clear benefits in treating patients with MCL with covalent BTK inhibitors, BTK inhibition is not curative and when patients relapse, outlook is poor and subsequent treatment options are not well defined (NCCN 2021b). Prospective studies evaluating therapy options in the post-BTK inhibitor setting of relapsed MCL are rare or not yet reported. Available data demonstrate that following progression on BTK inhibitors, survival of patients with MCL is very poor with median OS at only 2.5 to 8.4 months (Martin et al. 2016; Cheah et al. 2015; Epperla et al. 2017). Published data with bortezomib, lenalidomide, and temsirolimus predate use of BT inhibitors, but response rates to chemoimmunotherapy given as post-ibrutinib salvage therapy are as low as 27% (Martin et al. 2016; Jain et al. 2018).

As per current guidelines, the only authorised drug after BTKi is brexucabtagene autoleucel. This CD19-targeted CAR-T treatment option is limited by the known production difficulties inherent to CAR-T cells.

The management of patients with relapsed/refractory MCL post BTKi represents a clinical challenge. Patients typically receive salvage use of treatment for r/r MCL prior to the arrival of BTKi or use/re-use of previous lines therapies (e.g. rituximab-bendamustine-cytarabine regimen (R-BAC)).

2.2. About the product

Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest as it was not clear from available data at that time whether pirtobrutinib could fulfil the unmet medical need in the claimed indication.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  To confirm the positive benefit-risk profile the applicant has initiated a confirmatory Phase 3 Study in previously treated, but BTK inhibitor-naive, patients with MCL (Study 20019 [BRUIN-MCL-321]): a global, open-label, Phase 3 randomised study in previously treated, but BTK inhibitor-naive, patients with MCL, randomised 1:1 between pirtobrutinib experimental arm and the Investigator's choice of covalent BTK inhibitor.

  The primary endpoint of the study is PFS as assessed by the IRC per the Lugano 2014 criteria (Cheson et al. 2014). PFS, as the primary endpoint for this study, serves as a surrogate for OS and is used because of the protracted duration of follow-up expected to reach an OS endpoint. Overall survival is a secondary endpoint for the study. At the time of the primary PFS analysis, the secondary OS analysis will seek to establish that there is no detrimental impact on survival, with a potential to observe a positive trend in OS.
- Unmet medical needs will be addressed, as in this this post-BTK inhibitor setting there are no prospective data available on alternative commonly used pharmacologic approaches such as temsirolimus, bortezomib or lenalidomide.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Given the epidemiology of the condition, a substantial number of patients may potentially benefit from treatment with pirtobrutinib over the period between Conditional Marketing Authorisation and full approval.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as an immediate release film-coated tablet containing either 50 mg or 100 mg of pirtobrutinib.

Other ingredients are, for the tablet core: hypromellose acetate succinate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, colloidal hydrated silica, and for the film-coating: hypromellose, titanium dioxide, triacetin and indigo carmine (E132).

The product is available in polyvinylchloride/polychlorotrifluoroethylene blisters sealed with an aluminium foil.

2.3.2. Active substance

General information

The chemical name of pirtobrutinib is 5-amino-3-{4-[(5-fluoro-2-methoxybenzamido)methyl]phenyl}-1-[(2S)-1,1,1-trifluoropropan-2-yl]-1H-pyrazole-4-carboxamide corresponding to the molecular formula $C_{22}H_{21}F_4N_5O_3$. It has a relative molecular mass of 479.44 and the structure depicted in Figure 1.

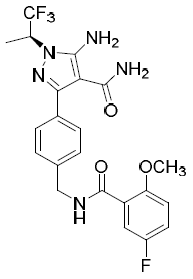


Figure 1: Active substance structure

The chemical structure of pirtobrutinib was elucidated by a combination of mass spectroscopy, FTIR analysis, NMR analysis, ultraviolet absorption, single crystal X-Ray analysis and elemental analysis.

The active substance is a white to practically white to light brown solid. The active substance not hygroscopic and it is practically insoluble over a pH range of 1.1 to 6.8.

Pirtobrutinib exhibits stereoisomerism due to the presence of one chiral centre having "S" configuration. The optical rotation analysis of pirtobrutinib is provided and is consistent with the presence of the chiral centre in the structure. Proof of structure and stereochemistry of pirtobrutinib was achieved by single crystal X-ray diffraction analysis. No significant change in the level of R-enantiomer has been observed on storage of pirtobrutinib active substance. In addition, solid samples of the active substance were stressed under conditions of heat, humidity, and light and were analysed by chiral HPLC.

Polymorphism has been observed for pirtobrutinib. The manufacturing process consistently delivers the desired form and the stability of active substance over storage have been shown.

Manufacture, characterisation and process controls

Pirtobrutinib active substance is manufactured using a convergent synthesis with sufficient synthetic steps from each selected starting material and several isolation and crystallisation steps. It starts from well-defined starting materials with acceptable specifications.

No reprocessing is applied and there is no use of recovered solvent. No aseptic or sterilisation process is performed in the manufacture of pirtobrutinib.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and multivariate bracketing studies. Based on these studies, proven acceptable ranges (PARs) have been defined for several steps of the manufacturing process of the active substance and for several material inputs. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. The proposed PARs are not intended to claim a design space and it has been confirmed that any movement within a PAR range will occur only when other parameters are held at their target values. Overall, there is a good correlation between the ranges explored through these experiments and the PARs. claimed in section 3.2.S.2.2.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The acceptance criteria have been justified by purge studies at appropriate levels.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. Process development changes have consisted of changes to solvents, reagents and processing conditions.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in a linear low-density polyethylene (LLDPE) primary liner which contains an antistatic additive. The LLDPE liner is placed in a laminated foil liner, individually cable tied or sealed. The liners may then be placed in an appropriate container such as a fibre drum, corrugated container, polyethylene drum, or metal drum for shipping and handling. The LLDPE primary liner complies with the Ph. Eur. and the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for identification (IR - Ph. Eur. 2.2.24), assay (HPLC), purity (HPLC), enantiomer content (HPLC), specified impurities (HPLC and GC), residual solvents (GC), description (visual), water content (Ph. Eur. 2.5.32) and residue on ignition (Ph. Eur. 2.4.14). The active substance specifications are based on the active substance critical quality attributes (CQA).

The active substance specifications are considered in line with guidance and acceptable. Exclusion of tests such as chiral identity, elemental impurities, microbial testing, particle size, and crystal form has

been appropriately justified. Limits for assay, has been tightened during the procedure, following a request from the CHMP.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for active substance process variants used in toxicology studies, clinical studies, stability studies, and establishment of the primary reference standard are provided. Batch analysis data from three commercial scale batches (validation batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance by a process representative of the commercial process, stored in a container closure system representative of that intended for the market for up to 12 months under long term conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The parameters assessed during primary stability studies are description, identity, assay, impurities, R-enantiomer and water. Analytical methods used for stability studies are the same as those used for release testing of the active substance. All parameters tested have remained within the limits of specification requirements for all samples. No significant trend in results at any time point or storage condition is observed.

Photostability testing following the ICH guideline Q1B was performed on solid samples of the active substance, the results confirm that the active substance in the solid state is photostable.

Samples of the active substance in the solid form and in solution were also placed under various stress conditions of heat and humidity for the solid state and of heat, light, oxidation, and over a wide pH range for the solutions. No degradation was observed for the solid state under the investigated stress conditions, while the solution state stress testing indicated that pirtobrutinib in solution is susceptible to oxidative degradation and photodegradation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months, without any storage conditions, when stored in the proposed container.

2.3.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as an immediate release film-coated tablet containing either 50 mg or 100 mg of pirtobrutinib.

Jaypirca 50 mg film coated tablet is blue, 9 x 9 mm, arc triangle shaped tablet debossed with "Lilly 50" on one side and "6902" on the other side. Jaypirca 100 mg film coated tablet is blue, 10 mm, round tablet debossed with "Lilly 100" on one side and "7026" on the other side. The two strengths have the same colour, but are adequately differentiated by shape, size and debossing.

All the excipients are of compendial quality (Ph. Eur., JP, USP-NF). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.3.1. of this report. Statement from the manufacturer of lactose monohydrate, sole excipient from animal origin, that confirms compliance with applicable BSE/TSE requirements is provided and it is satisfactory.

Pharmaceutical development of the finished product contains QbD elements.

The critical quality attributes (CQAs) identified were description, identification, potency, purity, content, uniformity and release.

The pharmaceutical development focused on addressing the low aqueous solubility of the active substance across the physiological pH range. An amorphous solid dispersion in a polymer matrix, produced by spray drying was chosen to improve the solubility and achieve the desired exposure for the clinical doses. This spray dried dispersion (SDD) is an intermediate product. The formulation development was based on the selection of excipients with appropriate attributes in combination with the relevant active substance and SDD properties to achieve the identified CQAs, as well as demonstration of product robustness across a range of process parameters that have potential impact to finished product performance. The choice of the SDD, of the polymer hypromellose acetate succinate, and of the ratio API:polymer has been justified. The other excipients are classical and within typical ranges for this kind of formulation. Characterisation of the optimised formulation has been conducted. the production of stable amorphous dispersion across a range of conditions has been supported.

The history of development of the SDD and of the tablet formulations up to final commercial formulation has been explained. Characterisation of the optimised formulation has been conducted to support the production of stable amorphous dispersion across a range of conditions. Suitability of the commercial formulation has been demonstrated.

The manufacturing development of the SDD and the tablet has been evaluated through the use of risk assessment, univariate and multivariate experiments and design of experiments to identify the critical product quality attributes and critical process parameters. A design space for the SDD and the tablet manufacturing was established. For SDD, based on the knowledge gained, process conditions for the spray-drying and the secondary drying steps have been optimised to remain below the SDD glass transition temperature and to maintain impurity profile within acceptable limits. A summary of SDD commercial process ranges is provided based on the results gathered from development experience at the commercial scale, historical data at the manufacturing site, and model-based assessments. SDD specifications were developed as part of an integrated approach to a quality attribute-based control strategy.

The tablet manufacturing process consists of typical finished product operations, film-coating and packaging. Each step of the tablet manufacturing process has been optimised on small and commercial scale equipment. Appropriate responses for the tablet manufacturing process were evaluated. As full testing of the finished product is routinely performed at release, design space is not the sole element of the control strategy contributing to the quality of finished product.

Sufficiently significant ranges of process parameters have been explored during development. Appropriate justification of parameters and ranges has been provided. When investigating downstream process steps, variability of the incoming materials from upstream step was taken into account. This allowed the multivariate assessment of the overall process. Outputs raw data have been provided, which allowed assessment to the specifications. The dissolution method was developed to be discriminating for properties that could impact *in vivo* performance. The discriminatory power of the dissolution method has been demonstrated. The proposed specification for dissolution has been

justified by dissolution data gathered during development of the commercial formulation and manufacturing process. The dissolution profiles of batches used in the pivotal study have also been provided.

The formulation used during clinical studies is the same as that intended for marketing.

The primary packaging is polyvinylchloride/polychlorotrifluoroethylene blisters sealed with an aluminium foil. The materials comply with Ph. Eur. and/or EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of two main steps: preparation of the SDD and preparation of the tablets.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces. IPC for SDD and for the finished product are satisfactory.

The process is considered to be a non-standard manufacturing process.

A traditional process validation has been performed at target conditions on three consecutive full-scale SDD batches and tablet batches per strength. The summary report has been presented. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Release specifications for the intermediate SDD have been established. Respective analytical procedures and their validation are provided.

Several hold times are specified. The hold time for bulk coated tablets is included in the calculation of the shelf-life.

Bulk packaging is described for SDD and film-coated tablets.

Risk assessment for the pirtobrutinib bulk tablet shipping was conducted and concluded to a low risk.

Product specification

The finished product release and shelf specifications include appropriate tests for this kind of dosage form: identity (HPLC), assay (HPLC), degradation products (HPLC), description (visual), uniformity of dosage unit (HPLC, Ph. Eur.), dissolution (HPLC, Ph. Eur.), dye identity for titanium and indigo carmine (colourimetric).

The finished product is released on the market based on the above release specification through traditional final product release testing. The tests and controls applied for the finished product at release and throughout shelf life are appropriate for the dosage form. Where applicable, the specifications comply with the Ph. Eur. requirements and with ICH guidelines.

Assay is consistent at release and is stable upon storage. A slightly wider specification limit at shelf-life has nevertheless been justified.

The proposed acceptance criteria for specified impurities are based on toxicologically established safety limits.

Justifications for not controlling residual solvents, other impurities, chiral purity, physical state, and water content in the finished product are acceptable.

An alternative method was initially proposed for assay. Following questions raised by the CHMP during the procedure, the alternative method has been removed from the application.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no specific risk of nitrosamine impurities in the active substance or the related finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for three batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of finished product stored under long term conditions and under accelerated conditions according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Multiple different batches of active substance and of SDD were used to manufacture the primary stability batches.

Samples were tested in line with the specification tests listed. All the results (long-term and accelerated) are compliant with specifications, no trend was evidenced.

SDD stability studies are presented for multiple SDD batches. Data are available up to 24 months. Results are compliant with specifications in all storage conditions. A statement indicates that the finished product dating or shelf-life begins with the introduction of the SDD into the finished product process. An end-to-end stability study with finished product manufactured with SDD aged and does not present any different trends as compared to the primary stability data, which is acceptable.

In addition, samples of the finished products were exposed to thermal/humidity stress testing (open dish) and was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In the open dish study, degradation products have increased but remained within the proposed commercial specification level. No significant change was observed in the photo-stability study, the finished product is photostable.

The analytical procedures used are stability indicating.

Based on available stability data, the proposed shelf-life of 2 years, without any storage condition, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and the finished product, and their manufacturing processes. Design spaces have been proposed for several steps in the manufacture of the finished product intermediate and the finished products. The design spaces have been adequately established. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. No major objections on quality aspects were raised during the procedure.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Pharmacology

2.4.1.1. Primary pharmacodynamic studies

The pharmacodynamic properties of pirtobrutinib were investigated in both *in vitro* and *in vivo* experimental systems, including BTK inhibition (potency and selectivity), comparability with other BTK inhibitors, target occupancy estimation and actions on animal models.

In vitro

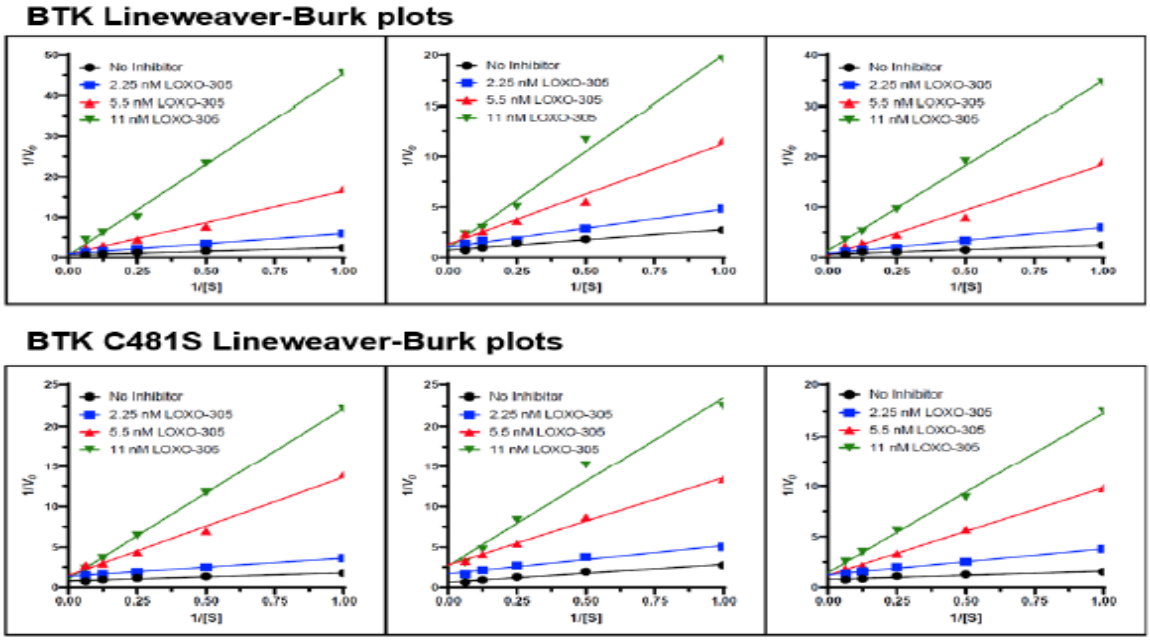
Inhibitory Activity of pirtobrutinib Against BTK and BTK C481S Proteins *in vitro*

The activity of pirtobrutinib on WT and C418S human BTK enzymes (LOXO-305-PHARM-031) was analysed in an enzymatic assay by using radiolabelled ATP. Values obtained for IC_{50} indicated an inhibition potency within the nanomolar range for both enzymes (3.15 and 1.42nM respectively).

Mechanism of Inhibition of BTK and BTK C481S by pirtobrutinib

Lineweaver-Burk analysis was used to determine the mechanism of inhibition of the wild-type and C481S BTK enzymes by pirtobrutinib (LOXO-305-PHARM-039). The results (**Figure 2**) of the kinetic analysis showed that pirtobrutinib is a competitive inhibitor (non-parallel lines intersecting lines at the Y-axis).

Figure 2. Lineweaver-Burk analysis of ATP competition with pirtobrutinib in BTK and BTK C418S



Effect of the pirtobrutinib metabolite M1, LOX-00023900-001, on BTK *in Vitro* Activity

The metabolite M1 (LOX-00023900-001/LSN3828720), was also tested against BTK (LOXO-305-PHARM-029). Results indicated M1 did not inhibit BTK activity in this test system (data now shown).

Binding Activity of pirtobrutinib with BTK and BTK C481 Resistance Mutants Using Surface Plasmon Resonance (SPR)

SPR assays (LOXO-305-PHARM-023, LOXO-305-PHARM-042) were performed to determine binding constants and kinetics of pirtobrutinib on common resistance mutations BTK protein. The average values of the dissociation equilibrium constant was 1.0nM for WT BTK and 1.7 nM for BTKC4181S.

Inhibition of BTK and BTK C481 Resistance Mutants Transiently Expressed in Human Embryonic Kidney Cells

The potency of pirtobrutinib was evaluated in a cell-based assay (catalytic activity of BTK after transient expression in HEK293T cells). WT BTK and relevant mutations at position C481 (C481S, C481T, C481G and C481R) were characterised. Other BTK inhibitors (ibrutinib, acalabrutinib, GDC-

0853/fenebrutinib, and SNS-0853/vecabrutinib) were analysed in this study by measuring the impact on BTK phosphorylation (LOXO-305-PHARM-041) (***Table 1***.)

Table 1. Inhibition of BTK Autophosphorylation in HEK293 Cells Transiently Expressing BTK C481 Resistance Mutants

	IC50 (Mean ± SD, nM)									
Kinase	**Pirtobrutinib**	**n**	**Ibrutinib**	**n**	**Acalabrutinib**	**n**	**Fenebrutinib**	**n**	**Vecabrutinib**	**n**
BTK	3.9 ± 1.6	3	2.0 ± 0.1	2	11.9 ± 3.7	2	2.9 ± 1.1	2	8.9 ± 9.1	2
BTK C481S	8.1 ± 1.3	2	120.0	1	N/D	2	10.4 ± 2.6	2	48.8 ± 0.2	2
BTK C481T	7.1 ± 3.3	2	>150.0	2	> 300.0	2	8.4 ± 7.5	2	9.1 ± 2.5	2
BTK C481G	13.9 ± 3.8	2	N/D	1	N/D	1	12.2 ± 2.2	2	N/D	1
BTK C481R	12.6 ± 5.2	2	N/D	1	N/D	1	19.0 ± 7.8	2	N/D	1

Inhibition of BTK and BTK C481S Stably Expressed in Human Embryonic Kidney Cells

Inhibition of BTK by pirtobrutinib and ibrutinib was compared in HEK293 cells stably expressing BTK wild type and the mutant form C481S (LOXO-305-PHARM-014). The results showed that pirtobrutinib inhibited autophosphorylation (Y223) of WT and C481S mutant expressing cells, while ibrutinib exhibited a similar potency for WT BTK but not for C418S mutant.

Effect of pirtobrutinib on Cellular Signalling in Human Lymphoma Cell Lines

Two cell lines involved in BTK dependent signalling (Ramos RA1 and TMD8) were used in these assays (LOXO-305-PHARM-013, LOXO-305-PHARM-040 and LOXO-305-PHARM-011). Ramos RA1 cells were shown to have BTK dependent signalling induced by activation of the B cell receptor (BCR) (Nisitani et al. 1999, Evans et al. 2013). TMD8 cells were characterised to be of the activated B-cell-like subtype of DLBCL (ABC-DLBCL) and dependent on BTK for survival (Davis et al. 2010).

Both cell lines were treated with pirtobrutinib and lysates analysed for levels of phosphorylated BTK Y223 and PLCγ2 Y217. The results showed the inihibition BTK Y223 autophosphorylation with IC50 values of nanomolar in TMD8 and Ramos RA1 cells, as well as PLCγ2 in Ramos RA1 (data not shown).

Effect of pirtobrutinib on Cell Proliferation in Human B-Cell Lymphoma Cell Lines

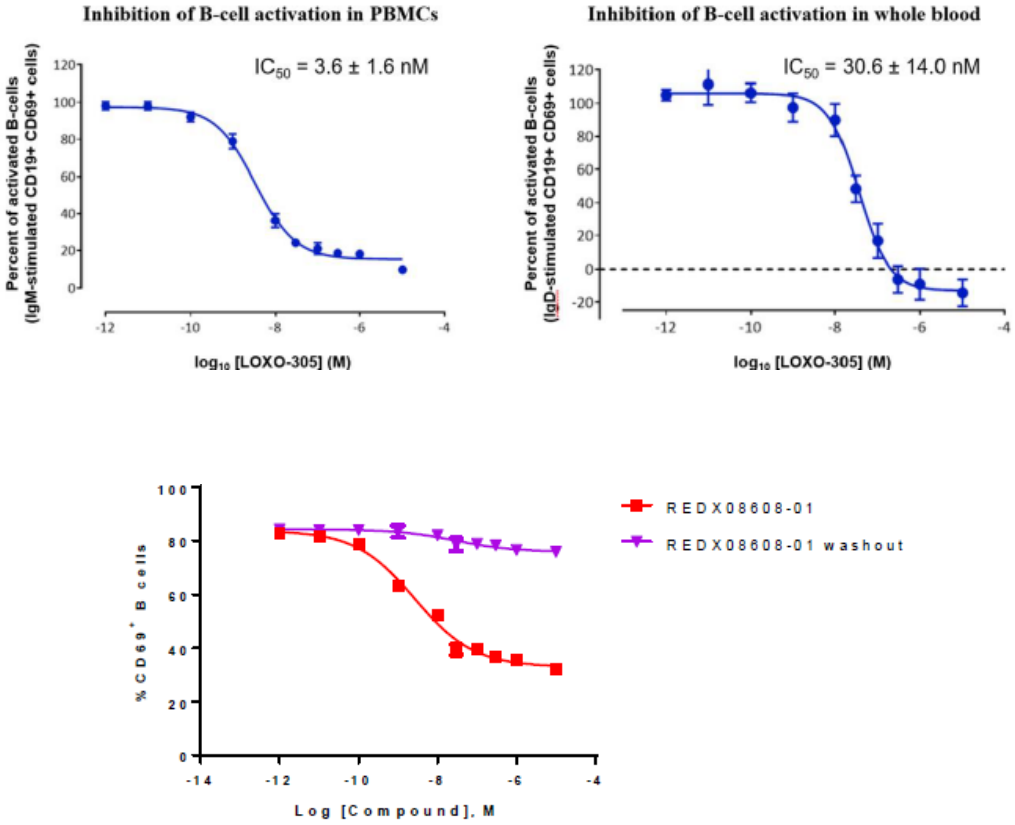
Pirtobrutinib inhibited cell proliferation of TMD8 and REC-1 cells with IC50 values of 2.33 nM and 3.13 nM, respectively, indicating that it potently inhibits cell proliferation in both DLBCL and MCL cell line models (LOXO-305-PHARM-040 and LOXO-305-PHARM-036).

Inhibition of Human B-Cell Activation in Peripheral Blood Mononuclear Cells and Whole Blood by pirtobrutinib and Demonstration of its Reversibility in Cells

The effect of pirtobrutinib on the activation of human B-cells was investigated using human whole blood and PBMC (LOXO-305-PHARM-016). The results (Figure 05, left) revealed a dose dependent reduction of B-cells activation in both isolated PBMCs and B-cells in human whole blood as measured

by inhibition of CD69 positive B-cells as detected with CD19 staining. This inhibitory effect was lost after washout, which is consistent with the potential reversibility of pirtobrutinib action (**Figure 3**).

Figure 3. Pirtobrutinib inhibition of B-Cell activation in human peripheral blood mononuclear cells and human whole blood (top). Reversibility of the inhibition after washout (bottom)



<u>*In Vitro* Occupancy of BTK by Pirtobrutinib in Human Peripheral Blood Mononuclear Cells</u>

The *in vitro* occupancy of Bruton's tyrosine kinase (BTK) by pirtobrutinib was evaluated in human PBMCs collected from healthy donors. With this aim, a cell permeable fluorophore-conjugated probe derivative of pirtobrutinib to label unoccupied BTK was used (LOXO-305-PHARM-037).

The assay showed pirtobrutinib with a dose-dependent occupancy of BTK in human PBMCs *in vitro*, resulting an EC_{50} value of 3.82 nM (3.24 nM adjusted). EC_{50} values were adjusted for FBS protein binding of 15.2% (LOXO-305-DMPK-016).

Pirtobrutinib showed more than 95% mean BTK occupancy at a concentration of 300 nM, and more than 97% mean BTK occupancy at a concentration of 1,000 nM. When the pirtobrutinib concentration is adjusted for FBS binding, the 300 nM concentration with 95% mean BTK occupancy corresponded to a free concentration of 254 nM, which is similar to the unbound plasma Cmin of 266 nM at the 200 mg clinical dose. When adjusted for FBS binding, the 1000 nM concentration corresponded to a free concentration of 850 nM, which is approximately 1.5-fold higher than the unbound plasma Cmax of 550 nM at the 200 mg clinical dose.

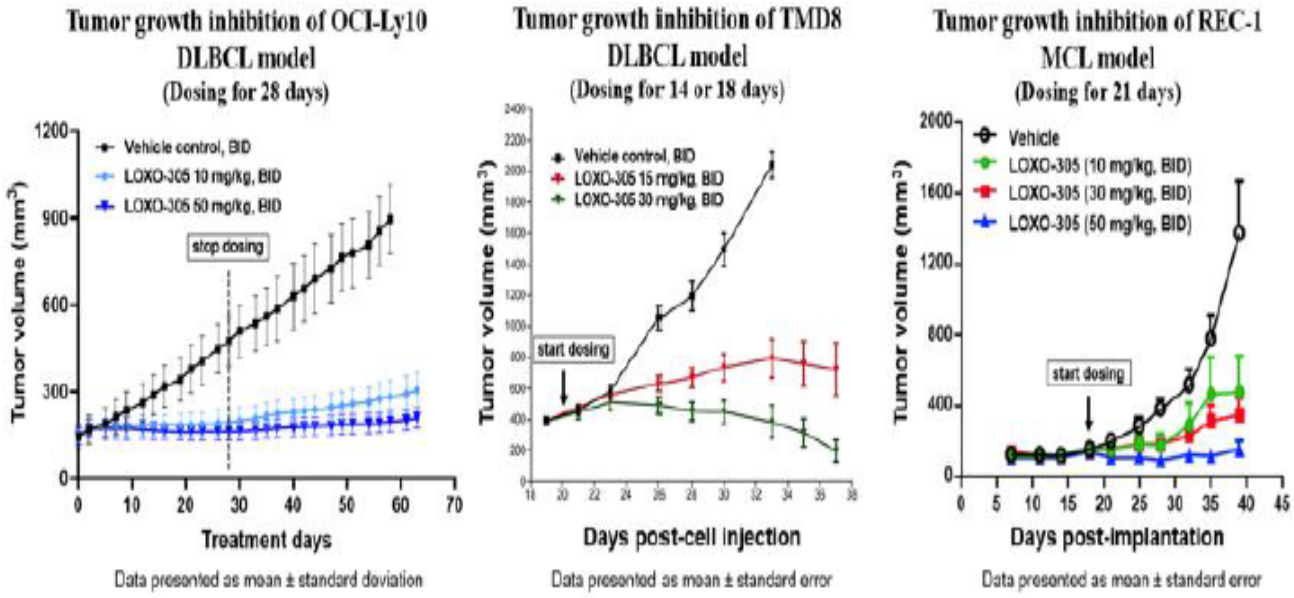
In vivo

In Vivo Efficacy of pirtobrutinib in Human B-cell Lymphoma Xenograft Models in Immunocompromised Mice

The *in vivo* effect of pirtobrutinib was evaluated in 3 tumour xenograft studies in mice (LOXO-305-PHARM-010, LOXO-305-PHARM-038 and LOXO-305-PHARM-030).

Treatment with pirtobrutinib caused tumour growth inhibition in the three models tested (***Figure* 4**).

Figure 4. Dose-dependent inhibition of tumour growth in human B-Cell lymphoma cell line xenograft tumour models



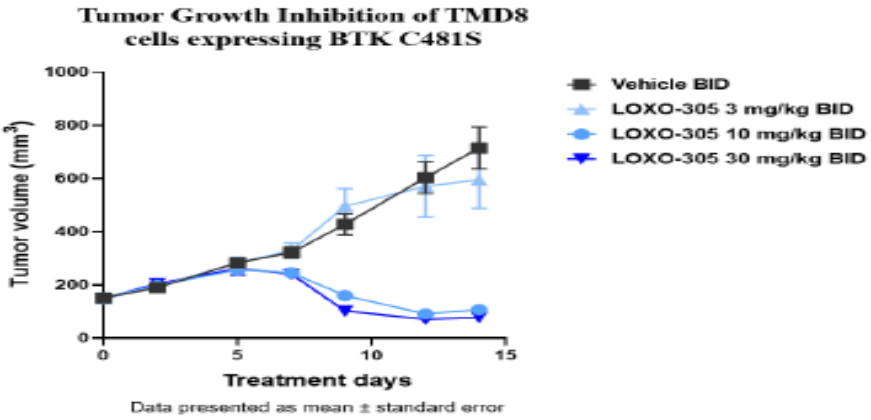
OCI-Ly10 model, 88% and 95% at 10 mg/kg and 50 mg/kg BID compared to vehicle, respectively on day 28 (LOXO-305-PHARM-010); TMD8 model, 61% and 81% at 15 mg/kg and 30 mg/kg, respectively on day 14 of dosing compared to vehicle (LOXO-305-PHARM-038); and in REC-1 MCL xenograft model, 80% and 84% at 10 mg/kg and 30 mg/kg BID, respectively, and tumour regression of -11% in the 50 mg/kg BID group (LOXO-305-PHARM-030).

All treatments were well-tolerated and no drug-related deaths occurred in the three lymphoma xenograft studies.

In Vivo Efficacy of pirtobrutinib in a Human DLBCL BTK C481S Xenograft Model in Immunocompromised Mice

The *in vivo* efficacy of pirtobrutinib was also evaluated in a human DLBCL TMD8 BTK C481S xenograft model (LOXO-035-PHARM-017). Pirtobrutinib treatment resulted in tumour growth inhibition at 10 mg/kg and 30 mg/kg BID (-29% and -48%, respectively) compared to vehicle treated control (**Figure 5**).

Figure 5. Dose-dependent inhibition of tumour growth in a TMD8 BTK C481S human xenograft B-Cell lymphoma model



2.4.1.2. Secondary pharmacodynamic studies

A screening assay (LOXO-305-PHARM-003) for inhibition of the kinase activity of 371 human wild-type kinases was reported with pirtobrutinib (1 μM is 320-fold greater than estimated IC_{50} value). Of the 371 kinases, 9 (including BTK) had percent of control values less than 50 (equivalent to more than 50% inhibition). Pirtobrutinib had the greatest inhibitory effect on BTK (data not shown). These kinases were additionally investigated in an assay (LOXO-305-PHARM-031) using radiolabelled ATP at a concentration near Km value. The IC_{50} values estimated for ERBB4, MEK2, BRK, MEK1, TXK, CSK, YES1, FYN and TEC were 13.25 nM, 82.7 nM, 54.25 nM, 147 nM, 209 nM, 552 nM, 157 nM, 1710 nM, and 1234 nM, respectively.

In a cell-based assay using a cell permeable fluorescent NanoBRET tracer (LOXO-305-PHARM-033), IC_{50} values for BTK, TEC and BRK were 0.66 nM, 70.46 nM, and 360.47 nM, respectively. In the case of TXK, YES1, CSK and FYN, cellular values were determined to be > 5 μM, the highest concentration tested.

The effect of pirtobrutinib on different kinases was investigated in additional cell-based assays (LOXO-305-PHARM-034 and LOXO-305-PHARM-035), in which pirtobrutinib did not inhibit these enzymes (**Table *2***).

Table 2. Effect of pirtobrutinib on BTK and Non-BTK kinases in cellular assays

Kinase	N	Pirtobrutinib IC_{50} (Mean ± SD, nM)	Fold Selectivity vs BTK#	Cell Assay Readout
BTK	3	0.66 ± 0.34	1	Competitive displacement of tracer
TEC	3	70.46 ± 20.30	106.8	Competitive displacement of tracer
BRK/PTK6	3	360.47 ± 198.56	546.2	Competitive displacement of tracer
TXK	3	> 5000*	> 7600	Competitive displacement of tracer
YES1	3	> 5000*	> 7600	Competitive displacement of tracer
CSK	3	> 5000*	> 7600	Competitive displacement of tracer
FYN	3	> 5000*	> 7600	Competitive displacement of tracer
ERBB4	2	> 10000*	N/D	Phosphorylation of C-terminal tail
MEK1/MEK2	3	12600 ± 2400	N/D	Phosphorylation of ERK1/2 (HCT116 cells)
MEK1/MEK2	3	3790 ± 1310	N/D	Phosphorylation of ERK1/2 (A375 cells)

Effect of pirtobrutinib at other receptors and enzymes

Pirtobrutinib was profiled in radioligand binding assays, and enzyme and uptake assays to detect potential off-target activity. Pirtobrutinib was evaluated at a concentration of 1 µM against 44 targets in radioligand binding, enzyme and uptake assays, which included primary molecular targets, transmembrane and soluble receptors, ion channels, monoamine transporters, and enzymes (LOXO305-PHARM-004). There was no significant inhibition (≥50%) of receptors or enzymes evaluated. The concentration of 1 µM is approximately 1.8-fold higher than the preliminary human PK unbound Cmax of 0.55 µM at the 200 mg clinical dose.

2.4.1.3. Safety pharmacology programme

Effects of LOXO-305 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (LOXO-305-SPHARM-003)

In this *in vitro* GLP study, pirtobrutinib inhibited the hERG channel with an IC_{50} of 32 µM (15 µg/mL). This is 55-fold higher than the preliminary unbound or free human C_{max} at 200 mg with 95.4% protein binding, 0.27 µg/mL, in humans.

LOXO-305: Effects on the Cardiovascular System in the Naïve Conscious Dog using Radiotelemetry Following Oral Administration (LOXO-305-SPHARM-002)

In this GLP study, dogs were administered with pirtobrutinib at 5, 20 or 60 mg/Kg on test sessions 1-4 (once weekly). Sessions 5 and 6 were for TK sampling, with no CV assessment. Endpoints and parameters recorded in this study were: haemodynamic data (heart rate and systolic, diastolic and mean arterial pressures); body temperature; and ECG parameters (PR, RR, QRS, QT, QTc). Pirtobrutinib had no effect on any parameter or endpoints assessed in this study. The exposure at the NOEL for cardiovascular effects in this study was approximately 6.5-fold higher than preliminary human exposure at 200 mg QD (**Table 11**, see also **Table 15** in pharmacokinetics section).

Table 3. Summary of the mean pirtobrutinib toxicokinetic parameters in male dog plasma

Dose Level (mg/kg)	Total C_{max} (ng/mL)	Unbound C_{max} (ng/mL)	C_{max} Exposure Multiple[a]	AUC_{0-24} (ng·h/mL)
20	2980	524	1.9x	37000
60	10000	1760	6.5x	139000

[a] Exposure multiple is unbound dog C_{max} divided by preliminary human unbound C_{max} at 200 mg of 270 ng/mL. Dog protein binding = 82.4% and human protein binding is 95.4%

2.4.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies of pirtobrutinib were submitted.

2.4.2. Pharmacokinetics

Absorption

Single Dose Studies

Rat

Two PK studies were conducted in rats following oral administration of a single dose of pirtobrutinib (**Table *4***and **Table *5***.

Table 4. Pharmacokinetic parameters for radioactivity and pirtobrutinib in male and female rats (po) of 35 mg/kg [^{14}C] pirtobrutinib in solution (LOXO-305-DMPK-035)

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

Table 5. Plasma pharmacokinetics after single 1 mg/kg iv dose of pirtobrutinib in male and female rats (LOXO-305-DMPK-005)

	Mean ± SD PK parameters	
Sex:	M	F
C_0 (ng/mL)	637 ± 206	1050 ± 114
AUC_{0-t} (ng•h/mL)	557 ± 132	3340 ± 1100
AUC_{0-inf} (ng•h/mL)	613 ± 143	3540 ± 1050
Cl (L/h/kg)	1.71 ± 0.433	0.305 ± 0.0966
V_d (L/kg)	4.98 ± 0.807	2.23 ± 1.27
$t_{1/2}$ (h)	2.16 ± 0.745	4.83 ± 1.21

Dog

Pirtobrutinib tablets were administered orally to dogs to determine the impact of food on the PK of pirtobrutinib (**Table *6***).

Table 6. PK Parameters in fed and fasted male and female beagle dogs following single oral administration of 3 x 100 mg (~30 mg/kg) pirtobrutinib tablets (LOXO-305-DMPK-025)

Feeding State	Fed	Fasted
Groups	1 and 4	2 and 3
Sex	4M/4F	4M/4F
C_{max} (ng/mL) [a]	16500 ± 8020	12900 ± 3400
T_{max} (h) [b]	1.00 (0.500-4.00)	2.00 (1.00-4.00)
AUC_{0-t} (ng·h/mL) [a]	133000 ± 27100	136000 ± 49300
	Ratio Fed: Fasted	
C_{max}	1.4 ± 0.9	
AUC_{0-t}	1.1 ± 0.5	

In study LOXO-305-SPHARM-002, crystalline pirtobrutinib was administered by PO gavage. The results are shown in table below (**Table *7***, see also **Table *3*** in Safety Pharmacology section).

Table 7. Toxicokinetics of pirtobrutinib after a single oral dose of 20 or 60 mg/kg of pirtobrutinib in male dogs (LOXO-305-SPHARM-002)

	Mean ± SD TK parameters	
Dose (mg/kg)	20[a]	60[b]
C_{max} (ng/mL)	2980 ± 588	10000 ± 1540
AUC_{0-24h} (ng•hr/mL)	37000 ± 5870	139000 ± 17900
AUC_{0-inf} (ng•hr/mL)	48100 ± 8620	136000 ± NA
T_{max} (h)[c]	2.00	6.00

Multiple Dose Studies

Rat

In study LOXO-305-DMPK-013, pirtobrutinib was administered by PO gavage to Sprague Dawley rat, two times on Day 1 (doses 1 and 2) and once (dose 3) on Day 2 (12 hours after dose 2) (**Table *8***).

Table 8. PK Parameters of pirtobrutinib after the third dose of oral administration to sprague dawley rats as a suspension (LOXO-305-DMPK-013)

Sex	Day	Dose (mg/kg/dose)	C_{max} (ng/mL)	AUC_{0-12h} (ng·h/mL)
M	2	500	2280	20600
	2	1000	1380	12500
F	2	500	27100	238000
	2	1000	22400	205000

Dog

In study LOXO-305-DMPK-020-A2, on Day 1, each dog received a single iv dose of 2 mg/kg pirtobrutinib. After a two-week washout, on Day 15 and Day 16, each dog received 2 po doses of 20 mg/kg pirtobrutinib each day, 12 hours apart On Day 17, each dog received a single iv dose of 2 mg/kg pirtobrutinib. Results are shown in **Table *9***).

Table 9. PK of pirtobrutinib following a single iv dose of 2 mg/kg deuterium-labelled pirtobrutinib or multiple oral doses of 20 mg/kg pirtobrutinib followed by iv administration of deuterium-labelled pirtobrutinib in male dogs (LOXO-305-DMPK-020-A2)

	PK parameters (Mean ± SD)			
Study Day	1	15	16	17
Study Drug Administered	Deuterium-labeled pirtobrutinib	pirtobrutinib	pirtobrutinib	Deuterium-labeled pirtobrutinib
Dose number for PK sampling	1	1[a]	3[a]	5[a]
Route	IV	Oral	Oral	IV
C_{max} (ng/mL)	NA	1920 ± 556	6770 ± 625	NA
C_0 (ng/mL)	1420 ± 137	NA	NA	1450 ± 113
AUC_{0-t} (ng•h/mL)	10000 ± 2430	11900 ± 4200 [b]	35500 ± 6430 [b]	11000 ± 3250
AUC_{0-inf} (ng•h/mL)	10700 ± 2400	NA	NA	11300 ± 3210
T_{max} (h)[c]	NA	2.00	1.00	NA
Cl (L/h/kg)	0.195 ± 0.0494	NA	NA	0.186 ± 0.0455
V_d (L/kg)	1.98 ± 0.476	NA	NA	1.83 ± 0.499
$t_{1/2}$ (h)	7.20 ± 1.69	NA	NA	7.17 ± 2.59

Toxicokinetics

The following toxicokinetics studies were submitted:

- **LOXO-305-TOX-003**: A 14-day dose range finding study Sprague Dawley rats were administered crystalline pirtobrutinib twice daily by PO gavage.
- **LOXO-305-TOX-007:** Pirtobrutinib was administered to Sprague Dawley rats at via oral gavage for 28 days.
- **LOXO-305-TOX-018**: Pirtobrutinib was administered to Sprague Dawley rats via oral gavage for 28 days.
- **LOXO-305-TOX-019**: in an enhanced pilot embryo-foetal development study, female Sprague Dawley rats were administered crystalline pirtobrutinib twice daily by PO gavage.

Results from these studies are summarised in **Table *10***

Table 10. Overview of pirtobrutinib toxicokinetics

	$AUC_{0\text{-}24}$ (ng·h/mL)				C_{max} (ng/mL)			
	Rat/Sprague Dawley		Dog/Beagle		Rat/Sprague Dawley		Dog/Beagle	
Dose (mg/kg BID)	Male	Female	Male	Female	Male	Female	Male	Female
0.5	-	-	2270[a]	2400[a]	-	-	258[a]	273[a]
2.5	-	-	13800[a]	17300[a]	-	-	1400[a]	2060[a]
5	-	-	14200[b] 32200[a]	18400[b] 44900[a]	-	-	935[b] 3950[a]	1210[b] 3900[a]
10	-	-	30500[b]	24900[b]	-	-	2010[b]	1560[b]
15	-	-	17300[c]	16700[c]	-	-	1560[c]	1470[c]
20	-	80700[d]	-	-	-	5410[d]	-	-
25	-	40200[e]	-	-	-	2360[e]	-	-
30	-	-	86200[f]	58800[f]	-	-	5560[f]	4010[f]
50	19500[d] 19100[g]	-	-	-	1550[d] 1380[g]	-	-	-
60	-	172000[d] 126000[g]	-	-	-	9680[d] 7980[g]	-	-
70	-	-	51300[c]	36000[c]	-	-	4080[c]	4090[c]
75	-	210000[h] 106000[e]	-	-	-	11300[h] 7030[e]	-	-
90	-	-	119000[f]	124000[f]	-	-	7320[f]	6590[f]
120	-	-	79400[c]	36400[c]	-	-	5390[c]	3940[c]
150	38600[d]	-	-	-	2420[d]	-	-	-
175	-	340000[h] 300000[d]	-	-	-	16200[h] 17500[d]	-	-
250	36900[h]	-	-	-	2910[h]	-	-	-
300	-	369000[g]	-	-	-	20800[g]	-	-
375	-	381000[h] 272000[e]	-	-	-	20400[h] 15900[e]	-	-
418	48200[d]	-	-	-	2820[d]	-	-	-
500	50200[h] 63000[g]	331000[e]	-	-	2640[h] 4990[g]	21600[e]	-	-
1000	59200[h]	-	-	-	3600[h]	-	-	-

Abbreviations: AUC = area under the plasma concentration vs. time curve, BID = twice daily, C_{max} = maximum concentration in plasma, GLP = Good Laboratory Practice

[a] GLP 3-month dog repeat-dose report, LOXO-305-TOX-017, Day 105

[b] GLP 28-day dog repeat-dose report, LOXO-305-TOX-008, Day 28

[c] Non-GLP 14-day dog repeat-dose report, LOXO-305-TOX-004, Day 14

[d] GLP 28-day rat repeat-dose report, LOXO-305-TOX-007, Day 28

[e] Pregnant rats in GLP rat enhanced embryofetal development report, LOXO-305-TOX-019, Day 17 postcoitum

[f] GLP 28-day dog repeat-dose report, LOXO-305-TOX-008, Day 4

[g] GLP 3-month rat repeat-dose report, LOXO-305-TOX-018, Day 105

[h] Non-GLP 14-day rat repeat-dose report, LOXO-305-TOX-003, Day 14

Interspecies comparison

The applicant presented a comparative table with the exposure multiples between the recommended clinical dose of 200 mg QD and relevant effect levels in rats and dogs treated for 3 months (**Table *11***).

Table 11. Exposure multiples for oral administration of pirtobrutinib

	Dose	Exposure AUC_{0-24}(ng·h/mL)	Exposure Multiple[a]
Human			
Recommended dose	200 mg QD	91000[b]	
Rat			
NOAEL (M)[c]	50 mg/kg BID	19100[e]	< 1
MTD (M)[c]	500 mg/kg BID	63000[e]	< 1
NOAEL/MTD (F)[c]	300 mg/kg BID	369000[e]	4.1x
Pregnant rats			
Fetal effects NOEL[i]	75 mg/kg BID	106000[j]	1.2x
Fetal effects LOEL[i]	375 mg/kg BID	272000[j]	3.0x
Dog			
NOAEL[d]	2.5 mg/kg BID	15600[f]	< 1
MTD[d]	5 mg/kg BID	38600[f]	< 1
Exceeded MTD[g]	30 mg/kg BID	72500[h]	< 1

a Exposure multiple is the exposure in animals divided by exposure in humans.
b Exploratory population PK. This preliminary analysis was based on 99 patients in Study 18001 who received 200 mg QD at the time of data cutoff (30 September 2020) using noncompartmental methods with nominal PK collection times
c NOAEL and MTD determined in a 3-month repeat dose toxicity study in rats (Report LOXO-305-TOX-018).
d NOAEL and MTD determined in a 3-month repeat dose toxicity study in dogs (Report LOXO-305-TOX-017).
e Exposure on Day 105.
f Average of male and female exposure on Day 105.
g In the 28-day dog study (Report LOXO-305-TOX-008), dogs did not tolerate dose levels as low as 30 mg/kg BID.
h Average of male and female exposure in Day 4.
i NOEL and LOEL determined in an embryofetal development study in rats (Report LOXO-305-TOX-019).
j Exposure on Day 17 postcoitum.

Distribution

Tissue Distribution

Male pigmented (Long Evans) rats were analysed by Quantitative Whole Body Autoradiography (QWBA) after receiving radiolabelled pirtobrutinib, 35 mg/kg dose containing 200 µCi/kg of radioactivity (LOXO-305-DMPK-035). Animals were analysed for 168 hours post dose.

Pirtobrutinib-associated radioactivity was highly distributed. The highest radioactivity concentrations were measured at 1 or 2 hours postdose for most of the tissues. The tissues exposed to the highest calculated radiation were oesophagus, gastrointestinal (GI) organs, urinary bladder, epididymis, liver, uveal tract, pigmented skin, and testis.

The radioactivity declined over time to below the lower limit of quantitation (< 178 ng-eq) by 168 hours post dose for all tissues but the uveal tract and liver (294 and 262 ng-eq, respectively at 168 hours), with a calculated t1/2 of 66.4 and 56.1 hours, respectively. 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.

Protein binding

Plasma protein binding (PPB) values for rat and dog plasma were determined in study LOXO-305-DMPK-016. The results are shown in **Table *12***.

Table 12. Plasma Protein binding in rat and dog (LOXO-305-DMPK-016)

	% Pirtobrutinib bound (mean ± SD, N = 3)	
Concentration tested	Rat Plasma	Dog Plasma
50 ng/mL	86.8 ± 1.31	82.2 ± 0.907
500 ng/mL	87.6 ± 0.153	83.0 ± 0.513
5000 ng/mL	86.9 ± 0.153	82.0 ± 0.600

Red Blood Cell Partitioning

The B:P ratio of pirtobrutinib was measured in rat and dog blood (LOXO-305-DMPK-009), resulting in 0.84 and 0.88, respectively.

In study LOXO-305-DMPK-035, B:P ratio of total radioactivity was measured. For male rats the B:P ratio ranged from 0.595 to 0.774 over the 72-hour time course. For female rats (N = 3 rats/time point) the B:P ratios were ranged from 0.701 to 0.815. The B:P ratio did not show time dependence.

Placental transfer studies were not submitted.

Metabolism

In vitro

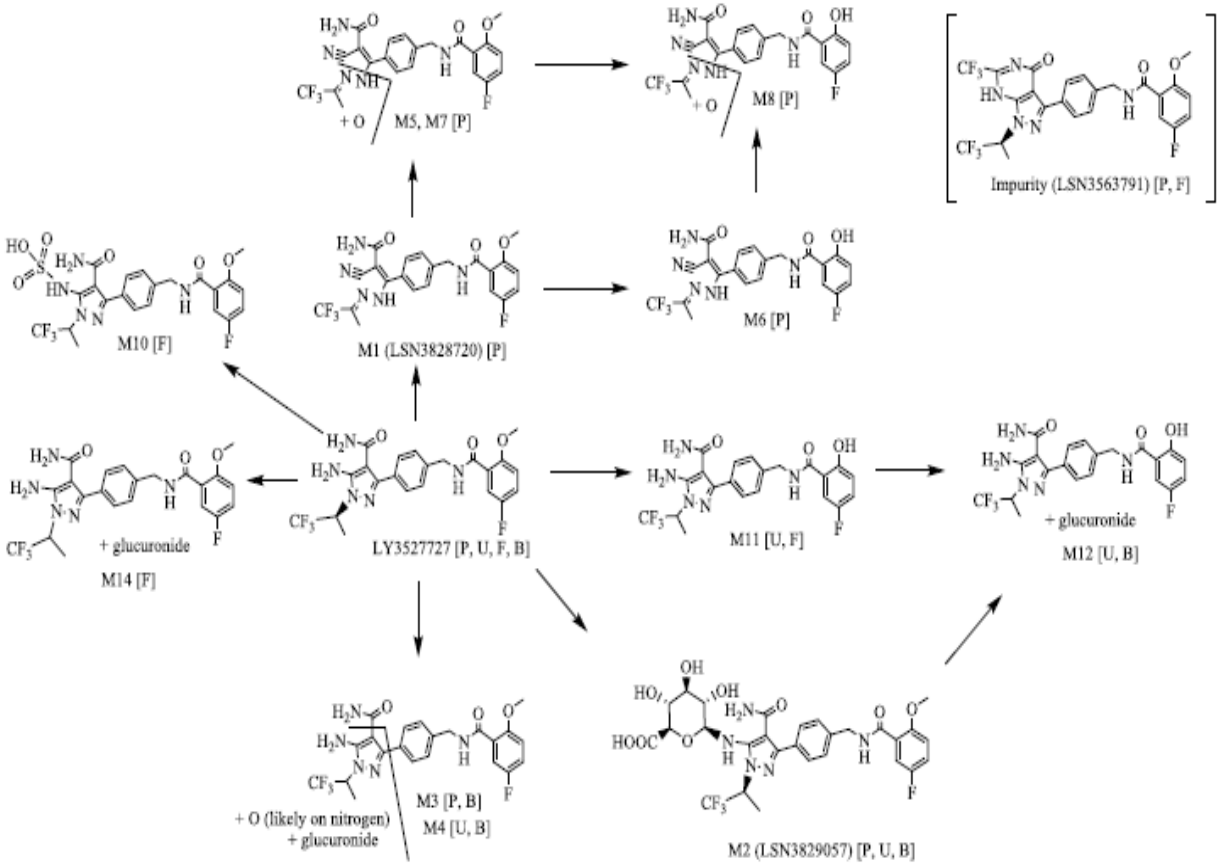
In vitro metabolism of pirtobrutinib was investigated in human, rat (Sprague Dawley), dog (Beagle) and non-human primate (Cynomolgus) co-cultured hepatocytes (LOXO-305-DMPK-037).

In humans, the *in vitro* metabolism of pirtobrutinib showed metabolic pathways consistent with hydroxylation (metabolites E and H), N-glucuronidation (A), O-demethylation followed by glucuronidation (C), and hydroxylation followed by glucuronidation (B). The *in vitro* human metabolites were detected in rat and/or dog. Addition of the pan-CYP450 inhibitor ABT to the incubations showed significant decrease in the formation of metabolites B, C, E and H indicating that their formation is P450 dependent.

In vivo

In Sprague Dawley rats, a dedicated radiolabelled study was conducted after a single PO dose of 35 mg/kg (approximately 100 µCi/kg) of [^{14}C]pirtobrutinib in bile-duct intact (intact) and bile-duct cannulated (BDC) animals (LOXO-305-DMPK-049). Results are shown in **Figure 6**.

Figure 6. Proposed Metabolic Pathway for Pirtobrutinib in Rats



In time averaged plasma AUC0-24h pools from intact male rats, a total of eight metabolites and one process impurity were quantified and identified.

In the AUC0-24h male sample, metabolites M1 and M5 concentrations were greater than pirtobrutinib, each individually representing 33.9% (M1), 20.1% (M5) and 17.9% (pirtobrutinib) of Total Radioactivity (TRA). The remaining plasma metabolites were considered minor each individually representing ≤ 3.7% of the TRA.

In the intact female rat plasma time averaged AUC0-24h pool, a total of three metabolites and one process impurity were quantified and identified.

In the AUC0-24h female sample, pirtobrutinib was the predominant component representing 74.2% of the TRA, while each of the remaining metabolites were considered minor each individually representing ≤ 5.6% of the TRA.

In male and female intact and BDC rats, urinary excretion was low (≤ 3%). Pirtobrutinib and 4 trace metabolites were found in urine (each representing ≤ 0.6% of dose). In male and female intact rats the majority of radioactivity was recovered in faeces (≥ 93%). From BDC rats the majority of radioactivity was recovered in bile and faeces with 52% and 39% of the dose recovered in bile, and 41% and 54% of the dose recovered in faeces from male and female rats, respectively. In rat faeces from intact male and female rats, pirtobrutinib was the largest component observed (57.7% M and 72.9% F). A sulfamate M10 (12.3% M, 1.8% F), O-desmethyl pirtobrutinib (M11, 5.7% M, 10.3% F) and process impurity LSN3563791 (3.4% M, 3.9% F) were identified in faeces of both males and females, while a direct glucuronide conjugate M14 (5.4% M) was identified only in male. In BDC rat

faeces, pirtobrutinib was the major component (34.8% M, 47.3% F), while two metabolites M10 (3.5% M, 0.7% F) and M11 (0.9% M, 2.9% F) and process impurity LSN3563791 were minor. In bile from the BDC rats, pirtobrutinib (14.8% M, 9.7% F), N-glucuronide M2 (LSN3829057, 3.8% M, 5.9% F), mono-oxy glucuronides M3 (10.5% M, 6.2% F) and M4 (16.8% M, 11.8% F) and O-desmethyl glucuronide M12 (1.3% M, 1.5% F) were identified.

Relative Exposure of Metabolites in Rat, Dog, and Human

In human plasma only three minor metabolites (M1, M2, and M4) were identified/quantified in the exploratory human plasma study (LOXO-305-DMPK-039), and in the [^{14}C]pirtobrutinib study (LOXO-BTK-20007). In the human [^{14}C]pirtobrutinib study (LOXO-BTK-20007) the mean percentages of pirtobrutinib, M1, M2 and M4 relative to total circulating radioactivity across subjects were 86.7%, 7.8%, 3.3% and 2.3%, respectively. After administration of [^{14}C]pirtobrutinib to rat (LOXO-305-DMPK-049) all three human circulating metabolites were observed.

In study LOXO-305-DMPK-052, human, rat and dog plasma were evaluated for the relative steady state exposure to pirtobrutinib metabolites M1, M2 and M4.

The relative exposure multiples for metabolite M1 were 17.97 and 18.79 in male and female rats and 0.05 and 0.04 in male and female dogs, respectively. Relative exposure multiples for M2 were 0.91 and 2.28 for male and female rats and were 0.23, and 0.35 for male and female dogs, respectively. Relative exposure multiples for M4 were 0.57 and 0.05 in male and female rats, respectively and M4 was below limit of detection in male and female dogs. Therefore, at relevant toxicological doses at steady state, the relative exposure multiples for M1 in rat provides adequate metabolite coverage. Since metabolites M2 and M4 were < 10% of total circulating radioactivity and are glucuronides, there is no need for further evaluation.

Excretion

The excretion and mass balance of pirtobrutinib was evaluated in male and female Sprague Dawley rats (LOXO-305-DMPK-035). In intact rats, approximately 96% of the administered dose was excreted in the first 48 hours post dose. The majority of the radioactivity was recovered in faeces, with a mean of 95.7% and 94.9% for male and female rats, respectively, excreted through 120 hours post dose. Urinary excretion of administered radioactivity was a mean of 1.72 and 3.64% for male and female rats, respectively, through 120 hours post dose. The mean overall recovery was 98.0 and 99.3% of the administered dose for male and female rats, respectively.

In BDC rats, the mean total recovery of radioactivity was 96.2 and 97.0%, for male and female rats, respectively, of which approximately 94% (males) and 96% (females) was excreted in the first 48 hours post dose. Bile, urine, and faeces accounted for 52.2, 1.40, and 41.6% of the administered dose for males, respectively, and 39.4, 3.04, and 53.7% for females, respectively, through 120 hours post dose.

The renal excretion of pirtobrutinib was also studied after IV administration (LOXO-305-DMPK-005). Pirtobrutinib was administered intravenously at 1 mg/kg in male and female Sprague Dawley rats. Urine was collected for 24 hours. Pirtobrutinib in the urine was measured by LC-MS/MS. From 0-8 hours, < 0.2% of the pirtobrutinib dose was eliminated in urine. After 24 hours the percent of dose in the urine was less than 0.6% for both male and female rats.

2.4.3. Toxicology

2.4.3.1. Single dose toxicity

No single-dose toxicity studies of pirtobrutinib were submitted. The applicant estimated the dose levels tolerated for each species (rat and dog) based on the clinical symptoms reported in the repeat-dose toxicity studies.

Female rats tolerated 375 mg/kg BID for 14 days in LOXO-305-TOX-003, so it was estimated that the rat LD_{50} is ≥ 375 mg/kg BID. In the case of dogs, they tolerated 35 mg/kg BID for 14-days (LOXO-305-TOX-004), so dog LD_{50} value is ≥ 35 mg/kg BID.

2.4.3.2. Repeat dose toxicity

Designs of the studies included here are described in the pharmacokinetics section of this report.

A 14-Day Repeated-Dose Toxicity Study in Sprague-Dawley Rat (LOXO-305-TOX-003, non-GLP):

Pirtobrutinib effects were limited to minor decreases in body weight, lymphoid organ effects, bone marrow effects, and rat-specific pancreatic findings. The NOAEL was 500 mg/kg BID in males, due to adverse bone marrow effects at 1000 mg/kg BID, and 75 mg/kg BID in females, due to adverse bone marrow effects at 175 mg/kg BID.

A 28-Day Toxicity and Toxicokinetic Study of LOXO-305 in Sprague-Dawley Rats with a 28 Day Recovery Phase (LOXO-305-TOX-007, GLP)

.Pirtobrutinib effects were limited to minor decreases in body weight, minor lymphoid organ effects, and rat-specific pancreatic findings. Due to the mild severity of findings and the lack of impact on the health and well-being of the treated animals, effects at all doses were non-adverse. Thus, the NOAEL is 500 mg/kg BID in males and 175 mg/kg BID in females.

A 3-Month Toxicity and Toxicokinetic Study of LY3527727 Administered by Oral Gavage Twice Daily to Rats (LOXO-305-TOX-018, GLP)

In this GLP study, pirtobrutinib was administered to Sprague Dawley rats at 0, 50, or 500 mg/kg in males or 0, 60, 300 mg/kg in females BID via oral gavage for 15 weeks. Exposures generally increased with increasing dose in males and females. Despite lower dose levels, exposure was generally higher in female rats compared to male rats. Pirtobrutinib effects were limited to minor decreases in body weight, lymphoid organ and immune system effects, and rat-specific pancreatic findings. Lymphoid organ effects consisted of decreased cellularity, accompanied by a relative decrease in B lymphocytes and a decrease or elimination of T-cell dependent antibody response (TDAR). These effects were considered likely related to the pharmacologic mechanism of action of pirtobrutinib. The NOAEL was 50 mg/kg BID in males, due to adverse effects on the TDAR response at 500 mg/kg BID, and 300 mg/kg BID in females, the highest dose tested in females.

A 14-Day Oral Dose Range-Finding Tolerability and Toxicokinetic Study of LOXO-305 in Beagle Dogs (LOX 305-TOX-004, non-GLP)

In this study dogs did not tolerate 60/120 mg/kg BID.

Pirtobrutinib effects were observed in stomach, bone marrow, and lymphoid organs. The NOAEL was 35/70 mg/kg BID, due to mortality and adverse bone marrow effects at 60/120 mg/kg BID.

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-TOX-008, GLP)

Dogs did not tolerate 90/60 mg/kg BID or 30 mg/kg BID. The 90/60 mg/kg BID group was euthanised on Day 13 (hypoactivity, dehydration, elevated body temperature, mucoid or red faeces, and decreases in circulating blood cells, particularly neutrophils). The 30 mg/kg BID group (hypoactivity, recumbency, non-formed faeces, vomitus and elevated temperature.) was lowered to 10 mg/kg BID, necessitating the lowering of the 10 mg/kg BID group to 5 mg/kg BID. There were no body weight effects observed in the low and mid dose groups, but a decreased body weight gain was observed in high dose animals.

Pirtobrutinib effects were observed in bone marrow, lymphoid organs, gastrointestinal tract, and lungs. All findings were reversible. The NOAEL was 10/5 mg/kg BID, due to adverse bone marrow, gastrointestinal and lung effects at ≥ 30/10 mg/kg BID.

A 3 Month Toxicity and Toxicokinetic Study of LY3527727/HPMC-AS-M as a Spray Dried Dispersion Administered by Twice Daily Oral Gavage to Dogs (LOXO-305-TOX-017, GLP)

Pirtobrutinib effects were observed in the cornea and lymphoid organs. Minimal to mild corneal lesions were observed in two high dose dogs at systemic exposure below human exposure at 200 mg QD. In addition, pirtobrutinib caused a decrease in B lymphocytes and a decrease in the TDAR following KLH immunisation.

The NOAEL was 2.5 mg/kg BID, due to adverse eye effects at 5 mg/kg BID. This dose level corresponds to a mean sex-combined Cmax value of 1.73 µg/mL, and an AUC(0-24) value of 15.6 hr*µg/mL, on Day 105.

2.4.3.3. Genotoxicity

Bacterial Reverse Mutation Assay (LOXO-305-TOX-009, GLP)

In the Ames test, pirtobrutinib did not induce mutation in four histidine-requiring strains of Salmonella typhimurium, and one tryptophan-requiring strain of Escherichia coli in the absence or in the presence of a rat liver metabolic-activation system (S9).

REDX08608: *In Vitro* Microwell Micronucleus Screening Assay in Chinese Hamster Ovary Cells (LOXO-305-TOX-013, non-GLP)

Pirtobrutinib was negative for the induction of micronuclei under the conditions of the study. It did not induce a significant increase in the frequency of bi-nucleated cells with micronuclei at any dose level when compared with the concurrent solvent control group in S9-activated or non-activated 3-hour treatment series, but a dose-related increase (Cochran-Armitage analysis, $p \leq 0.05$) was observed in the non-activated 3-hour treatment series. In the non-activated 24-hour treatment series, a significant increase in the frequency of MN-BN cells was observed at 5 µg/mL and a dose-related increase in micronucleus frequency was identified by Cochran-Armitage analysis ($p \leq 0.05$). However, the increase was within the range of the historical negative control data (0.72% to 2.05%). Thus, the significant increase and the dose-related increase in the frequency of MN-BN cells were considered not to be a positive signal of micronucleus induction.

In Vitro Mammalian Cell Micronucleus Assay in HPBL (LOXO-305-TOX-010, GLP)

Pirtobrutinib was positive for the induction of micronuclei in the absence and presence of the exogenous metabolic activation system (**Table *13***).

Table 13. Micronucleus staining frequency in hpbl exposed to pirtobrutinib

Duration: (treatment/harvest)	4h/24h		4h/24h		24h/24h	
Metabolic (S9) Activation:	-		+		-	
Treatment Group	µg/mL[a]	%[b]	µg/mL[a]	%[b]	µg/mL[a]	%[b]
Vehicle control	0	0.4	0	0.5	0	0.35
Pirtobrutinib Low Dose	50	0.85*	50	0.55	5	1.5**
Pirtobrutinib Mid Dose	120	1.3**	100	1.2**	12	4.0**
Pirtobrutinib High Dose	150	3.5**	225	3.3**	16	3.7**

a Concentration of pirtobrutinib that cells were exposed to

b Percentage of micronucleated binucleated cells per dose

LOXO-305: *In Vitro* Human Lymphocyte Micronucleus Assay with Mechanistic Fluorescent in situ Hybridisation (FISH) Analysis of Micronuclei (LOXO-305-TOX-014, GLP)

Pirtobrutinib was positive for the induction of micronuclei under the conditions of this study at concentrations ≥ 12 µg/mL. Based on the high level of centromere-positive staining, the micronuclei were induced via a predominantly aneugenic mechanism (chromosome loss).

In addition, the applicant estimated a presented a safe exposure limit for the potential aneugenic effects of pirtobrutinib. It was based on the NOEL values obtained in the micronuclei assays (**Table *14***).

Table 14. Summary of micronuclei induction effect and no-effect levels for pirtobrutinib

Study	Report	Micronuclei-induction NOEL	Micronuclei-induction LOEL	Margin of Safety[a]
In-vitro micronucleus study in HPBL	LOXO-305-TOX-010	ND	5 µg/mL	--
In-vitro micronucleus study with centromere staining in HPBL	LOXO-305-TOX-014	5 µg/mL	12 µg/mL	19x
In-vitro micronucleus study in CHO cells	LOXO-305-TOX-013	5 µg/mL	ND	19x
In-vivo (rat) micronucleus study	LOXO-305-TOX-016	3.3 µg/mL (2000 mg/kg, unbound)	ND	12x

a Micronulei-induction NOEL divided by preliminary human unbound or free human Cmax at 200 mg QD: 0.27 µg/mL. Protein binding in humans is 95.4%

In Vivo Mammalian Erythrocyte Micronucleus Assay in Rats (LOXO-305-TOX-016, GLP)

Pirtobrutinib was tested for the ability to induce micronuclei in rat bone marrow. Rats were given a single dose of vehicle, 0.5% (w/v) hydroxypropyl methylcellulose in deionised water, or 250, 500, 1000 or 2000 mg/kg pirtobrutinib by oral gavage. Pirtobrutinib was negative for the induction of micronuclei up to the limit dose of 2000 mg/kg (data not shown).

2.4.3.4. Carcinogenicity

No carcinogenicity studies with pirtobrutinib were submitted as these studies are not warranted for advanced cancer indications (ICH S9).

2.4.3.5. Reproductive and developmental toxicity

An Enhanced Pilot Embryo-fetal Development Study of LY3527727 Administered by Oral Gavage Twice Daily to Rats (LOXO-305-TOX-019, GLP)

Female rats were given pirtobrutinib by twice daily oral gavage at doses of 25, 75, 375 and 500 mg/kg BID on Days 6 to 17 postcoitum.

There were no adverse maternal effects at any dose. Embryolethality was evidenced at 1000 mg/kg/day by higher numbers of resorptions and a higher post-implantation loss. Adverse effects on embryo-foetal development were evidenced at ≥ 750 mg/kg/day by foetal dysmorphology (malformations and variations) and effects on foetal growth (foetotoxicity). Based on these results, the maternal NOAEL was considered to be 1000 mg/kg/day (maternal Cmax 21.6 µg/mL and AUC(0-24) 331 hr*µg/mL on Day 17 pc), and the embryo-foetal development NOAEL was considered to be 150 mg/kg/day (maternal Cmax 7.03 µg/mL and AUC(0-24) 106 hr*µg/mL on Day 17 pc).

2.4.3.6. Toxicokinetic data

See the pharmacokinetics section.

2.4.3.7. Local tolerance

No local tolerance studies were conducted with pirtobrutinib, given the oral route of delivery.

2.4.3.8. Other toxicity studies

A neutral red uptake phototoxicity assay in BALB/c mouse 3T3 fibroblasts was used to assess the phototoxicity of pirtobrutinib ((LOXO-305-TOX-005, GLP). Pirtobrutinib did not have phototoxic potential in this assay.

2.4.3.9. Studies on impurities

Three impurities were specified at limits above the ICH Q3A and Q3B qualification threshold:

- LSN3804363 (enantiomer) in drug substance: 1%

- Sum of LSN3849804 and LSN3849825 in drug product: 1.3%

LSN3804363 (enantiomer) was qualified in the 28-day repeat-dose studies of pirtobrutinib at 1% in rats and dogs. LSN3849804 and LSN3849825 were individually qualified at 1.3% in a 14-day repeat-dose study in rats (Report LOXO-305-TOX-020).

Impurity LSN3804363 is an enantiomer of pirtobrutinib. As an enantiomer, the applicant notes that LSN3804363 is expected to behave very similarly to pirtobrutinib in genotoxicity studies. Therefore, LSN3804363 was not tested in an Ames study, but is expected to be negative, as pirtobrutinib was negative in an Ames study. In addition, the risk of induction of chromosome aberrations by LSN3804363 is expected to be very similar to the risk from pirtobrutinib.

Impurities LSN3849804 and LSN3849825 were negative in Ames tests. While the risk of the induction of chromosome aberrations for LSN3849804 and LSN3849825 is unknown, the additional risk of chromosome aberrations from low exposures to LSN3849804 and LSN3849825 is expected to be negligible relative to the risk from exposure to pirtobrutinib. Therefore, studies assessing chromosome aberration induced by LSN3849804 and LSN3849825 are not warranted.

2.4.4. Ecotoxicity/environmental risk assessment

Table 15. Summary of main study results

Substance (INN/Invented Name): pirtobrutinib			
CAS-number (if available): 2101700-15-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	pH 5 = 2.965 pH 7 = 2.850 pH 9 = 2.757	log K_{ow} <4.5 No bioaccumulation potential
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD 107	pH 5 = 2.965 pH 7 = 2.850 pH 9 = 2.757	not B
Persistence	OECD 308 DT_{50} at 12°C	Sediments from two different river systems: - DT_{50} water:148.7 d - DT_{50} whole system: 40, 393 d	vP
Toxicity	CMR	Toxicity to reproduction observed	T
PBT-statement:	Pirtobrutinib is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	0.0094	µg/L	< 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Soil: K_{Foc} = 731 L·kg^{-1} (soil 1) K_{Foc} = 720 L·kg^{-1} (soil 2) K_{Foc} = 414 L·kg^{-1} (soil 3) K_{Foc} = 768 L·kg^{-1} (soil 4) Sludge: K_{oc} = 114 L·kg^{-1} (sludge 1) K_{oc} = 234 L·kg^{-1} (sludge 2) K_{oc} = 197 L·kg^{-1} (sludge 3)	Soil: average K_{Foc} used in ERA, 658 L·kg^{-1}
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 10.8 d (1), 69.7 d* (2) $DT_{50, sediment}$ = 36.7 d (1), nd (2) $DT_{50, system}$ = 18.7 d (1), 185 d (2) (1) = Tarnock (HOC) sediment, (2) = Ashpringtон (LOC) sediment % shifting to sediment = 25.4/41.6% % CO_2 = 0.1% (1), 0.6% (2) % NER = 20.5% (1),13.5% (2)	at 20°C. *DFOP, k2DT50, slow phase. Sediment from two different river systems evaluated. At day 14, (%parent + %NER), Sediment risk assessment triggered At test end At test end

		Transformation products >10% = YES, TP RRT 0.80: RT: 0.79-0.81, HPLC: 12.5% TP RRT 1.02: RT: 1.01-1.03, HPLC: 47.6%			Water, day 101 (2) Sediment, d 101 (1) TP RRT: 0.80: molecular formula: C14H13O3N4F3 TP RRT: 1.02: molecular formula: C21H19F4N5O3
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC	504	µg/L	Growth rate and yield
Daphnia sp. Reproduction Test/*Daphnia magna*	OECD 211	NOEC	1760	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	9950	µg/L	Total length, wet weight, dry weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000000	µg/L	Heterotrophic, nitrification and total respiration
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC NOEC	31 182	mg/kg	1.7% o.c. content Emergence ratio, male and female development rate, normalised to 10% organic carbon

2.4.5. Discussion on non-clinical aspects

Primary pharmacodynamic studies showed a potency for BTK inhibition by pirtobrutinib within the nanomolar range. This inhibition was characterised as a competitive inhibition of BTK wild type and C418 mutants, after a Lineweaver-Burk analysis. The main metabolite M1 showed no activity on BTK inhibition assays.

BTK occupancy was also determined. A 95% of receptor occupancy was reported at 300 nM (254 nM adjusted), which is comparable to the value obtained for unbound plasma Cmin (266 nM) at the 200 mg clinical dose. At 1000 nM (850 nM adjusted) in the *in vitro* assays with PBMCs, the value exhibited 1.5-fold the unbound plasma Cmax of 550 nM.

In vivo xenograft models demonstrated the growth inhibition of tumours after pirtobrutinib treatment.

No off-target action is expected, given that no significant results were obtained in the tested panels.

In terms of safety pharmacology assessment, potential cardiovascular effects were investigated in dedicated studies, in which pirtobrutinib had no effect on any parameter or endpoints assessed.

Respiratory and central nervous systems were analysed via endpoints incorporated to the repeat dose toxicity studies, in line with ICH S7A guideline. The applicant reported no effect on CNS and respiratory systems.

The absence of pharmacodynamic drug interactions studies with pirtobrutinib studies is acceptable as no issues were identified that warranted such studies.

For the pharmacokinetics characterisation, pirtobrutinib was investigated in rats and dogs after single or multiple doses. Different formulations were tested, with the highest bioavailability reported for the SDD formulation (amorphous form), which was selected for the repeat dose toxicity studies. The results of the toxicokinetic studies showed no accumulation after chronic administration of pirtobrutinib. In rats a greater exposure in females than in males was reported (also observed under feeding conditions), although no sex difference in dogs was noted in chronic studies.

Tissue distribution study informed for the extended distribution of the radiolabelled compound, especially in the uveal tract and liver. Likewise, pigmented skin was one of the tissues with the highest radio signal. Additional phototoxicity assay (BALB/c 3T3 mouse fibroblasts) concluded no phototoxic potential for pirtobrutinib. Other tissues, such as testis and brain showed rapid absorption (1 hour) followed by exposure declination at 24 hours post dose (below limit of quantification). Despite the exposure levels presented in the brain, the applicant reported no effect in CNS-endpoints and locomotor activity evaluated in the 1-month rat study.

PPB in rats and dogs was moderate, and blood-to-plasma ratio values were similar in rats and dogs.

The major excretion route (via bile) was faecal elimination, with limited urinary excretion.

The potential placental transfer and excretion in milk were not investigated in nonclinical species.

With regards to the toxicological profile of pirtobrutinib, general toxicity, genotoxicity, embryo-foetal development, phototoxicity and impurities studies have been presented. The duration of the chronic studies (up to 3 months) is in line with ICH guideline S9.

Key findings in rats consisted of lymphoid organ effects and decreases in B lymphocytes and other markers of immune system function. Lymphoid organ effects commonly consisted of decreases in size, weight, or cellularity of spleen, lymph nodes, and gut-associated lymphoid tissue. These findings were generally not adverse, as they did not impact the well-being of the animals and are consistent with the intended pharmacology of pirtobrutinib and the clinical safety profile.

Effects on immune system function consisted of a shift in the balance of T, B, and NK lymphocytes, largely due to a decrease in B lymphocytes, and decreased TDAR response to KLH, a foreign antigen. With the exception of the anti-KLH TDAR in male rats, these effects were not considered adverse due to the lack of effect on the overall well-being of the animals. While in most animals the TDAR was suppressed but not eliminated, the TDAR to KLH was eliminated in many male rats. Thus, the effect was considered adverse in male rats and is described in the product information as it was observed at 0.69-fold human exposure (at the recommended dose of 200 mg based on AUC).

Effects on lymphoid organs and immune system were also reported in dogs and similarly was attributed to the pharmacological action of pirtobrutinib. Gastrointestinal tract, lungs and eye were also affected in dog studies. 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 but is nevertheless described in the product information as it was observed at 0.42-fold human exposure (at the recommended dose of 200 mg based on AUC).

Pirtobrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay. Pirtobrutinib was aneugenic in two *in vitro* micronucleus assays using human peripheral blood lymphocytes. Pirtobrutinib had no effect in an *in vivo* rat bone marrow micronucleus assay at doses up to 2 000 mg/kg (single dose), which is approximately 11-fold higher exposure (considering unbound Cmax value in female animals) than human exposure at 200 mg. As a potential foetal harm when pirtobrutinib is administered to a pregnant woman cannot be excluded, women of childbearing potential should use an effective method

of contraception during treatment and for 5 weeks after the last dose of pirtobrutinib. Men are advised to use an effective method of contraception and not father a child during treatment and for 3 months after the last dose of pirtobrutinib.

The absence of carcinogenicity studies is in line with ICH guideline S9 and the assessment relied on the lack of hyperplastic changes in chronic studies (up to 3 months).

The studies in pregnant animals revealed similar exposures to non-pregnant animals.

For the reproductive toxicity assessment, the absence of fertility and PPND studies is in line with ICH guideline S9. Administration of pirtobrutinib to pregnant rats during organogenesis resulted in decreased foetal weight, embryo foetal mortality, and foetal malformations at maternal exposures 3.0-fold human exposure at the recommended dose of 200 mg based on AUC and is reflected in the product information (section 5.3).

The excretion of pirtobrutinib in milk has not been investigated but breastfeeding is not recommended (see clinical section).

The absence of local tolerance studies is acceptable, considering the intended route of administration. No additional immunotoxicity studies were considered necessary, considering the proposed mechanism of action for pirtobrutinib.

ERA

In the Phase I exposure assessment, the PECsurface water for pirtobrutinib 0.0094 µg/L almost met the EMA guideline action limit of 0.01 µg/L. Therefore, a Phase II Tier A assessment was triggered.

The Log KOW values were <4.5 at environmentally relevant pH-range and pirtobrutinib was thus not considered a PBT substance in the screening for persistence, bioaccumulation, and toxicity (PBT). As these log KOW values also were <3, a bioconcentration study in Tier B was not triggered.

The KOC for pirtobrutinib was below 10000 L/kg for sludge, not triggering the Tier B for the terrestrial compartment. Pirtobrutinib was primarily partitioned to the sediment layers. A Phase II Tier B extended effects on water sediment was therefore triggered.

Based on the PEC/PNEC ratios for microorganisms, surface water, ground water and sediment were below the trigger ratios, no further evaluation of pirtobrutinib was needed in Tier B.

Pirtobrutinib is not expected to pose a risk to the environment.

2.4.6. Conclusion on the non-clinical aspects

From a non-clinical point of view Jaypirca (pirtobrutinib) has been adequately characterised and is recommended for marketing authorisation.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Study identifier	Objectives	Treatment	Participants
Phase 1			
LOXO-BTK-2000**6** Completed	DDI study with itraconazole and rifampicin.	200 mg single dose Formulation: T2	Healthy male and female 24
LOXO-BTK-2000**7** Completed	Absorption, metabolism, and excretion and absolute bioavailability	Part 1: Single 200 mg dose containing [14C]-pirtobrutinib (approximately 200 µCi) Part 2: Single 200 mg oral dose followed by single IV dose of < 100 µg of [14C]-pirtobrutinib Formulation: T2	Healthy male 9 Part 1: 4 Part 2: 5
LOXO-BTK-2000**8** Completed	DDI study with midazolam	200 mg QD Formulation: T2 13 days	Healthy male and female 16
LOXO-BTK-2000**9** Completed	Food effect study	200 mg single dose Formulation: T2	Healthy male and female 20
LOXO-BTK-200**10** Completed	DDI study with caffeine (CYP, S-warfarin, and omeprazole)	200 mg QD Formulation: T2 14 days	Healthy male and female 16
LOXO-BTK-200**11** Completed	QTc study	Single dose Placebo or pirtobrutinib 900 mg; moxifloxacin 400 mg (positive control) Formulation: T2	Healthy male and female 31
LOXO-BTK-200**12** **Completed**	Hepatic impairment study	200 mg single dose Formulation: T2	Otherwise healthy 24

LOXO-BTK-200**13** Completed	Renal impairment study	200 mg single dose as 2x100 mg-tablet Formulation: T2	Otherwise healthy 24
LOXO-BTK-200**14** Completed	Effect of food and effect of a gastric pH change after multiple doses of a PPI.	200 mg single dose Formulation: T1	Healthy male and female 10
LOXO-BTK-200**16** Completed	DDI study with repaglinide	200 mg QD Formulation: T2 11 days	Healthy male and female 16
LOXO-BTK-200**17** Completed	Single ascending dose study	Cohort 1: 300 mg, SD Cohort 2: 600 mg, SD Cohort 3: 800 mg, SD Cohort 4: 900 mg, SD Formulation: T2	Healthy male and female 24
LOXO-BTK-200**21** Completed	DDI study with digoxin	200 mg QD Formulation: T2 9 days	Healthy male and female 16
J2N-MC-JZNW **Completed**	DDI study with rosuvastatin	200 mg QD Formulation: T2 12 days	Healthy male and female 32
Phase 1/2			
LOXO-BTK-18001 **BRUIN** Ongoing / interim report **PIVOTAL**	MTD, efficacy, safety, and PK	**Monotherapy:** **Phase 1:** 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg QD (determine recommended Phase 2 dose) Formulation: T1 and T2 **Phase 2:** 200 mg QD	Patients with histologically confirmed B-cell malignancy 725[e] (monotherapy) 25[e] (combination therapy)

		Formulation: T1 and T2 **Combination Phase 1b:** <u>Arm A:</u> 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; 6 cycles; total 6 doses Continuous 28-day cycles	
	PK samples: <u>Phase 1 dose escalation and Phase 1b:</u> Pre-dose, 1, 2, 4, 8 h C1D1 C1D8 (±2 days) C2D1 (±3 days) subset of patients: C4D1 (±3 days) <u>Phase 1 dose expansion and Phase 2:</u> Pre-dose C1D8 (±2 days) C4D1 (±3 days)		
Phase 2			
J2N-MC-JZNJ **Ongoing**	Efficacy, safety, and PK	200 mg QD Formulation: T2 Continuous 28-day cycles	Patients with histologically confirmed B-cell malignancy 74 randomised[a]
Phase 3			
LOXO-BTK-200**19** **Ongoing**	Safety and efficacy	<u>Arm A:</u> pirtobrutinib 200 mg QD Formulation: T2 <u>Arm B:</u> Investigator's choice of ibrutinib (560 mg QD), acalabrutinib (100 mg BID), or zanubrutinib (160 mg BID or 320 mg QD) Continuous 28-day cycles	R/R MCL patients 98 randomised[a]
LOXO-BTK-200**20** **Ongoing**	Safety and efficacy	<u>Arm A:</u> pirtobrutinib 200 mg QD Formulation: T2	R/R CLL/SLL patients pre-treated with covalent BTK inhibitor 63 randomised[a]

		Arm B: Investigator's choice of idelalisib (150 mg BID) plus rituximabb or bendamustine (70 mg/m2 IV) plus rituximab Continuous 28-day cycles	
LOXO-BTK-200**22** **Ongoing**	Safety and efficacy	Arm A: pirtobrutinib 200 mg QD, C1-C28, Formulation: T2 venetoclax 20-400 mg ramp-up, C4-C28, rituximab 375 mg/m2 C1; 500 mg/m2 C2-6 Arm B: venetoclax 20-400 mg ramp-up, C1-C25, rituximab 375 mg/m2 C2; 500 mg/m2 C3-7 Fixed duration (C1-28) 28-day cycles	Relapsed CLL/SLL patients who are venetoclax naïve. Most patients will be refractory to covalent BTK treatment 98 randomised[a]
LOXO-BTK-200**23** **Ongoing**	Safety and efficacy	Arm A: pirtobrutinib 200 mg QD Formulation: T2 Arm B: bendamustine (90 mg/m2 IV) and rituximab (375 mg/m2 C1; 500 mg/m2 C2-6) Continuous 28-day cycles	Untreated CLL/SLL patients 27 randomised[a]

ABT = 1-aminobenzotriazole; BA = bioavailability; BCRP = breast cancer resistance protein; BID = twice daily; BTK = Bruton tyrosine kinase; C = cycle; CLL = chronic lymphocytic leukemia; CSR = clinical study report; CYP = cytochrome P450; D = day; DDI = drug-drug interaction; HPLC/MS/MS = high performance liquid chromatography with tandem mass spectrometry; IV = intravenous; MTD = maximum tolerated dose; N/A = not applicable; PK = pharmacokinetics; OATP = organic anion transporting polypeptide; PPI = proton pump inhibitor; QD = once daily; QTc = corrected QT interval; RBC = red blood cell; R/R = Relapsed/ refractory SD = single dose; SLC = solute carrier; SLL = small lymphocytic lymphoma.

[a] Enrolment as of 06-May-2022

[b] Day 1 of Cycle 1, first dose of rituximab at 375 mg/m2 , next 4 infusions at 500 mg/m2 every 2 weeks (Q2W), next 3 infusions at 500 mg/m2 every 4 weeks (Q4W)

[c] Day 1 of Cycle 1, first dose of rituximab at 375 mg/m2 , next 5 infusions Day 1 of Cycle 2 through Cycle 6 at 500 mg/m2

[e] Enrolment as of 31-Jan-2022

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Two different tablet formulations were developed (T1 and T2). The T1 tablet formulation (25 mg and 100 mg tablets) was used in the majority of the Phase 1 portion of the pivotal Phase 1/2 study (LOXO-BTK-18001) and in study LOXO-BTK-20014. T2 of 25 mg and 100 mg tablet strengths have been used in the clinical programme and was used in all other clinical pharmacology studies. T2 was also used in the majority of the Phase 2 portion of LOXO-BTK-18001 in strengths of 25 mg, 50 mg, and 100 mg tablets. However, PK data using the 50 mg strength tablet in LOXO-BTK-18001, were not available at the time of this application.

The PK of pirtobrutinib has been investigated by non-compartmental analysis (NCA), as well as by population PK modelling and simulation, The exposure-response (E-R) relationship for efficacy and safety was also investigated using modelling and simulation techniques.

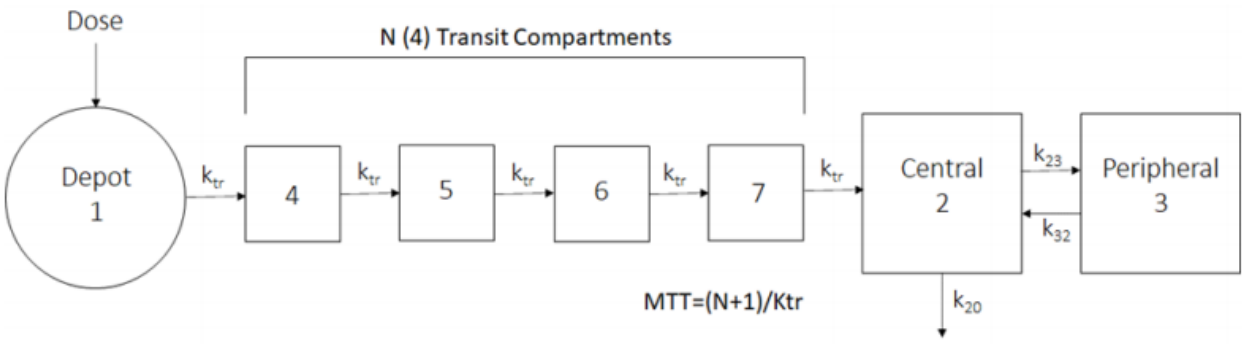
Pharmacokinetics in target population

In total, 4487 evaluable pirtobrutinib concentrations obtained from 595 patients in study LOXO-BTK-18001 were included in the population PK analysis.

In total, 66% of the analysed patients were male and 34% female. MCL was diagnosed in 140 patients (23%), while the majority of the patients had CLL/SLL (44%, n=263), and 192 patients (32%) had other NHL diagnoses. Overall, 210 patients (35%) received pirtobrutinib as formulation T1 and 385 patients (65%) as formulation T2. In total, 510 patients (85.7%) in the PK dataset received doses of 200 mg pirtobrutinib. PK data of the other doses of 25, 50, 100, 150, 250, and 300 mg were available from 5, 6, 9, 20, 25, and 20 patients (in total about 14.3%).

The final population PK model (**Figure *7***) is a linear 2-compartment model with 4 transit absorption compartments leading to a typical population MTT of 1.14 h (IIV = 23.8% CV, IOV = 43.6% CV). F was fixed to 1. The typical population CL was estimated to 2.04 L/h (37.7% CV) with volume of distributions of 29 L (Vc) and 23 L (Vp; 35.4% CV). Allometric scaling was applied for CL, Q, Vc, and Vp. A median body weight of 70 kg was used. For CL and Q the estimated factor was 0.392, and for Vc and Vp a factor of 0.806 was estimated. In addition, eGFR and albumin were identified as statistically significant covariates on CL (factor 0.00289 and – 0.668, respectively). Albumin was identified as covariate on Vc (factor -0.583). RSE (or SEE) were low (≤ 30.7%) and the proportional residual error was estimated to 19.7% (2.49% RSE).

Figure 7. Graphical illustration for the final population PK model



Abbreviations: k_{20} = rate constant describing elimination from compartment 2; k_{23} = rate constant describing transfer between compartments 2 and 3; k_{32} = rate constant describing transfer between compartments 3 and 2; k_{tr} = transit rate constant; MTT = mean transit time; N = number of transit compartments; PK = pharmacokinetic.

Absorption

Based on population PK analysis the estimated mean transit time (MTT) was 1.14 h with IIV = 23.8% CV and IOV = 43.6% CV. The IOV in MTT could maybe be partly explained by an influence of food intake later during the study, which slightly affects t_{max}. The influence of the varying MTT was considered to minimally affect exposure metrics and thus not anticipated to impact clinical outcome.

Pirtobrutinib has a moderate rate of absorption with the median Tmax reached in approximately 2 hours in fasted state. Absolute bioavailability study indicated that pirtobrutinib is a highly permeable compound having absolute bioavailability 85.5%. Solubility of pirtobrutinib is pH-independent in relevant GI pH range and in *in vivo* study it was confirmed that administration of gastric acid reducing agents do not result in a clinically relevant effect on exposure.

Among the 595 patients from study LOXO-BTK-18001 included in the population PK analysis 210 (35%) received formulation T1 and 385 (65%) formulation T2. Based on population PK analysis tablet formulation type (T1 and T2) was not identified as a statistically significant covariate. For the to-be-marketed formulation T2, geometric mean $AUC_{0\text{-}24,ss}$ is about 88800 ng*h/mL (66% CV), $C_{max,ss}$ = 6270 ng/mL (63% CV), and $C_{min,ss}$ = 2210 (88% CV), after administration of 200 mg (i.e. 2x 100 mg) QD. For the T1 formulation results are similar: $AUC_{0\text{-}24,ss}$ = 92500 ng*h/mL (51% CV), $C_{max,ss}$ = 6360 ng/mL (51% CV), and $C_{min,ss}$ = 2340 (71% CV), after administration of 200 mg (i.e. 2x 100 mg) QD. Overall, exposures appear comparable between both formulations after administration of 200 mg QD. For Phase 2 patients who received the proposed dose of 200 mg QD, popPK model-estimated mean Cmax,ss, Cmin,ss, and AUC0-24,ss were 6460 ng/mL (26% CV), 2260 ng/mL (65% CV), and 91300 ng*h/mL (41% CV), respectively.

The to-be-marketed formulation T2 was tested as 100 mg strength only and the 50 mg tablet has not been administered yet and no PK results are available. No bioequivalence study was presented.

- To bridge the different tablets used in the development, the applicant presented a biowaiver based on the following: Both 50 mg and 100 mg drug product are tablet dosage forms. The pharmaceutical products are manufactured by the same manufacturing process.
- The composition of the different strengths is quantitatively proportional.

- The dissolution profile similarity test result (25 mg versus 50 mg and 50 mg versus 100 mg) meets the criteria of f2 > 50, indicating similarity of dissolution profiles. The *in vitro* dissolution tests demonstrate similar performance of the dosage form across the dose strengths.
- Pirtobrutinib has linear disposition pharmacokinetics over the therapeutic dose range as demonstrated by a lack of dose dependence of MTT or CL/F.
- Pirtobrutinib exhibited dose proportional pharmacokinetics across the 25 mg to 300 mg QD dose range in patients and the 300 mg to 800 mg single dose range in healthy participants.

In Study LOXO-BTK-20014, a standard breakfast administered to healthy participants decreased the Cmax of pirtobrutinib by 20% and delayed Tmax by 0.5 hours. There was no effect on pirtobrutinib AUC.

In Study LOXO-BTK-20009, high-fat high-calorie meal administered to healthy participants decreased the Cmax of pirtobrutinib by 22.5% and delayed Tmax by 1 hour. There was no effect on pirtobrutinib AUC.

Distribution

Based on population PK analysis the typical overall pirtobrutinib overall volume of distribution (V) is 52 L with 29 L for the central compartment (Vc) and 23 L for the peripheral compartment (Vp).

Pirtobrutinib is ≈96% protein bound and protein binding appears to be concentration independent. In blood, pirtobrutinib is mainly distributed into plasma (mean blood to-plasma ratio 0.79) and found to bind predominantly to the albumin. Renal impairment had no impact on the extent of pirtobrutinib protein binding.

Body weight was identified as statistically significant covariate on Vc and Vp with an estimated factor of 0.806. Decreasing body weight (35 kg) is associated with a decreasing V (Vc of about L16.6 L (-42%)) and increasing body weight (150 kg) with an increasing V (Vc of about 53.6 L for), (+84%), compared to a population typical body weight of 70 kg.

Serum albumin was identified as statistically significant covariate on Vc with an estimated factor of -0.583. Lower baseline serum albumin (19 to 37 g/L) is associated with an increasing Vc of about 31 to 45 L) (+ 6 to 56%) and higher baseline serum albumin (>44 g/L) with a decreasing Vc of about 24 L), (- 17%), compared to a population typical baseline serum albumin level of 41 g/L.

NC analysis confirmed the population PK estimate for distribution as results from both analyses appeared similar.

Elimination

Based on population PK analysis the typical pirtobrutinib clearance (CL) is 2.04 L/h (IIV 37.7% CV), the mean elimination half-life of is estimated to be 18.8 hours (37% CV) and the typical intercompartmental CL (Q) is 13.5L/h. (16.7% CV). NC analysis confirms the population PK estimate for elimination.

Body weight, eGFR, and albumin were identified as statistically significant covariates on CL with estimated factors of 0.06329, 0.0289, and -0.668, respectively. Please also see section "Special populations".

Decreasing body weight is associated with a decreasing CL (CL = 1.55 L/h for 35 kg, -24% compared to the population typical) and increasing body weight with an increasing CL (CL = 2.75 L/h for 152150 kg, +35% compared to the population typical).

Lower baseline serum albumin is associated with an increasing CL (CL = 2.2– 3.4 L/h for 19 to 37 g/L, + 7 to 67% compared to the population typical) and higher baseline serum albumin with a decreasing CL (CL = 1.64 L/h for >44 g/L, - 19% compared to the population typical). Please also see section "Special populations".

Following a single oral dose of 200 mg 14C-pirtobrutinib (study LOXO-BTK-20007), approximately 37.3% of the total radioactive dose was recovered in faeces and 57.0% in urine. Pirtobrutinib is cleared both in faeces and renally with 18.2% and 10% of the radioactive dose.

The primary clearance pathways involved in pirtobrutinib metabolism are oxidative, hydrolytic, and direct glucuronidation. The metabolic clearance of pirtobrutinib occurs predominantly through CYP3A4. The formation of the direct glucuronide, metabolite M2 involves mainly UGT1A8 and UGT1A9.

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.

Dose proportionality and time dependencies

Dose proportionality was evaluated in Study LOXO-BTK-20017 (T2 tablets) and Study 18001 (T1 and T2 tablets) (Study 18001; LOXO-305-DMPK-081).

After single dose 300 to 900 mg (Study LOXO-BTK-20017), AUCs show dose proportionality, but Cmax is sub-proportional but includes 1 in the CI range.

For Study 18001, after multiple doses 25 to 300 mg, AUC Cmax dose proportionality ratios consistently included unity within the 90% confidence interval.

In Study LOXO-BTK-18001, no signs of risks of time dependency were observed, and accumulation ratio was 1.67; compatible with a 18 or 19 hours terminal elimination half-life.

Special populations

- Impaired renal function

A dedicated renal impairment study of pirtobrutinib (LOXO-BTK-20013) was performed. Absolute GFR (mL/min) has been used to estimate renal function. In total, eight participants had normal renal function, three moderate renal impairment, and five severe renal impairment. Of the latter, results of one participant were not analysed due to emesis before the t_{max}. According to the presented results of Study LOXO-BTK-20013 (after reclassification using absolute GFR values), CL in four otherwise healthy patients with severe renal impairment was reduced by about 35% leading to about + 65% increase in $AUC_{0\text{-}inf}$ (11500 vs. 75100 ng*h/mL) and a decrease in C_{max} of about -15% (Cmax = 2980 vs 3450 ng/mL) compared to participants with normal renal function.

The majority of patients (46%) contributing to the population PK analysis of study LOXO-BTK-18001 had mild renal impairment. Normal renal function were observed in 32% and moderate renal impairment in 21% of the patients. Only four patients (< 1%) had severe renal. Patients on dialysis have not been studied. Model-based clearance is expected to vary between about 1.7 to 2.3 L/h from

severe renal impaired patients to those with normal renal function (typical population CL = 2.04 L/h [37.7% CV]).

No dose adjustments have been proposed.

- Impaired hepatic function

A dedicated hepatic impairment study of pirtobrutinib LOXO-BTK-20012) was performed, using both Child-Pugh and NCI hepatic function classification. The mean AUC and C_{max} of pirtobrutinib were similar between subjects with mild hepatic impairment (Child-Pugh A) and subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh B) the AUC was 15% lower compared to normal hepatic function and the C_{max} was similar. In subjects with severe hepatic impairment (Child-Pugh C) the AUC of pirtobrutinib was 21% lower and mean C_{max} was 24% lower compared to subjects with normal hepatic function. The slight differences observed between subjects with hepatic impairment and subjects with normal liver function were attributed to differences in pirtobrutinib plasma protein binding. The results were demonstrated to be similar when either Child-Pugh or NCI liver impairment classification systems were applied to categorise study subjects.

The effect of hepatic function on the PK of pirtobrutinib was investigated during population PK analysis of Study LOXO-BTK-18001 data. The NCI classification was applied. Most patients (80%) included in the analysis had normal hepatic function as defined by NCI classification (TBI ≤ ULN and AST ≤ ULN). Mild and moderate hepatic impairment were identified for 18% and 2% of the study population, respectively. Only one patient had severe hepatic impairment. No statistically significant effect of hepatic function on the PK of pirtobrutinib was identified.

- Gender

Among the 595 patients contributing to the population PK analysis of study LOXO-BTK-18001, 201 (34%) were female and 394 (66%) male. During model development, no statistically significant effect of sex on the PK of pirtobrutinib was identified.

- Race/ethnicity

The vast majority of patients (86%) included in the population PK analysis of study LOXO-BTK-18001 were White/Caucasian and Non-Hispanic (92%). During model development, no statistically significant effect of race or ethnicity on the PK of pirtobrutinib was identified.

- Body weight

The median body weight in the PK population of study LOXO-BTK-18001 was 76.6 kg, ranging from 35.7 to 152.5 kg (mean = 78.3 [22.5% CV]). Body weight was identified as a statistically significant covariate on CL and intercompartmental clearance (factor = 0.392) as well as on volume of distribution (Vc and Vp; factor = 0.806). Based on population PK modelling and assuming a population typical body weight of 70 kg, for patients weighing 35 kg the clearance is expected to decrease down to about 1.55 L/h (-24%) and the volume of distribution down to about 16.6 L (- 42%). For patients weighing 85 – 150 kg, the clearance is expected to increase up to about 2.22– 2.75 L/h (+ 9 to 35%) and the volume of distribution up to about 34.5 to 53.6 L (+ 19 to 84%).

- Age

Patients included in the population PK analysis of study LOXO-BTK-18001 were aged 27-95 years (median = 68 years, mean = 67.6 years [14.7% CV]). Overall, 242 patients (40.7%) were aged 65 to 74 years, 119 patients (20%) aged 75 to 84 years, and 20 patients (3.4%) were aged 85 years or older.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
LOXO-BTK-18001	242 / 595	119 / 595	20 / 595

During model development, no statistically significant effect of age on the PK of pirtobrutinib was identified.

No PK data with pirtobrutinib in paediatrics < 18 years of age are available.

- Cancer type

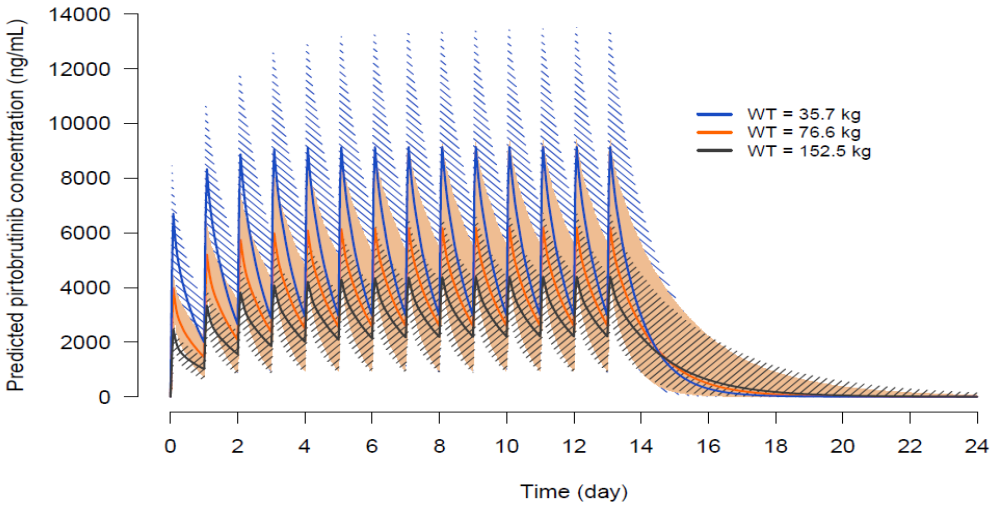
Of the 595 patients included in the population PK analysis, MCL was diagnosed in 140 patients (23%), while the majority of the patients had CLL/SLL (44%, n=263), and 192 patients (32%) had other NHL diagnoses. During model development, no statistically significant effect of cancer type on the PK of pirtobrutinib was identified. Phase 1 data were not investigated using a population PK modelling approach. A comparison of exposure between healthy volunteer and cancer patients was provided. This revealed about 15 to 24% lower AUC and 13 to 34% lower C_{max} in cancer patients compared to healthy volunteers. Apparent clearance appeared similar between both groups (geo. Mean range from 1.68 – 2.04 L/h across groups / studies). Variability in cancer patients is higher compared to healthy volunteers, but this could also partly be attributed to the quality of the data.

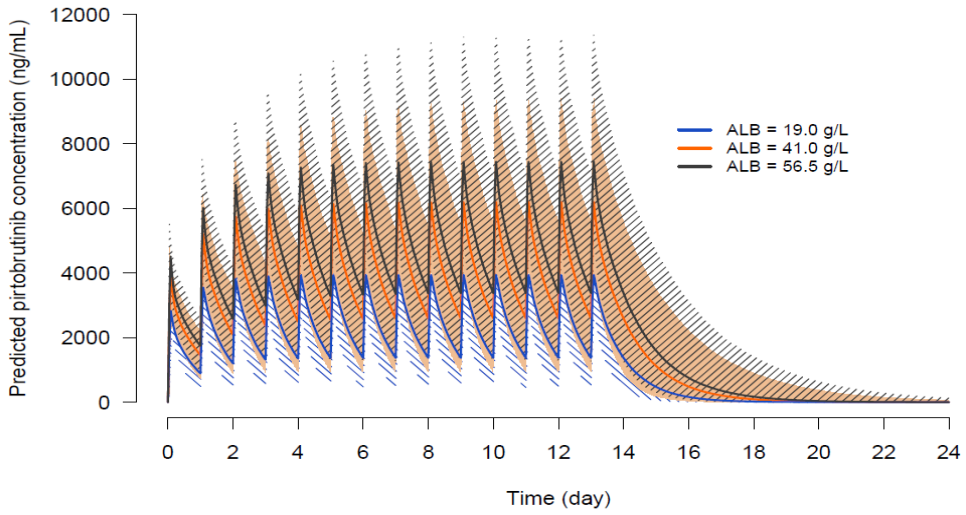
- Serum albumin

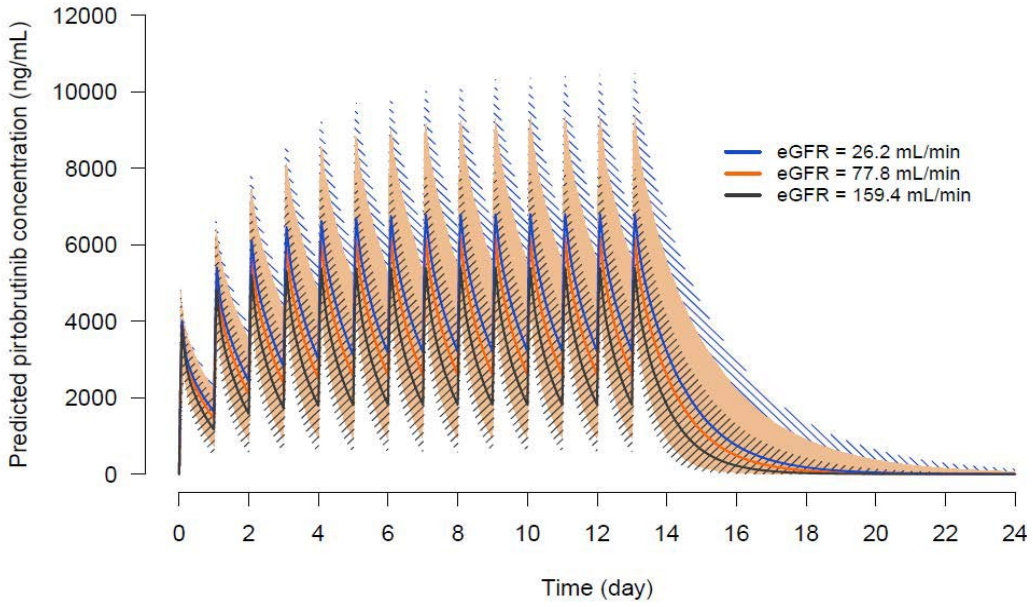
Patients included in the population PK analysis of study LOXO-BTK-18001 had serum albumin levels of 19 – 56.5 g/L (median = 41 g/L, mean = 40.1 g/L [13.2% CV]). Based on population PK modelling, patients with a baseline serum albumin level of 19 g/L (lowest observed in study LOXO-BTK-18001) are expected to have a CL of about 3.4 L/h (about +67% higher compared to the population typical CL of 2.0204 L/h) and a Vc of about 45 L (about +56% higher compared to the population typical Vc of 29 L). In contrast, patients with a baseline serum albumin level of 56.6 g/L (highest observed in study LOXO-BTK-18001) is expected to have a CL of about 1.6964 L/h (about -19% compared to the population typical CL of 2.04 L/h) and a Vc of about 2824 L (about -17% compared to the population typical Vc of 29 L).

To further investigate the predicted impact of patient factors, which were identified as influencing the PK of pirtobrutinib (body weight, eGFR and serum albumin) simulations based on different values and including the including the minimum and maximum of those parameters as observed in Study 18001 were provided (**Figure 8***).*

Figure 8. Simulated PK profiles at 200 mg QD for patients with body weights (top panel), serum albumin (middle panel), and absolute eGFR (bottom panel) values, which are minimum, median, and maximum values of observed patient characteristics in Study LOXO-BTK-18001.







Abbreviations: ALB = serum albumin; eGFR = absolute estimated glomerular filtration rate; 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.

Pharmacokinetic interaction studies

Pirtobrutinib as perpetrator drug

Pirtobrutinib is a CYP3A4 substrate, a time-dependent inhibitor (TDI), and inducer of CYP3A4. The net effect of pirtobrutinib was assessed *in vivo* in the DDI study LOXO-BTK-20008 conducted with CYP3A4 substrates (midazolam) showing pirtobrutinib is a mild CYP3A4 inhibitor leading to a 70% midazolam exposure increase (AUC 0-inf GMR = 1.70 with 90% CI (1.55, 1.86)) and 58% increase in Cmax after single dose of 200 mg pirtobrutinib administration.

Based on the cocktail study (study LOXO-BTK-20010), pirtobrutinib is a mild inhibitor of CYP2C19. Following repeated daily administration of 200 mg pirtobrutinib, omeprazole exposure (AUC0-inf) was increased by 56% with GMR test vs reference 1.56 and 90% CI (1.35, 1.80) and Cmax by 49% with GMR test vs reference 1.49 and 90% CI (1.31, 1.70).

Pirtobrutinib inhibition for CYP2C8 substrate was assessed in study LOXO BTK-20016 where repaglinide, probe substrate of CYP2C8 was administered with daily 200 mg pirtobrutinib repeatedly. Pirtobrutinib was shown to be a moderate CYP2C8 inhibitor which increased by 2.3-fold repaglinide exposure (AUC0-inf) with GMR estimated to 2.30 and 90% CI (1.86, 2.84) and 2-fold repaglinide Cmax with GMR 1.98 and 90% CI (1.62, 2.43). Caution of use with CYP2C8 substrate recommended in SmPC submitted in initial application.

Pirtobrutinib is a mild inhibitor of P-gp based on the clinical DDI study conducted with digoxin where a 35% increase in digoxin exposure (AUC0-inf) was observed (GMR = 1.35 with 90% CI (1.29, 1.42)); a 55% increase in Cmax (GMR = 1.55 with 90% CI 1.35, 1.78)), and a 12% decreased in digoxin renal clearance (GMR = 0.878 with 90% CI (0.841, 0.917)) were observed.

Pirtobrutinib inhibition of BCRP substrates at clinically relevant concentrations *in vivo* could not be excluded based on *in vitro* study. A Drug Interaction Study to Investigate the Effect of Single and

Multiple Doses of Pirtobrutinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants (Study J2N-MC-JZNW) was conducted. The results show that pirtobrutinib increased AUC and Cmax of rosuvastatin (a sensitive BCRP substrate) by 140% (GMR 2.40 and 90% CI: 2.21, 2.62) and 146% (GMR 2.46 and 90% CI: 2.20, 2.75), respectively. Pirtobrutinib is considered a moderate breast cancer resistant protein (BCRP) inhibitor.

Based on *in vitro* studies, clinical inhibition of UGT1A1 by pirtobrutinib cannot be excluded at clinically relevant concentrations.

Pirtobrutinib as victim drug

Pirtobrutinib was shown to be metabolised by CYP3A4 and glucuronidation, being substrate of UGT1A8 and UGT1A9.

Pirtobrutinib exposure is increased mildly when co-administered with itraconazole, a strong CYP3A4 inhibitor, with a 49% pirtobrutinib exposure (AUC0-inf) increase with GMR test vs reference of 1.49 and 90% CI of (1.40, 1.58) and no change in Cmax with GMR test vs reference of 1.04 and 90% CI of (0.951, 1.13).

Following 200 mg administration with repeated 600 mg rifampicin, a strong CYP3A4 inducer, led to 71% decrease in pirtobrutinib exposure (AUC0-inf) with GMR test vs reference of 0.293 and 90% CI of (0.271, 0.316), and a decrease in Cmax by 42% with GMR test vs reference of 0.576 and 90% CI of (0.537, 0.617).

No effect on pirtobrutinib PK was observed following co-administration of a single 40 mg dose of omeprazole, with a single dose of 200 mg pirtobrutinib under fasting conditions.

2.5.2.2. Pharmacodynamics

Mechanism of action

Pirtobrutinib is a small molecule reversible, noncovalent inhibitor of BTK.

BTK is a signalling protein of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Pirtobrutinib binds to wild type BTK as well as BTK harbouring C481 mutations leading to inhibition of BTK kinase activity.

Primary and Secondary pharmacology

For primary pharmacodynamic studies please refer to the non-clinical section of this report.

Secondary pharmacology

A thorough QT study was conducted to detect any effect of pirtobrutinib on QT interval. The design of the study was a cross over study, controlled versus placebo and a positive control (moxifloxacin) at the appropriate dose. The chosen supratherapeutic dose of 900 mg for pirtobrutinib achieved a mean C_{max} at least twice the mean Cmax observed with the intended dose of 200 mg.

Results of this study showed that Δ Δ QTcF varied within 1.9 msec (at 0.75 hour postdose) to 2.6 msec (at 6 hours postdose), with all upper bounds of the 90% CI of the estimated effect below 5.3 msec and therefore under 10 ms which is considered the threshold for a negative thorough QT/QTc study.

Relationship between plasma concentration and effect

Data from the pivotal Phase 1/2 study LOXO-BTK-18001 (data cut-off date 31 January 2022) were used for population E-R analysis for efficacy (Overall response rate [ORR]) and safety (TEAEs: Grade ≥3 anaemia, neutropenia, and infections/infestations, and hypertension).

The base models consisted of a logistic regression model which estimated the incidence of the endpoint for the entire study population independent of drug exposure. Afterwards, the relationship between predicted pirtobrutinib concentration and efficacy (**Figure 9** and **Table *16***) and safety endpoint (**Figure 10**) was evaluated. Due to the use of intra-patient dose escalation in Study LOXO-BTK-18001, C_{avg} of pirtobrutinib from the start of treatment up to the time of event was tested. In addition, for safety, C_{max} of pirtobrutinib from the start of treatment up to the time of event, was investigated. The relationship between pirtobrutinib concentration and the safety or efficacy endpoint was tested using linear, log-linear, and Emax models. A statistical significance of Δ OFV = 3.841 points for 1 degree of freedom, $p<0.05$ was assumed.

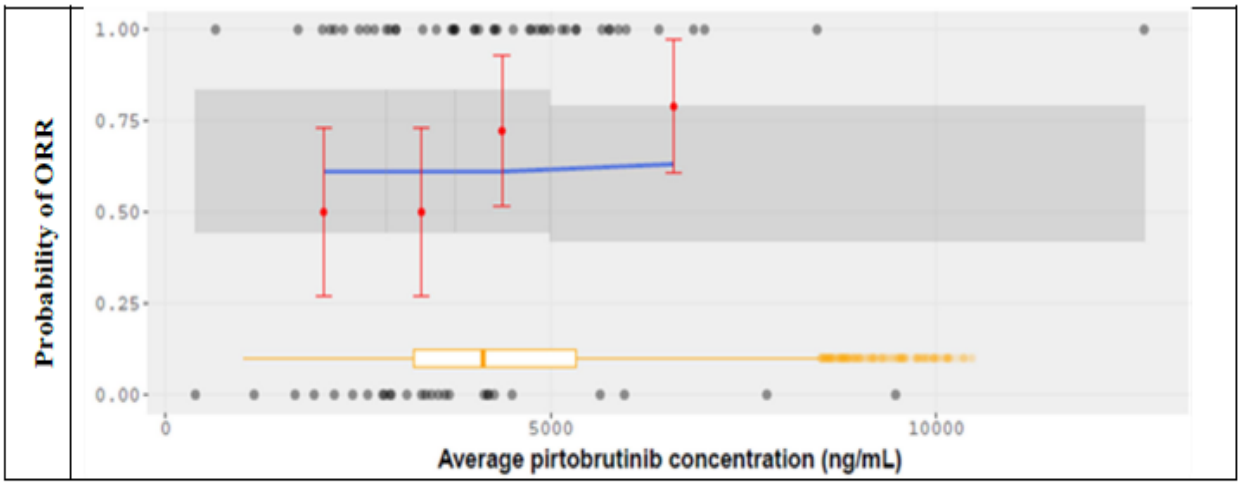
The relationship between C_{avg} up to the time of the best overall response (BOR) and ORR was not statistically significant. No statistically significant covariates were identified.

No statistically significant relationship was identified between incidence of TEAE and C_{avg} or $C_{max.}$ No patient factors were identified as predictors of increased risk of Grade ≥3 anaemia, neutropenia, or infection/infestation. A statistically significant relationship between cancer type and incidence of any grade hypertension was identified. The likelihood of experiencing hypertension was 2.74-fold higher in patients with CLL/SLL compared to MCL or other NHL. Considering that the duration of treatment for CLL/SLL was significantly longer than for MCL patients, it is possible that this relationship was due to these differences in treatment duration and reduced follow-up time for MCL patients.

Overall, no statistically significant relationship between pirtobrutinib exposure and investigated efficacy and safety measures were suggested over the dose range of 25 to 300 mg QD.

E-R analyses evaluating the range of safe and efficacious exposures in MCL patients suggested a wide therapeutic window for pirtobrutinib with mean average concentrations of $C_{avg,ss}$ = 399 ng/mL (28% CV) to 6370 ng/mL (51% CV) for 25 mg and 300 mg, respectively. For the proposed 200 mg QD dosing, a model-predicted $C_{avg,ss}$ of 3800 ng/mL (41% CV) is expected.

Figure 9. Exposure-response relationship for pirtobrutinib and ORR in patients with MCL PAS in study LOXO-BTK-18001



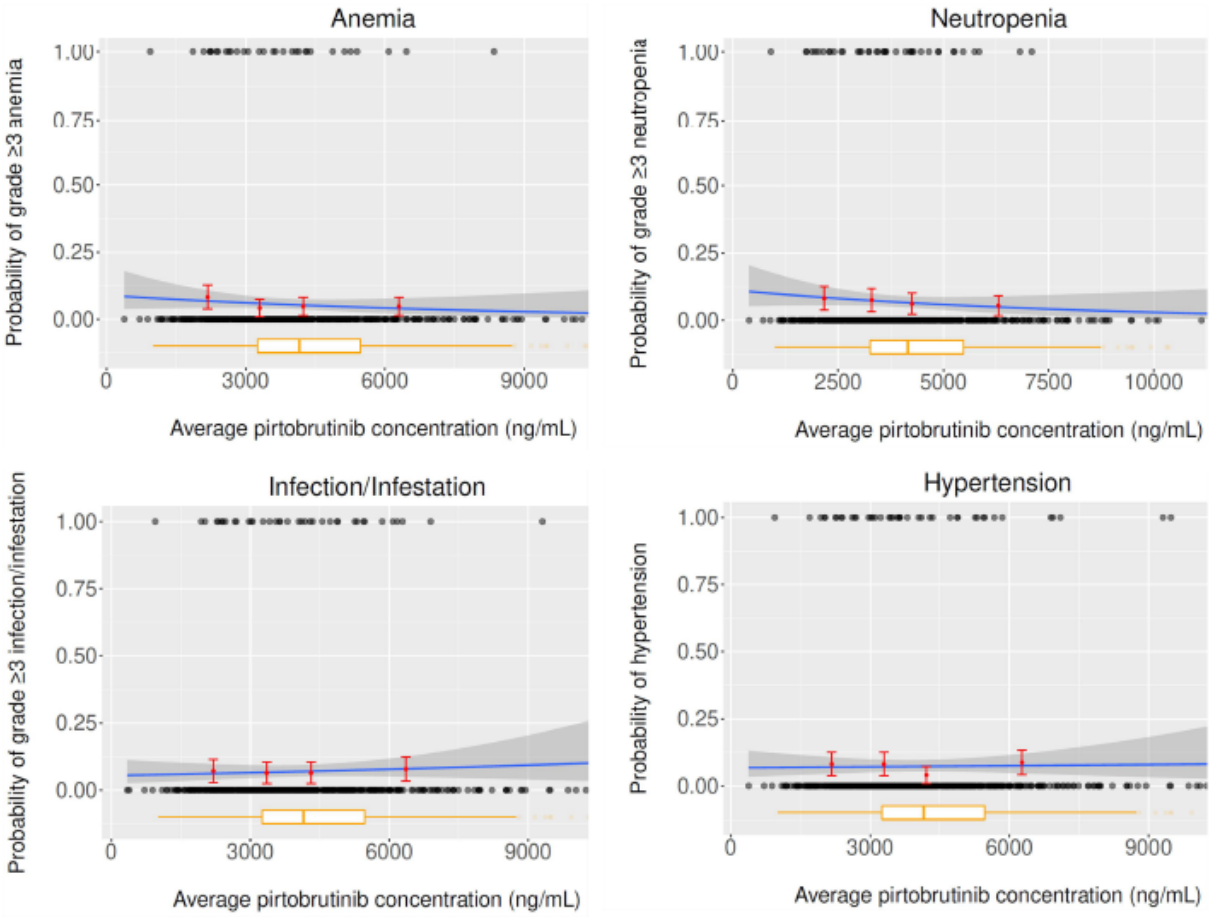
Abbreviations: CI = confidence interval; MCL = mantle cell lymphoma; ORR = overall response rate; PAS = Primary Analysis Set.
Solid blue lines and grey shaded areas are the logistic regressions and 95% CIs of the predicted probability of ORR. Black open circles reflect the observed ORR in pirtobrutinib 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 interquartile range.Source: LOXO-305-DMPK-081, Figure 9.3

Table 16. 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: ORR = overall response rate; SEE = standard error of the estimate.
[a] L = EXP(LOGIT)/(1+EXP(LOGIT))Source: LOXO-305-DMPK-081, Table 9.3

Figure 10. Exposure-response relationship for pirtobrutinib and TEAE in OMTSAS patients in Study LOXO-BTK-18001



Abbreviations: CI = confidence interval; OMTSAS = Overall Monotherapy Safety Analysis Set; TEAE = treatment-emergent adverse event.
Solid blue lines and grey 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 interquartile range.

2.5.3. Discussion on clinical pharmacology

Two formulations T1 and T2 were used in the clinical development programme. According to the presented overview, the to-be-marketed formulation T2 was tested as 100 mg strength only and the 50 mg tablet was not administered. No bioequivalence study was presented, however the waiver for a BE study between the tablets was well justified and acceptable.

A population PK model was developed using data from adult cancer patients participating in the pivotal Phase 1/2 study BTK-LOXO-18001. Results reveal an overall acceptable descriptive and predictive performance of the model.

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

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

The mean apparent central volume of distribution of pirtobrutinib is 29.0 L in cancer patients. The plasma protein binding is 96% and was independent of concentration between 0.5 and 50 µM. In plasma from healthy subjects and subjects with severe renal impairment the protein binding was 96%. Mean blood-to-plasma ratio is 0.79.

Hepatic metabolism is the main route of clearance for pirtobrutinib. Pirtobrutinib is metabolised to several inactive metabolites by CYP3A4, UGT1A8 and UGT1A9. There was no clinically meaningful impact of CYP3A modulation on pirtobrutinib exposures.

The mean apparent clearance of pirtobrutinib is 2.04 L/h with an effective half-life of approximately 19 hours. Following a single radio-labelled dose of pirtobrutinib 200 mg to healthy subjects, 37% of the dose was recovered in faeces (18% unchanged) and 57% in urine (10% unchanged).

In vitro and *in vivo* studies investigating the efficacy of pirtobrutinib on WT and mutated BTK were submitted.

Pirtobrutinib was shown to be able to inhibit *in vitro* WT BTK and BTK C481S with IC50 values of 3.15 nM and 1.42 nM respectively. Lineweaver-Burk analysis demonstrated that pirtobrutinib is a competitive inhibitor with respect to ATP in BTK and BTK C481, these studies also showed that M1 metabolite has no *in vitro* activity. Pirtobrutinib activity was also maintained in a number of BTK C481 resistance mutants transiently expressed in Human Embryonic Kidney cells and in human DLBCL TMD8 and human MCL REC-1 cell lines.

In vivo, pirtobrutinib was assessed in Human B-cell Lymphoma Xenograft Models in Immunocompromised Mice, In the REC 1 MCL xenograft model, pirtobrutinib demonstrated significant tumour growth inhibition of 80% and 84% at 10 mg/kg and 30 mg/kg BID, respectively, and tumour regression of -11% in the 50 mg/kg BID group.

The relationship between concentration and effect in patients with MCL was evaluated using dose-ranging data from the Phase 1/2 study, Study 18001. Overall, no statistically significant relationship between pirtobrutinib exposure and investigated efficacy and safety measures were suggested over the dose range of 25 to 300 mg QD.

For efficacy, according to the applicant, there was no meaningful relationship between pirtobrutinib exposure and efficacy (ORR) within the range of exposures achieved, however, considering the intra patient dose escalation, no conclusion could be made on other dose regimens. It should be noted that at doses ≥100 mg QD, ≥79% of patients are predicted to achieve concentrations of pirtobrutinib that exceed 90% inhibition of BTK across the entire dosing interval, which cannot be considered sufficient for a reduce dose regiment.

Considering safety, no apparent relationship exists between pirtobrutinib exposure and key safety endpoints.

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

Special populations

Based on the population PK analysis, body weight, renal function (eGFR), and albumin were found to statistically affect the PK of pirtobrutinib. Simulations including the minimum and maximum values of those parameters as observed in Study 18001 were provided. The degree of overlap between profiles suggested a minimal impact of these patient factors especially considering the degree of natural PK variability in the patient population. For example, a patient with low body weight would be predicted to have higher pirtobrutinib PK exposures but due to other factors affecting PK variability, may indeed have a lower exposure than would be predicted based on body weight alone. As these factors alone are unlikely to result in meaningful changes to pirtobrutinib PK no dose adjustments are recommended.

- Renal impairment

There were no clinically significant differences in the PK of pirtobrutinib for any degree of renal impairment (mild, moderate and severe).

In a population PK analysis of cancer patients, patients with mild (eGFR 60 to < 90 ml/min) or moderate renal impairment (eGFR 30 to < 60 ml/min), pirtobrutinib clearance was 16% to 27% lower compared to clearance in patients with normal renal function, resulting in expected exposure of AUC = 94 100 ng*h/mL and Cmax = 6 680 ng/mL in patients with mild renal impairment (16-19% higher compared to patients with normal renal function) and AUC = 108 000 ng*h/mL and Cmax = 7 360 ng/mL in patients with moderate renal impairment (28 to 36% higher compared to patients with normal renal function).

In a clinical pharmacology study of otherwise healthy volunteers, apparent clearance was 35% lower in four participants with severe renal impairment (eGFR 15 to < 30 ml/min) compared to eight participants with normal renal function (eGFR ≥ 90 ml/min), resulting in exposures of AUC0-inf = 115 000 ng*h/mL and Cmax = 2 980 ng/mL (62% higher and 7% lower, respectively, compared to normal renal function).

Patients with end-stage renal disease receiving dialysis were not studied.

- Hepatic impairment

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

- Paediatric population

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

- Pregnancy and lactation

There are no data from the use of pirtobrutinib in pregnant women. Studies in animals have shown reproductive toxicity and therefore pirtobrutinib should not be used during pregnancy.

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

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

Interaction with other medicinal products

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

- CYP3A inhibitors

In a clinical study, itraconazole, a strong CYP3A4 inhibitor, increased the AUC of pirtobrutinib by 48% and did not change Cmax of pirtobrutinib. This increase in pirtobrutinib exposure is not clinically meaningful. Therefore, no dose adjustment of Jaypirca is necessary with CYP3A inhibitors.

- CYP3A inducers

In a clinical study, rifampicin, a strong CYP3A inducer, decreased the AUC and Cmax of pirtobrutinib by 71% and 42%, respectively. Though this decrease in pirtobrutinib exposure is not expected to be clinically meaningful, if possible avoid strong CYP3A inducers (e.g. rifampicin, carbamazepine, phenytoin).

- Proton pump inhibitors

No clinically significant differences in pirtobrutinib pharmacokinetics were observed when administered concomitantly with omeprazole, a proton pump inhibitor.

- CYP2C8 substrates

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

- BCRP substrates

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

- P-gp substrates

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

- CYP2C19 substrates

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

- CYP3A substrates

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

2.5.4. Conclusions on clinical pharmacology

The applicant has adequately characterised the pharmacokinetic and pharmacodynamic properties of pirtobrutinib which therefore can be recommended for marketing authorisation.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study

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.

By comparing the simulated population PK profiles of each administered dose of pirtobrutinib to the protein binding-adjusted IC50 for BTK *in vitro*, it was demonstrated that at doses ≥100 mg QD, 79% of patients are predicted to achieve concentrations of pirtobrutinib which exceed 90% inhibition of BTK across the entire dosing interval. 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.

2.5.5.2. Main study

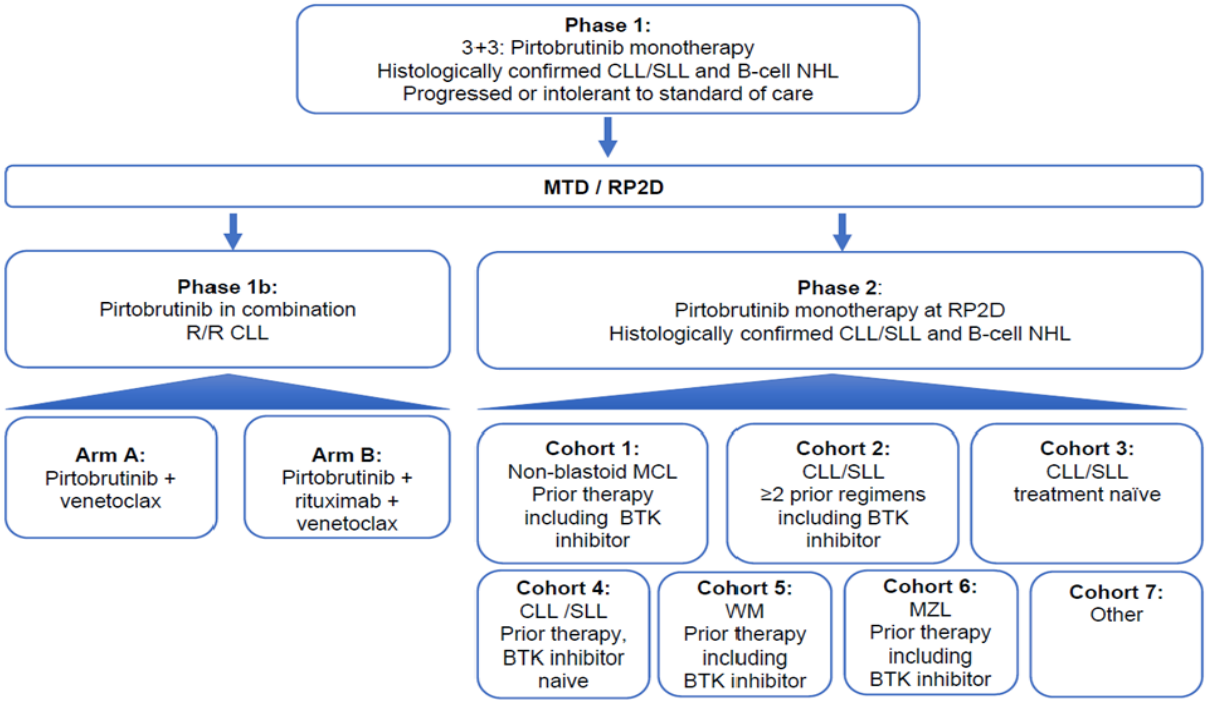
Study LOXO-BTK-18001: A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL) or NHL.

Methods

This is an open-label, multicentre 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. This application relies only on the monotherapy portion of the study which includes Phase 1 dose escalation and dose expansion, as well as Phase 2 and focuses on Cohorts 1 and 7.

The study schema is provided in **Figure 11**.

Figure 11. Study schema of study LOXO-BTK-18001



Abbreviations: BTK = Bruton's tyrosine kinase; CLL = chronic lymphocytic leukaemia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin's lymphoma; RP2D = recommended phase 2 dose; SLL = small lymphocytic lymphoma

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.

- **Study Participants**

Main inclusion criteria:

For all participants:

- ECOG PS 0-2
- At least 18 years of age
- Adequate coagulation, defined as aPTT and prothrombin time or (INR) not greater than 1.5 × the ULN
- Adequate hepatic function, defined as:
    - ALT or AST ≤ 2.5 × the ULN or ≤ 5 × ULN with documented liver metastases
    - Total bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN with documented liver metastases and/or Gilbert's Disease. If total bilirubin is > 1.5 × ULN then direct/indirect or conjugated/unconjugated bilirubin tests should be performed and meet the parameter specified. For patients with haemolysis and/or Gilbert's syndrome, they may be enrolled if unconjugated/indirect bilirubin is < 3 × ULN.

- Adequate renal function defined as creatinine clearance ≥ 30 mL/ minute using Cockcroft/Gault Formula: (140 – age) × body weight (kg) × 0.85 (if female) serum creatinine (mg/dL) × 72

Specific to Phase I dose escalation and expansion phase II

- Histologically confirmed B-cell malignancy (e.g., CLL/SLL, WM, NHL) failed or intolerant to either ≥ 2 prior standard of care regimens given in combination or sequentially OR have received 1 prior BTK inhibitor-containing regimen when a BTK inhibitor is approved as first line therapy.
- During dose escalation and DLT assessment: Adequate haemtologic status, defined as the following on or within 7 days of C1D1 before treatment

  a. Phase 1 dose escalation and expansion: ANC ≥ 0.75 × 109/L; Phase 1 and Phase 2: the patient may enrol below this threshold if there is documented bone marrow involvement considered to impair haematopoiesis.

  b. Phase 1 dose escalation and expansion: Platelet count ≥ 50 × 10^9/L not requiring transfusion support; Phase 1 and Phase 2: the patient may enrol below this threshold if there is documented bone marrow involvement considered to impair haematopoiesis.

  c. Phase 1 dose escalation and expansion: Hb ≥ 8 g/dL not requiring transfusion support or growth factors; Phase 1 and Phase 2: the patient may enrol below this threshold if there is documented bone marrow involvement considered to impair haematopoiesis.

  d. Phase 1 and Phase 2: Patient must be responsive to transfusion support. Patients known to be refractory to transfusion support are not eligible

Specific to phase II cohort 1 (MCL):

- Confirmed diagnosis of non-blastoid MCL with documentation of overexpression of cyclin D1 and/or t(11;14) and treated with a prior BTK inhibitor-containing regimen

Specific to Phase II cohort 7:

- Defined as 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/or patients with history of CNS involvement or primary CNS lymphoma. In the event the Sponsor electively closes Cohorts 2 through 4 prior to completion, patients with CLL/SLL who are ineligible to participate in or unable to access late phase studies of pirtobrutinib would remain eligible to enrol in this cohort. DLBCL is excluded. MCL without prior BTK inhibitor treatment is excluded. Patients enrolling to Cohort 7 must have received one or more prior therapies or have no available approved therapy with demonstrated clinical benefit with the exception of untreated Richter's transformation, which is allowed.

Main exclusion criteria:

- Investigational agent or anticancer therapy within 5 half-lives or 14 half-lives, whichever is shorter, prior to planned start of specified study therapy except antineoplastic and immunosuppressant monoclonal antibody treatment must be discontinued a minimum of 4 weeks prior to the first dose of pirtobrutinib. In addition, no concurrent systemic anticancer therapy is permitted.

- Continuation of certain standard of care anticancer therapies, including hormonal therapy for localised breast and prostate cancer, is allowed, provided they are not on the list of prohibited concomitant medications.
- Major surgery within 4 weeks prior to planned start of specified study therapy
- Radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of study treatment, except for patients receiving radiation to more than 30% of the bone marrow, or receiving whole brain radiotherapy, which must be completed at least 4 weeks prior to the first dose of study treatment.
- History of allogeneic or autologous SCT or CAR-T therapy within the 60 days prior to planned start of specified study therapy or with any of the following:

  a. Active GVHD;

  b. Cytopenias from incomplete blood cell count recovery post-transplant;

  c. Need for anti-cytokine therapy for toxicity from CAR-T therapy; residual symptoms of neurotoxicity > Grade 1 from CAR-T therapy;

  d. Ongoing immunosuppressive therapy
- Known CNS involvement by systemic lymphoma. Patients with previous treatment for CNS involvement who are neurologically stable and without evidence of disease may be eligible and enrolled to Phase 2 Cohort 7 if a compelling clinical rationale is provided by the Investigator and with documented Sponsor approval.
- Active uncontrolled autoimmune cytopenia (e.g., AIHA, ITP) where new therapy introduced or concomitant therapy escalated within the 4 weeks prior to study enrolment is required to maintain adequate blood counts.
- Significant cardiovascular disease defined as:

  a. Unstable angina, or

  b. History of myocardial infarction within 6 months prior to planned start of pirtobrutinib, or

  c. Previously documented LVEF by any method of ≤ 45% in the 12 months prior to planned start of pirtobrutinib; assessment of LVEF via echocardiogram or MUGA scan during Screening should be performed in selected patients as medically indicated, or

  d. Any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or

  e. Uncontrolled or symptomatic arrhythmias
- Patients who experienced a major bleeding event with a BTK inhibitor NOTE: Major bleeding is defined as bleeding having one or more of the following features: potentially life-threatening bleeding with signs or symptoms of haemodynamic compromise; bleeding associated with a decrease in the haemoglobin level of at least 2g per decilitre; or bleeding in a critical area or organ (e.g., retroperitoneal, intra articular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome).
- Current treatment with certain strong CYP3A4 inhibitors or inducers and/or strong P-gp inhibitors
- Pregnancy or lactation
- Active second malignancy unless in remission with life expectancy > 2 years and with

documented Sponsor approval.

- Prior treatment with pirtobrutinib

- **Treatments**

Pirtobrutinib was provided for oral dosing in 3 film-coated tablet strengths: 25 mg, 50 mg, or 100 mg. No 50 mg tablets were used prior to the data cut-off date for this interim CSR. Two tablet formulations (T1 and T2 tablets) were used. The initial T1 tablet formulation was used in the majority of the Phase 1 portion and the majority of the Phase 2 portion used the T2 formulation.

- **Objectives**

For the Phase 1

The primary objective of the monotherapy Phase 1 part of the study was to determine the MTD/RP2D of oral pirtobrutinib in patients with previously treated CLL/SLL and B-cell NHL.

Secondary objectives for monotherapy Phase 1:

- To determine the safety and tolerability of pirtobrutinib as monotherapy including acute and chronic toxicities
- To characterise the PK properties of pirtobrutinib as monotherapy
- To assess the preliminary antitumor activity of pirtobrutinib as monotherapy based on ORR; according to International Workshop Guidelines for CLL/SLL with incorporation of the clarification for treatment-related lymphocytosis — hereafter referred to as iwCLL 2018 criteria, and WM Lugano Treatment Response Criteria for MCL, MZL, and other NHL, Primary CNS Lymphoma or other criteria as appropriate to tumour type, as assessed by the Investigator.

Exploratory objectives for monotherapy Phase 1 include:

- To determine the relationship between PK and drug effects including efficacy and safety
- To evaluate MRD in select patients during therapy with pirtobrutinib

For the monotherapy phase 2:

The primary objective is to assess the preliminary antitumor activity of pirtobrutinib based on ORR as assessed by anIRC.

The secondary objectives are:

- To assess, for each Phase 2 cohort, the preliminary antitumor activity of pirtobrutinib by determining:
    - ORR as assessed by the Investigator
    - BOR as assessed by the Investigator and IRC
    - DOR as assessed by the Investigator and IRC
    - PFS as assessed by the Investigator and IRC
    - OS
- To determine the safety and tolerability of pirtobrutinib

- To characterise the PK properties of pirtobrutinib
- To determine the association of clinical response categories with:
    - Symptomatic Response: Improvement in cancer-related symptoms among patients with MCL associated with BOR
    - Functional Response: Improvement in physical function among patients with MCL

Exploratory objectives for monotherapy Phase 2 are the same as those for monotherapy Phase 1.

- **Outcomes/endpoints**

Monotherapy Phase 1

Primary Endpoint

MTD/RP2D

Secondary Endpoints

- AEs and SAEs, changes in haematology and blood chemistry values, assessments of physical examinations, vital signs, and ECGs
- Plasma concentration of pirtobrutinib and PK parameters including, but not limited to, AUC, Cmax, Tmax, T1/2, and degree of accumulation
- ORR by Investigator

Monotherapy Phase 2

Primary Endpoint

The primary endpoint is ORR based on IRC assessment. The ORR was defined as the proportion of patients with BOR of CR or PR based on Lugano Treatment Response Criteria for malignant lymphoma. BOR was defined as the best response designation for each patient recorded between the first dose of pirtobrutinib and earliest date of the data cut-off of 31 January 2021, or the date of documented disease progression by Lugano Treatment Response Criteria, or date of subsequent therapy.

Secondary Endpoints

The secondary endpoints for monotherapy Phase 2 were:

- ORR (by Investigator), BOR, DOR, time to any and best response, and PFS (by Investigator and IRC)
- OS
- AEs and SAEs, changes in haematology and blood chemistry values, assessments of physical examinations, vital signs, and ECGs
- Plasma concentration of pirtobrutinib and PK parameters including, but not limited to, AUC0-24, Cmax, Tmax, T1/2, and degree of accumulation
- Symptomatic Response: Improvement in cancer-related symptoms among patients with MCL associated with BOR
- Functional Response: Improvement in physical function among patients with MCL associated with BOR

- **Sample size**

Phase 1 – Dose Escalation and Phase 1b-Dose Combinations

During the dose escalation phase, approximately 25 patients were estimated to be needed to define the MTD/RP2D of pirtobrutinib. Up to 150 additional patients were to be enrolled across all dose cohorts previously declared safe by the SRC to further investigate the tolerability, PK, and biological activity of pirtobrutinib.

Phase 1b was to evaluate safety of pirtobrutinib in combination with other defined drugs. It was estimated that a minimum of 3 and up to 6 patients per treatment arm would be needed to determine safety of each specified combination, but the total number of patients enrolled was dependent on the observed safety profile. Up to 30 additional patients may be enrolled to each of the Phase 1b treatment arms at the defined dosing combinations once declared safe by the SRC to further investigate the tolerability, PK, and biological activity of pirtobrutinib in combination. This number of patients was considered sufficient to further assess preliminary safety and efficacy. It has 95% probability of identifying AEs occurring in > 10% of patients.

Phase 2 – Dose Expansion

The description below focuses on Cohorts 1 and 7, as they include MCL patients relevant to the present application.

For Cohort 1 (Non-blastoid MCL patients treated with a prior BTK inhibitor-containing regimen), a true ORR of ≥ 40% was hypothesised when pirtobrutinib was administered for these patients. A sample size of 65 patients was estimated to provide 92% statistical power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. The sample size in the primary analysis set (PAS) was increased to N = 90 due to FDA feedback.

Ruling out a lower limit of 20% for ORR was considered clinically meaningful for MCL patients who have failed prior therapy was considered clinically meaningful for patients with MCL who have discontinued prior BTK inhibitor therapy, as ORRs of 20% to 30% were reported in clinical studies testing 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]). There are no published data on the activity of these agents in a BTK-pretreated MCL population, which is a more treatment refractory population with a high unmet need. Under the primary analysis, the lower limit of the 95% CI was to exceed 20% when the estimated ORR is 32% or greater (Clopper-Pearson method).

Cohort 7 enrolled patients with B-cell neoplasms not otherwise specified in Cohorts 1 through 6, as well as those with Richter's transformation, patients with CNS metastasis, or patients with non-measurable disease regardless of underlying diagnosis. Up to 20 patients for any specific diagnosis as defined by World Health Organization Classification (e.g., non-GCB DLBCL) could be enrolled into Cohort 7. Enrolment was to be stopped on a diagnosis-specific basis if the response rate < 20% out of approximately 20 patients in that given diagnosis. The decision to further investigate beyond 20 patients for any specific diagnosis was based on comprehensive evaluation of the risk-benefit profile.

Patients enrolled in LOXO-BTK-18001 study Phase 1 who meet the eligibility criteria for the Phase 2 cohort PAS may be included in the efficacy analysis for that cohort and counted into the cohort sample size.

Interim analyses

A futility analysis of the overall response rate (including PR-L or better per iwCLL 2018 criteria, PR or better per Lugano Classification of Response, and minor response or better per IWWM) was to be performed for each cohort of the Phase 2 and Phase 1b portions. The futility analysis would be

performed after the first 20 patients were enrolled in each cohort and had the opportunity to be followed until the second disease assessment. The purpose of the futility assessment was to safeguard future patients from exposure to unequivocally inferior treatment. Enrolment was to be stopped if the overall response rate out of the first 20 efficacy evaluable patients was less than the given rate (**Table *17***). Otherwise, the enrolment was to proceed without interruption.

Table 17. Stopping Boundaries for Efficacy Monitoring in Patients Enrolled in Phase 2 and Phase 1b

Cohorts	Stop enrollment if the response rate from the first 20 efficacy evaluable patients is:
Phase 2	
Cohort 1 (MCL, prior BTK inhibitor)	< 20%
Cohort 2 (CLL/SLL, ≥ 2 regimens including BTK inhibitor)	< 25%
Cohort 3[1] (CLL/SLL, treatment naïve)	< 50%
Cohort 4 (CLL/SLL, previously treated, BTK inhibitor naïve)	< 30%
Cohort 5 (WM, previously treated including BTK inhibitor)	< 20%
Cohort 6 (MZL, previously treated including BTK inhibitor)	< 20%
Cohort 7[2] (not specified for Cohort 1-6)	< 20%
Phase 1b	
Phase 1b Arm A (CLL, previously treated)	< 45%
Phase 1b Arm B (CLL, previously treated)	< 45%

[1] Sponsor electively chose to close Cohort 3 prior to enrolling any patients.

[2] Cohort 7 was assessed on a diagnosis-specific basis.

- **Randomisation and Blinding (masking)**

This is an open label study.

- **Statistical methods**

Two statistical analysis plans (SAP) have been provided by the applicant: an interim clinical study report (CSR) SAP (v2.0, 14 January 2022) and a Summary of Clinical Efficacy (CSE) SAP (v2.0, 24 January 2022). When definitions differ between SAPs, both SAPs specifications are included in the sections below.

Primary endpoint – Overall Response Rate (ORR)

The primary analysis was based on the time point responses recorded by the IRC.

BOR was derived from the time point responses. BOR was defined as the best response designation for each patient that was recorded between the date of the first dose of pirtobrutinib and the date of documented PD per Lugano criteria or the date of subsequent anti-cancer therapy, whichever was earlier.

ORR and the corresponding 95% two-sided CI were calculated. ORR was estimated based on the proportion of patients with BOR of CR or PR in efficacy evaluable patients. Two-sided 95% CI were calculated using the exact binomial distribution.

The efficacy of pirtobrutinib in the PAS was to be demonstrated if the lower limit of the two-sided 95% CI exceeded 20%.

Secondary endpoints

Duration of Response (DOR)

DOR was calculated for patients who achieved a response of 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. Patients who are alive and without documented PD as of the data analysis cut-off date were censored.

The number and percentage of patients were tabulated based on the patient's response duration (patient's follow up time on disease assessment post the initial response): < 6 months, 6 to < 9 months, 9 to < 12 months, 12 to < 18 months, ≥ 18 months.

DOR was summarised descriptively using the Kaplan-Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method were provided for DOR time quartiles. The event-free rate with 95% CI using Greenwood's formula was provided for selected timepoints (e.g., 6, 9, 12, and 18 months.) The reason for censoring was summarised. Median follow-up for responders was estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996).

Time to Response

TTR was defined as the number of months elapsed between the date of the first dose of pirtobrutinib and the first documentation of overall response (CR or PR, whichever occurs earlier).

TTR was summarised descriptively by calculating the median, interquartile range, and minimum and maximum values. The number and percentage of patients with TTR by the following time points, measured relative to the date of the first dose of pirtobrutinib, were tabulated: < 2 months, 2 to < 4 months, 4 to < 6 months, ≥ 6 months.

Time to Best Response

TTBR was defined as the number of months elapsed between the date of the first dose of pirtobrutinib and the first documentation of CR (if patient's BOR is CR) or PR (if patient's BOR is PR).

TTBR was summarised descriptively in the same manner as TTR.

Progression-free Survival

PFS was defined as the number of months from the date of the first dose of pirtobrutinib to the earlier of the documentation of PD or death from any cause. Patients who were alive and without documented PD as of the data analysis cut-off date were censored.

Unless specified otherwise, the analysis methods described for DOR were used for PFS.

IRC and investigator assessments

IRC assessments served as the principal data source for BOR, DOR, TTR/TTBR, and PFS. Supplemental analyses based on Investigator assessments were provided.

Sensitivity analysis

To address FDA and EMA's questions on heterogeneity in patients enrolled between Phase 1 and Phase 2 portion of the study, key demographics and baseline characteristics were summarised by Phase 1 and Phase 2.

Sensitivity analyses were performed to assess MCL patients enrolled in the Phase 2 portion of the study who meet PAS criteria addressing scientific advice received from the EMA. This subset of patients is referred to as the Phase 2 Analysis Set.

Results

- **Participant flow**

Patient disposition in study LOXO-BTK-18001 is summarised in **Table 18**.

Table 18. Patient disposition in study LOXO-BTK-18001

	MSAS (N = 164)	CSAS (N = 311)	OMTSAS (N = 725)
Patients treated	164	311	725
On treatment, n (%)	55 (33.5)	190 (61.1)	360 (49.7)
Off treatment, n (%)	109 (66.5)	121 (38.9)	365 (50.3)
Progressive disease	78 (47.6)	69 (22.2)	245 (33.8)
Adverse event	13 (7.9)	20 (6.4)	40 (5.5)
Intercurrent illness	0	2 (0.6)	3 (0.4)
Requirement for alternative treatment	4 (2.4)	3 (1.0)	12 (1.7)
Withdrawal of consent	3 (1.8)	4 (1.3)	12 (1.7)
Death	7 (4.3)	16 (5.1)	31 (4.3)
Other	4 (2.4)	7 (2.3)	22 (3.0)
Patient status, n (%)			
On study	100 (61.0)	240 (77.2)	506 (69.8)
Discontinued	64 (39.0)	71 (22.8)	219 (30.2)
Withdrawal of consent	15 (9.1)	18 (5.8)	51 (7.0)
Lost to follow-up	0	1 (0.3)	3 (0.4)
Death	43 (26.2)	51 (16.4)	155 (21.4)
Other	6 (3.7)	1 (0.3)	10 (1.4)
Time on treatment, months			
N			
Mean (SD)	6.75 (7.038)	13.38 (7.623)	9.70 (7.770)
Median	4.52	12.65	8.05
Min, Max	0.2, 33.7	0.1, 34.0	0.0, 34.0

Abbreviations: CLL = chronic lymphocytic leukaemia; CSAS = CLL/SLL Safety Analysis Set; MCL = mantle cell lymphoma; MSAS = MCL Safety Analysis Set; N = number of patients; n = number of patients in the specified category; OMTSAS = Overall Monotherapy Safety Analysis Set; SD = standard deviation; SLL = small lymphocytic lymphoma.

- **Recruitment**

First patient enrolled: 15 March 2019

The study is ongoing at the time of this report.

- **Conduct of the study**

Changes to planned analyses

The study protocol was amended a number of times (from version 1.0 on 27 August 2018 to version 10.0 on 21 January 2022) before the data cut-off of 31st January 2022. During the procedure the applicant provided updated data with cut-off date of 29 July 2022.

The most significant amendments to the statistical section were made as part of Version 6.0 (24 June 2020, in order to address necessary updates to the Phase 2 design for LOXO-305 monotherapy which reflected the applicant's intent of the study to support registration. The Phase 2 cohorts were redefined to be disease specific rather than by BTK mutational status. As a result, analysis populations and sample size considerations were modified. In addition, the RP2D was determined to be 200 mg QD.

Both SAPs have also been revised once each. For the SCE SAP this was to change the data cut-off date and to increase the sample size of the primary analysis set from 65 to 90 based on FDA feedback. were summarised by the applicant in the tables below.

In the Efficacy Analysis Set (EAS) as defined in the CSR SAP (see below, section: Numbers analysed), major protocol deviations were reported for 7 (5.7%) patients in Cohort 1. These were due to errors with the study procedures (3 patients), investigational product (2 patients), and safety reporting/follow-up (2 patients). A major protocol deviation due to errors with study assessment was reported for 1 patient with MCL in Cohort 7

- **Baseline data**

Table 19 summarises the demographics characteristics for all treated patients in the efficacy populations. The baseline disease characteristics are presented in **Table 20**. Prior anti-cancer medications for MCL and reason for discontinuing prior BTK treatment is presented in **Table 21**.

Table 19. Demographic characteristics in study LOXO-BTK-18001 – MCL Patients by Analysis Sets

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
Age at Enrolment (years)					
Median	70.0	72.0	66.5	67.0	70.0
Range	46, 87	54, 88	50, 85	60, 86	46, 88
Categorical Age (years)					
<50	1 (1.1)	0	0	0	1 (0.6)
50 to <65	23 (25.6)	11 (23.9)	6 (42.9)	6 (42.9)	46 (28.0)
65 to <75	39 (43.3)	21 (45.7)	4 (28.6)	6 (42.9)	70 (42.7)
75 to <85	24 (26.7)	11 (23.9)	3 (21.4)	1 (7.1)	39 (23.8)
≥85	3 (3.3)	3 (6.5)	1 (7.1)	1 (7.1)	8 (4.9)
Sex, n (%)					
Male	72 (80.0)	34 (73.9)	12 (85.7)	10 (71.4)	128 (78.0)
Female	18 (20.0)	12 (26.1)	2 (14.3)	4 (28.6)	36 (22.0)
Race, n (%)					

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
American Indian or Alaskan Native	0	2 (4.3)	0	0	2 (1.2)
Asian	6 (6.7)	11 (23.9)	1 (7.1)	2 (14.3)	20 (12.2)
Black or African American	1 (1.1)	1 (2.2)	1 (7.1)	0	3 (1.8)
Native Hawaiian or Pacific Islander	0	0	0	0	0
White	76 (84.4)	32 (69.6)	12 (85.7)	9 (64.3)	129 (78.7)
Other	7 (7.8)	0	0	3 (21.4)	10 (6.1)
Height (cm)					
Median	172.00	169.80	173.40	166.70	170.00
Range	146.2, 193.0	146.0, 189.3	154.0, 190.0	150.8, 180.0	146.0, 193.0
Weight (kg)					
Median	78.10	69.50	81.15	76.80	76.70
Range	46.6, 149.5	40.0, 120.0	66.0, 103.7	51.6, 105.3	40.0, 149.5

Abbreviations: SAS = Supplemental Analysis Set; PAS = Primary Analysis Set.

Table 20. Baseline disease characteristics in study LOXO-BTK-18001 – MCL Patients by analysis sets

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
ECOG Score at Baseline, n (%)					
0	61 (67.8)	20 (43.5)	11 (78.6)	5 (35.7)	97 (59.1)
1	28 (31.1)	24 (52.2)	3 (21.4)	8 (57.1)	63 (38.4)
2	1 (1.1)	2 (4.3)	0	1 (7.1)	4 (2.4)
Time Since Initial Diagnosis of Primary Cancer to First Pirtobrutinib Dose (months)					
n	89	46	14	14	163
Median	70.34	70.83	82.38	61.22	72.38
Range	4.5, 183.7	6.6, 209.6	22.6, 199.1	10.0, 159.2	4.5, 209.6
Ann Arbor Staging for Lymphoma, n (%)					
Stage I	4 (4.4)	0	0	0	4 (2.4)
Stage II	7 (7.8)	4 (8.7)	0	0	11 (6.7)
Stage III	8 (8.9)	6 (13.0)	1 (7.1)	7 (50.0)	22 (13.4)
Stage IV	69 (76.7)	35 (76.1)	13 (92.9)	7 (50.0)	124 (75.6)
Missing	2 (2.2)	1 (2.2)	0	0	3 (1.8)
s-MIPI Score, n (%)					
Low Risk	20 (22.2)	5 (10.9)	4 (28.6)	3 (21.4)	32 (19.5)
Intermediate Risk	50 (55.6)	26 (56.5)	3 (21.4)	5 (35.7)	84 (51.2)

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
High Risk	20 (22.2)	15 (32.6)	7 (50.0)	6 (42.9)	48 (29.3)
Tumour Bulk (cm), n (%)					
<5	59 (65.6)	30 (65.2)	3 (21.4)	8 (57.1)	100 (61.0)
≥5	24 (26.7)	12 (26.1)	0	5 (35.7)	41 (25.0)
<10	80 (88.9)	41 (89.1)	3 (21.4)	11 (78.6)	135 (82.3)
≥10	3 (3.3)	1 (2.2)	0	2 (14.3)	6 (3.7)
Nonmeasurable Lymph Node	7 (7.8)	4 (8.7)	11 (78.6)	1 (7.1)	23 (14.0)
Extranodal Disease, n (%)					
Yes	35 (38.9)	19 (41.3)	3 (21.4)	6 (42.9)	63 (38.4)
No	55 (61.1)	27 (58.7)	11 (78.6)	8 (57.1)	101 (61.6)
Bone Marrow Involvement, n (%)					
Yes	46 (51.1)	23 (50.0)	11 (78.6)	4 (28.6)	84 (51.2)
No	44 (48.9)	23 (50.0)	3 (21.4)	10 (71.4)	80 (48.8)
Gastrointestinal Involvement, n (%)					
Yes	7 (7.8)	4 (8.7)	0	1 (7.1)	12 (7.3)
No	83 (92.2)	42 (91.3)	14 (100.0)	13 (92.9)	152 (92.7)
MCL Histology, n (%)					
Classic/Leukemic	70 (77.8)	35 (76.1)	13 (92.9)	11 (78.6)	129 (78.7)
Blastoid	8 (8.9)	6 (13.0)	1 (7.1)	1 (7.1)	16 (9.8)
Pleomorphic	12 (13.3)	5 (10.9)	0	2 (14.3)	19 (11.6)

Table 21. Prior therapies in study LOXO-BTK-18001 – MCL Patients by analysis sets

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
Prior Systemic Therapies, n (%)	90 (100.0)	46 (100.0)	14 (100.0)	14 (100.0)	164 (100.0)
Prior BTK inhibitor	90 (100.0)	46 (100.0)	14 (100.0)	0	150 (91.5)
Prior BCL2 inhibitor	14 (15.6)	8 (17.4)	2 (14.3)	0	24 (14.6)
Prior Chemotherapy	79 (87.8)	43 (93.5)	13 (92.9)	14 (100.0)	149 (90.9)
Prior Anti-CD20 Antibody	86 (95.6)	45 (97.8)	14 (100.0)	14 (100.0)	159 (97.0)
Prior PI3K Agent	3 (3.3)	3 (6.5)	0	1 (7.1)	7 (4.3)
Prior Immunomodulator	19 (21.1)	5 (10.9)	2 (14.3)	1 (7.1)	27 (16.5)
Prior CAR-T	4 (4.4)	7 (15.2)	2 (14.3)	0	13 (7.9)
Prior Stem Cell Transplant	19 (21.1)	8 (17.4)	6 (42.9)	7 (50.0)	40 (24.4)
Auto-SCT	17 (18.9)	7 (15.2)	6 (42.9)	7 (50.0)	37 (22.6)
Allo-SCT	4 (4.4)	3 (6.5)	0	0	7 (4.3)

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
Other Systemic Therapy	22 (24.4)	11 (23.9)	4 (28.6)	2 (14.3)	39 (23.8)
Prior mTOR inhibitors	2 (2.2)	0	0	0	2 (1.2)
Prior other immunotherapies excluding anti-CD20	5 (5.6)	2 (4.3)	0	1 (7.1)	8 (4.9)
Prior PD/PDL1 immunotherapies	0	1 (2.2)	0	0	1 (0.6)
Prior Proteasome inhibitors	14 (15.6)	8 (17.4)	2 (14.3)	1 (7.1)	25 (15.2)
Other Prior Molecular Pathways/small molecule inhibitors	3 (3.3)	1 (2.2)	2 (14.3)	0	6 (3.7)
Number of Lines of Prior Systemic Therapy, n (%)					
Median	3.0	3.0	3.0	2.0	3.0
Range	1, 8	1, 9	2, 7	1, 3	1, 9
1	6 (6.7)	3 (6.5)	0	4 (28.6)	13 (7.9)
2	35 (38.9)	14 (30.4)	5 (35.7)	6 (42.9)	60 (36.6)
3	18 (20.0)	9 (19.6)	3 (21.4)	4 (28.6)	34 (20.7)
≥4	31 (34.4)	20 (43.5)	6 (42.9)	0	57 (34.8)
Number of Lines of Prior BTK Inhibitor, n (%)					
Median	1.0	1.0	1.0	0.0	1.0
Range	1, 3	1, 3	1, 3	0, 0	0, 3
0	0	0	0	14 (100.0)	14 (8.5)
1	72 (80.0)	39 (84.8)	11 (78.6)	0	122 (74.4)
2	17 (18.9)	5 (10.9)	2 (14.3)	0	24 (14.6)
≥3	1 (1.1)	2 (4.3)	1 (7.1)	0	4 (2.4)
Reason for Discontinuation from the Most Recent Prior BTK Inhibitor, n (%)	90 (100.0)	46 (100.0)	14 (100.0)	NA	150 (91.5)
Disease Progression	73 (81.1)	39 (84.8)	13 (92.9)	NA	125 (76.2)
Toxicity	12 (13.3)	3 (6.5)	0	NA	15 (9.1)
Other Reason for Discontinuation	5 (5.6)	2 (4.3)	1 (7.1)	NA	8 (4.9)
Missing	0	2 (4.3)	0	NA	2 (1.2)
Reason for Discontinuation from Any Prior BTK Inhibitor, n (%)	90 (100.0)	46 (100.0)	14 (100.0)	NA	150 (91.5)
Disease Progression	74 (82.2)	39 (84.8)	14 (100.0)	NA	127 (77.4)
Toxicity	12 (13.3)	3 (6.5)	0	NA	15 (9.1)

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
Other Reason for Discontinuation	4 (4.4)	2 (4.3)	0	NA	6 (3.7)
Missing	0	2 (4.3)	0	NA	2 (1.2)

Abbreviations: BCL2 = -cell lymphoma 2 protein; BTK = Bruton's tyrosine kinase; CAR-T = chimeric antigen receptor-modified T-cells; mTOR = mammalian target of rapamycin; SAS = Supplemental Analysis Set; SCT = stem cell transplantation; PAS = Primary Analysis Set; PD/PDL1 = programmed death/programmed death-ligand 1; PI3K = phosphatidyl inositol kinase 3.

Among all patients with MCL, 151 (92.1%) patients received at least 1 dose of 200 mg pirtobrutinib QD. Dosing was consistent across analysis sets.

Table 22. Pirtobrutinib starting doses in study LOXO-BTK-18001 – MCL Patients by analysis sets

	PAS (N = 90)	SAS1 (N = 46)	SAS2 (N = 14)	SAS3 (N = 14)	Total (N = 164)
Starting dose of pirtobrutinib, n (%)					
25 mg QD	3 (3.3)	0	0	0	3 (1.8)
50 mg QD	0	0	0	0	0
100 mg QD	2 (2.2)	0	0	1 (7.1)	3 (1.8)
150 mg QD	1 (1.1)	0	0	0	1 (0.6)
200 mg QD	77 (85.6)	46 (100.0)	14 (100.0)	11 (78.6)	148 (90.2)
250 mg QD	2 (2.2)	0	0	1 (7.1)	3 (1.8)
300 mg QD	5 (5.6)	0	0	1 (7.1)	6 (3.7)
Patients who received at least 1 dose of 200 mg QD, n (%)	79 (87.8)	46 (100.0)	14 (100.0)	12 (85.7)	151 (92.1)
Intrapatient dose escalated to 200 mg QD	1 (1.1)	0	0	0	1 (0.6)
Dose reduced to 200 mg QD	1 (1.1)	0	0	1 (7.1)	2 (1.2)
Patients who received at least 1 dose of 200 mg QD or above, n (%)	86 (95.6)	46 (100.0)	14 (100.0)	13 (92.9)	159 (97.0)

Abbreviations: SAS = Supplemental Analysis Set; PAS = Primary Analysis Set; QD = once daily

- **Numbers analysed**

Analysis populations in the interim CSR SAP

The Overall Monotherapy Safety Analysis Set (OMTSAS) included all enrolled MCL, CLL/SLL, and NHL patients from Phase 1 and Phase 2 who received 1 or more doses of pirtobrutinib. Additional safety analysis sets specific for MCL (MSAS) and CLL (CSAS) were included to assess any potential disease-specific differences in safety (**Table 23**)

Table 23. Analysis sets for safety

Analysis Set	Analysis Set Description	Number of Patients
OMTSAS (Overall Monotherapy Safety Analysis Set)	All patients with CLL/SLL, MCL, and other NHL[1] who were enrolled in Study 18001 and received 1 or more doses of pirtobrutinib monotherapy as of the data cut-off date	725
MSAS (MCL Safety Analysis Set)	All patients with MCL who were enrolled in Study 18001 and received 1 or more doses of pirtobrutinib monotherapy as of the data cut-off date	164
CSAS (CLL/SLL Safety Analysis Set)	All patients with CLL/SLL who were enrolled in Study 18001 and received 1 or more doses of pirtobrutinib monotherapy as of the data cut-off date	311

Abbreviations: CLL = chronic lymphocytic leukaemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; SLL = small lymphocytic lymphoma; WM = Waldenström's macroglobulinaemia.
[1]Other NHL includes DLBCL, MZL, Richter´s Transformation, FL, and WM.

The Efficacy Analysis Set (EAS) included all MCL and CLL/SLL patients enrolled in the Phase 1 and Phase 2 portions of the study who met the following criteria:

- Treated with prior BTK inhibitor-containing regimen
- Received 1 or more doses of pirtobrutinib

The efficacy analysis was conducted on the EAS by Phase 2 cohort. Patients treated during Phase 1 dose escalation and expansion (backfill) who also met the disease definitions and pre-treatment criteria for one of the Phase 2 disease-defined cohorts could be considered as part of the efficacy evaluable patients for that Phase 2 cohort.

Analysis populations in the SCE SAP

The main efficacy analysis sets are summarised in **Table *24***

Table 24. Analysis sets for MCL efficacy

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.	
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
Phase 2	Subset of PAS including only Phase 2 patients	56

Abbreviations: BTK = Bruton's tyrosine kinase CNS = central nervous system; CT = computed tomography; LDi = lymph node longest diameter; MCL = mantle cell lymphoma; PAS = primary analysis set; SAS = supplementary analysis set.
Note: Data from patients treated during Phase 1 who met the disease definition and pretreatment criteria for one of the disease-specific cohorts defined for Phase 2 (Cohort 1 or 7) were pooled with the data from patients enrolled in that disease-specific cohort for the purposes of efficacy analysis.

- **Outcomes and estimation**

Primary endpoint

The updated 29 July 2022 efficacy analyses for the PAS and the PAS Subgroup 200 mg QD are shown in this section, representing the most current results with the longest follow-up available to date.

Table 25. Best Overall response and overall response rate in study LOXO-BTK-18001- Primary analysis set- IRC and investigators assessments

Data Cutoff Date	**29 July 2022**			
	PAS Subgroup 200 mg QD	**PAS**	**PAS Subgroup 200 mg QD**	**PAS**
	IRC Assessment (N = 77)	**IRC Assessment (N = 90)**	**Investigator Assessment (N = 77)**	**Investigator Assessment (N = 90)**
Best Overall Response, n (%)				
CR	14 (18.2)	17 (18.9)	21 (27.3)	25 (27.8)
PR	30 (39.0)	34 (37.8)	20 (26.0)	22 (24.4)
SD	15 (19.5)	16 (17.8)	12 (15.6)	13 (14.4)
PD	9 (11.7)	14 (15.6)	15 (19.5)	21 (23.3)
NE	9 (11.7)	9 (10.0)	9 (11.7)	9 (10.0)
Overall Response Rate				
n (%)	44 (57.1)	51 (56.7)	41 (53.2)	47 (52.2)
95% confidence interval	45.4, 68.4	45.8, 67.1	41.5, 64.7	41.4, 62.9

Abbreviations: CR = complete response; IRC = Independent Review Committee; N = number of participants; n = number of participants in the specified category; NE = not estimable; PAS = Primary Analysis Set; PD = progressive disease; PR = partial response; QD = once daily; SD = stable disease.

Duration of response

Table 26. Duration of response in study LOXO-BTK-18001-Primary analysis set- Independent Review Committee and investigator assessments

Data Cutoff Date	**29 July 2022**			
	PAS Subgroup 200 mg QD	**PAS**	**PAS Subgroup 200 mg QD**	**PAS**
	IRC Assessment (N = 77)	**IRC Assessment (N = 90)**	**Investigator Assessment (N = 77)**	**Investigator Assessment (N = 90)**
Number of Responders	44	51	41	47
Overall Response Status, n (%)				
Disease progression	16 (36.4)	18 (35.3)	18 (43.9)	19 (40.4)
Died (no disease progression beforehand)	5 (11.4)	5 (9.8)	5 (12.2)	6 (12.8)
Censored	23 (52.3)	28 (54.9)	18 (43.9)	22 (46.8)
Reason Censored, n (%)				
Alive without documented PD on or before data cutoff	10 (22.7)	11 (21.6)	13 (31.7)	14 (29.8)
Subsequent anticancer therapy without documented PD	8 (18.2)	9 (17.6)	3 (7.3)	3 (6.4)
Documented PD or death after subsequent anticancer therapy	2 (4.5)	5 (9.8)	1 (2.4)	3 (6.4)
Discontinued from study without documented PD or death	2 (4.5)	2 (3.9)	0	1 (2.1)
Death or PD after 2 or more missed disease assessments	1 (2.3)	1 (2.0)	1 (2.4)	1 (2.1)
Duration of Response (months), n (%)				
<6	21 (47.7)	24 (47.1)	20 (48.8)	22 (46.8)
6 to <9	6 (13.6)	6 (11.8)	4 (9.8)	4 (8.5)
9 to <12	5 (11.4)	5 (9.8)	4 (9.8)	4 (8.5)
12 to <18	4 (9.1)	6 (11.8)	3 (7.3)	6 (12.8)
≥18	8 (18.2)	10 (19.6)	10 (24.4)	11 (23.4)
Duration of Response (months)				
Median	17.61	17.61	7.46	11.93
95% CI for median	6.93, 27.24	7.29, 27.24	3.71, NE	5.55, NE
Minimum, Maximum	0.03+, 29.70+	0.03+, 32.99+	0.99+, 32.46+	0.03+, 36.73+
Duration of Follow-up (months)				
Median	12.02	12.68	23.26	18.00
Q1, Q3	5.78, 25.82	5.78, 25.82	11.93, 26.02	12.02, 26.02
Rate (%) of Duration of Response				
6 months or more	74.1	75.0	60.7	63.0
95% CI	56.9, 85.2	59.2, 85.4	43.4, 74.2	46.8, 75.5
9 months or more	58.0	61.1	49.1	52.9
95% CI	39.8, 72.4	44.1, 74.3	32.3, 64.0	36.9, 66.6
12 months or more (95% CI)	54.3	58.0	43.0	47.6
95% CI	36.1, 69.4	41.0, 71.7	26.7, 58.3	31.9, 61.8
18 months or more (95% CI)	43.5	44.6	43.0	43.7
95% CI	24.3, 61.2	26.5, 61.2	26.7, 58.3	27.7, 58.6

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; N = number of participants; n = number of participants in the specified category; NE = not estimable; PAS = Primary Analysis Set; PD = progressive disease; QD = once daily.

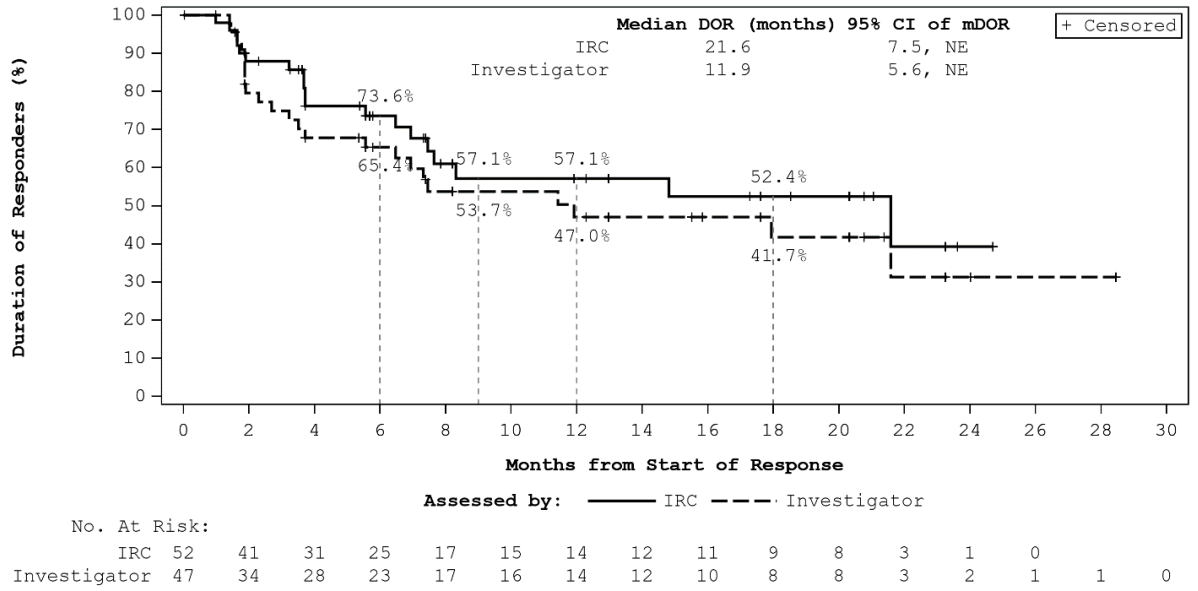
Concordance of IRC and investigator assessment

Table 27. Concordance of best overall response in study LOXO-BTK-18001between Independent Review Committee and investigator assessment primary analysis set-data cut-off date: 31 January 2022

IRC Assessment, n (%)	Investigator Assessment, n (%)	
	Responder	**Non-responder**
Responder	46	6
Non-responder	1	37
Concordance Rate		
n (%)	83 (92.2)	
95% CI	84.6, 96.8	
Kappa Coefficient (95% CI)	0.843 (0.733, 0.954)	

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; n = number of participants in the specified category.

Figure 12. Kaplan-Meier plot of duration of response - Independent Review Committee assessments and investigator assessments - primary analysis set-Data cut-off:31 January 2022



Time to Response and Time to Best Response

With the latest data cut-off (29 July 2022) the median time on treatment was 5.24 months (range: 0.2 to 39.6 months). Time to response and time to best response is summarised in **Table *28***

Table 28.Time to response and time to best response in study LOXO-BTK-18001 Based on Independent Review Committee and investigators assessments – Primary analysis set

Data Cutoff Date	29 July 2022			
	PAS Subgroup 200mg QD	PAS	PAS Subgroup 200mg QD	PAS
Parameter	IRC Assessment (N = 77)	IRC Assessment (N = 90)	Investigator Assessment (N = 77)	Investigator Assessment (N = 90)
Number of Responders	44	51	41	47
Time to Response (months)				
Median	1.84	1.84	1.87	1.87
Q1, Q3	1.84, 1.87	1.84, 1.87	1.84, 1.91	1.84, 1.94
Range	1.0, 4.8	1.0, 7.5	0.7, 6.0	0.4, 6.0
Time to Response (n, %)				
<2 months	37 (84.1)	41 (80.4)	32 (78.0)	36 (76.6)
2 to <4 months	5 (11.4)	6 (11.8)	6 (14.6)	8 (17.0)
4 to <6 months	2 (4.5)	3 (5.9)	3 (7.3)	3 (6.4)
≥ 6 months	0	1 (2.0)	0	0
Time to Best Response (months)				
Median	1.86	1.87	1.87	1.87
Q1, Q3	1.84, 2.05	1.84, 2.23	1.84, 3.68	1.84, 3.71
Range	1.0, 9.2	1.0, 16.4	1.4, 9.2	0.4, 38.4
Time to Best Response (n, %)				
< 2 months	32 (72.7)	36 (70.6)	26 (63.4)	28 (59.6)
2 to <4 months	7 (15.9)	8 (15.7)	7 (17.1)	8 (17.0)
4 to <6 months	3 (6.8)	3 (5.9)	5 (12.2)	6 (12.8)
≥6 months	2 (4.5)	4 (7.8)	3 (7.3)	5 (10.6)

Abbreviations: IRC = Independent Review Committee; N = number of participants; n = number of participants in the specified category; PAS = Primary Analysis Set; QD = once daily.

Overall survival

Table 29. Overall survival in study LOXO-BTK-18001- Primary analysis set

Data Cutoff Date	29 July 2022	
Status	PAS Subgroup 200 mg QD (N = 77)	PAS (N = 90)
Survival Status, n (%)		
Died	33 (42.9)	37 (41.1)
Censored	44 (57.1)	53 (58.9)
Reason of Censored, n (%)		
Alive	31 (40.3)	34 (37.8)
Discontinued from study	13 (16.9)	19 (21.1)
Overall Survival (months), n (%)		
<6	20 (26.0)	23 (25.6)

Data Cutoff Date	29 July 2022	
Status	**PAS Subgroup 200 mg QD (N = 77)**	**PAS (N = 90)**
6 to <9	8 (10.4)	9 (10.0)
9 to <12	6 (7.8)	6 (6.7)
12 to <18	18 (23.4)	21 (23.3)
≥18	25 (32.5)	31 (34.4)
Overall Survival (months)		
Median	23.46	23.49
95% confidence interval for median	14.72, NE	15.90, NE
Range	0.46, 33.15+	0.46, 40.31+
Duration of Follow-Up (months)		
Median	20.60	23.52
Q1, Q3	15.21, 27.83	15.21, 28.65
Rate (%) of Overall Survival		
6 months or more	83.6	84.7
95% confidence interval	72.9, 90.3	75.1, 90.8
9 months or more	74.5	75.6
95% confidence interval	62.6, 83.2	64.7, 83.6
12 months or more	66.9	69.1
95% confidence interval	54.4, 76.7	57.7, 78.0
18 months or more	58.7	59.0
95% confidence interval	45.8, 69.5	47.0, 69.1

Abbreviations: N = number of participants; n = number of participants in the specified category; NE = not estimable; PAS = Primary Analysis Set; QD = once daily.

Progression free survival

Table 30. Progression-free survival in study LOXO-BTK-18001 based on Independent Review Committee assessments - primary analysis set.

Data Cutoff Date	29 July 2022			
Parameter	**PAS Subgroup 200mg QD**	**PAS**	**PAS Subgroup 200mg QD**	**PAS**
	IRC Assessment (N = 77)	**IRC Assessment (N = 90)**	**Investigator Assessment (N = 77)**	**Investigator Assessment (N = 90)**
Progression Status, n (%)				
Disease progression	32 (41.6)	39 (43.3)	40 (51.9)	48 (53.3)
Died (no disease progression beforehand)	10 (13.0)	11 (12.2)	10 (13.0)	11 (12.2)
Censored	35 (45.5)	40 (44.4)	27 (35.1)	31 (34.4)
Reason Censored, n (%)				
Alive without documented PD on or before data cutoff	10 (13.0)	11 (12.2)	13 (16.9)	14 (15.6)
Subsequent anticancer therapy without documented PD	8 (10.4)	9 (10.0)	3 (3.9)	3 (3.3)

Data Cutoff Date	29 July 2022			
Parameter	**PAS Subgroup 200mg QD**	**PAS**	**PAS Subgroup 200mg QD**	**PAS**
	IRC Assessment (N = 77)	**IRC Assessment (N = 90)**	**Investigator Assessment (N = 77)**	**Investigator Assessment (N = 90)**
Documented PD or death after subsequent anticancer therapy	7 (9.1)	10 (11.1)	5 (6.5)	7 (7.8)
Discontinued from study without documented PD or death	7 (9.1)	7 (7.8)	4 (5.2)	5 (5.6)
Death or PD after two or more missed disease assessments	3 (3.9)	3 (3.3)	2 (2.6)	2 (2.2)
Duration of Progression-Free Survival (months), n (%)				
<6	50 (64.9)	59 (65.6)	49 (63.6)	58 (64.4)
6 to <9	6 (7.8)	6 (6.7)	8 (10.4)	8 (8.9)
9 to <12	5 (6.5)	5 (5.6)	4 (5.2)	4 (4.4)
12 to <18	6 (7.8)	8 (8.9)	6 (7.8)	7 (7.8)
≥18	10 (13.0)	12 (13.3)	10 (13.0)	13 (14.4)
Duration of Progression-Free Survival (months)				
Median	7.36	7.36	5.39	5.32
95% confidence interval for median	5.49, 13.34	5.32, 13.34	3.71, 7.62	3.71, 7.62
Range	0.03+, 33.15+	0.03+, 38.44+	0.03+, 33.15+	0.03+, 38.44+
Duration of Follow-Up (months)				
Median	13.67	13.77	13.83	19.45
Q1, Q3	4.76, 27.63	4.76, 27.63	9.66, 27.86	9.66, 27.86
Rate (%) of Progression-Free Survival				
6 months or more	53.7	51.7	45.5	44.1
95% confidence interval	40.3, 65.4	39.5, 62.6	33.2, 57.0	32.9, 54.7
9 months or more	45.4	44.8	33.9	34.2
95% confidence interval	32.1, 57.9	32.6, 56.2	22.6, 45.5	23.8, 44.9
12 months or more	38.9	39.4	30.5	31.4
95% confidence interval	25.9, 51.7	27.5, 51.0	19.6, 42.0	21.3, 42.0
18 months or more	36.5	34.6	26.5	28.2
95% confidence interval	23.7, 49.4	22.6, 46.8	16.2, 38.0	18.4, 38.7

Abbreviations: IRC = Independent Review Committee; n = number of participants in the specified category; N = number of participants, PD = progressive disease; PAS = Primary Analysis Set; QD = once daily.

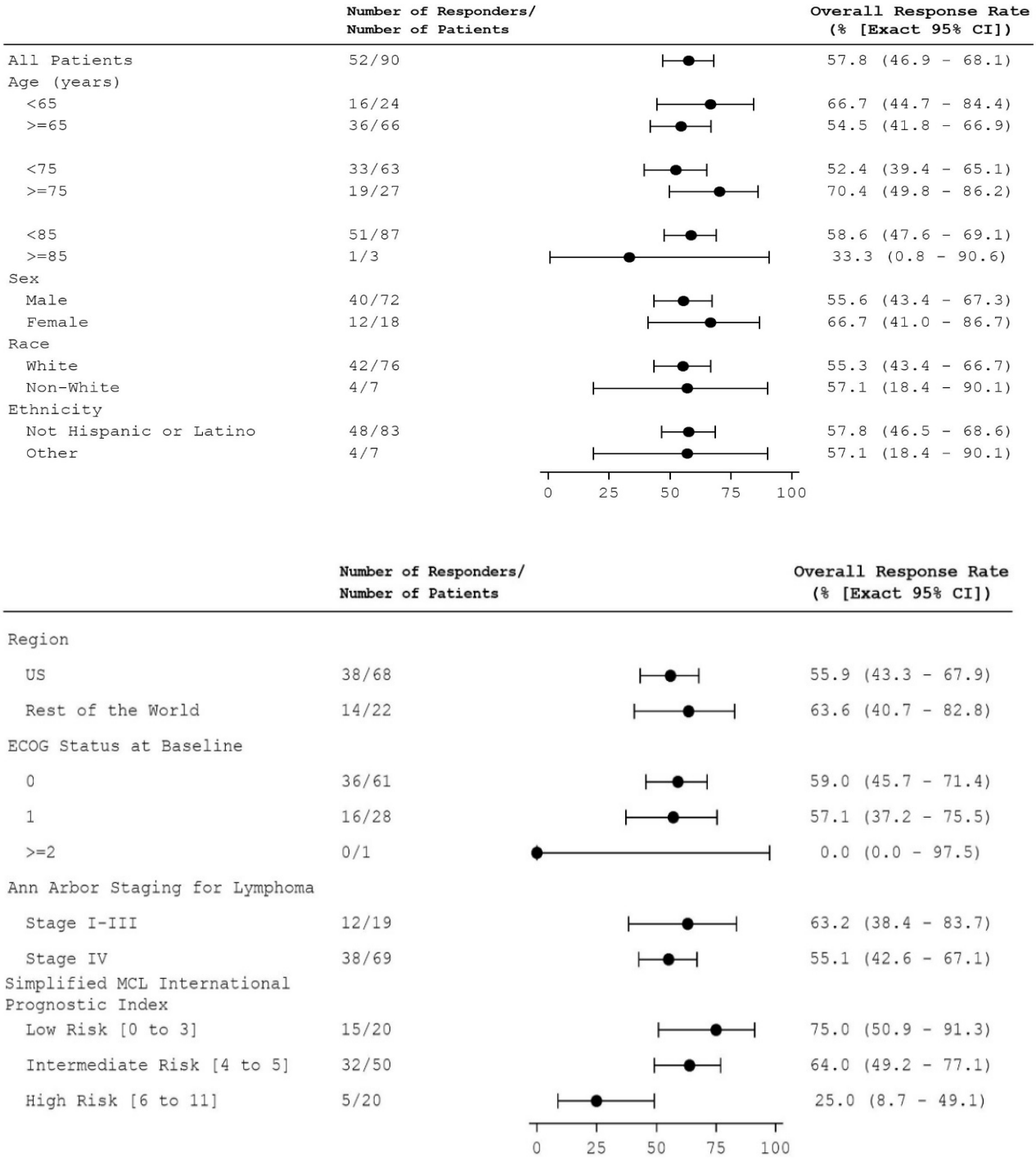
- **Ancillary analyses**

All results presented in this section are based on a data cut-off fate of 31 January 2022.

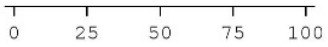
Subgroup Analysis

A forest plot analysis of ORR by IRC assessment for demographic subgroups is displayed in **Figure 13**.

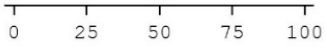
Figure 13. Forest plot of overall response rate in study LOXO-BTK-18001 in subgroups based on Independent Review Committee assessments - primary analysis set.

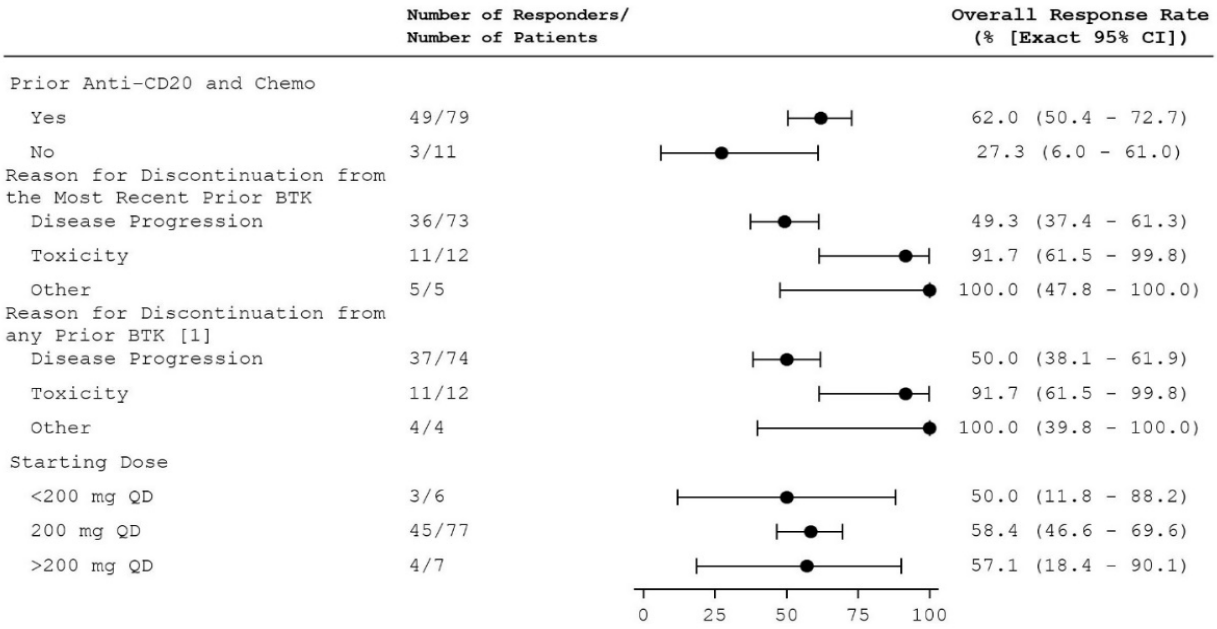


	Number of Responders/ Number of Patients	Overall Response Rate (% [Exact 95% CI])
Tumor Bulk (largest diameter)		
<5cm	34/59	57.6 (44.1 - 70.4)
>=5cm	11/24	45.8 (25.6 - 67.2)
Extranodal Disease		
Yes	24/35	68.6 (50.7 - 83.1)
No	28/55	50.9 (37.1 - 64.6)
Bone Marrow Involvement		
Yes	25/46	54.3 (39.0 - 69.1)
No	27/44	61.4 (45.5 - 75.6)
Gastrointestinal Involvement		
Yes	3/7	42.9 (9.9 - 81.6)
No	49/83	59.0 (47.7 - 69.7)
MCL Histology		
Classic/Leukemic	40/70	57.1 (44.7 - 68.9)
Blastoid	6/8	75.0 (34.9 - 96.8)
Pleomorphic	6/12	50.0 (21.1 - 78.9)



	Number of Responders/ Number of Patients	Overall Response Rate (% [Exact 95% CI])
Prior Lines of Systemic Therapies		
<=3	30/59	50.8 (37.5 - 64.1)
>3	22/31	71.0 (52.0 - 85.8)
1-2	22/41	53.7 (37.4 - 69.3)
3	8/18	44.4 (21.5 - 69.2)
>3	22/31	71.0 (52.0 - 85.8)
Prior BCL2		
Yes	7/14	50.0 (23.0 - 77.0)
No	45/76	59.2 (47.3 - 70.4)
Prior Stem Cell Transplant		
Yes	11/19	57.9 (33.5 - 79.7)
No	41/71	57.7 (45.4 - 69.4)
Prior CART		
Yes	2/4	50.0 (6.8 - 93.2)
No	50/86	58.1 (47.0 - 68.7)





Abbreviations: BCL2 = -cell lymphoma 2 protein; BTK = Bruton's tyrosine kinase; CAR-T = chimeric antigen receptor-modified T-cells; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; MCL = mantle cell lymphoma; N = number of participants; n = number of participants in the specified category; NE = not estimable.

Phase 2 Sensitivity Analyses

The PAS included patients enrolled across Phase 1 and Phase 2 portions of Study 18001, including 56 patients who were treated in the Phase 2 portion and referred to as the Phase 2 Analysis Set.

Sensitivity analyses , including overall response rates (**Table 31**), duration of responses (**Table 32**) and overall survival were conducted to evaluate potential concerns of heterogeneity caused by pooling of Phase 1 and Phase 2 patients, primarily in terms of starting dose.

Table 31. Overall response rate including best overall response rate in study LOXO-BTK-18001 by Independent Review Committee and investigators assessment–Phase 2 analysis set

	Phase 2 Analysis Set	
	IRC Assessment (N = 56)	**Investigator Assessment (N = 56)**
Best Overall Response, n (%)		
CR	9 (16.1)	12 (21.4)
PR	20 (35.7)	13 (23.2)
SD	13 (23.2)	12 (21.4)

PD	6 (10.7)	12 (21.4)
NE	8 (14.3)	7 (12.5)
Overall Response Rate		
n (%)	29 (51.8)	25 (44.6)
95% Confidence Interval	38.0, 65.3	31.3, 58.5

Table 32. Duration of response in study LOXO-BTK-18001 Based on Independent Review Committee and investigator assessments - Phase 2 analysis set

	Phase 2 Analysis Set	
	IRC Assessment (N = 56)	**Investigator Assessment (N = 56)**
Number of Responders	29	25
Overall Response Status, n (%)		
Disease Progression	9 (31.0)	11 (44.0)
Died (No Disease Progression Beforehand)	3 (10.3)	3 (12.0)
Censored	17 (58.6)	11 (44.0)
Reason of Censored, n (%)		
Alive without Documented PD on or before Data Cutoff	9 (31.0)	7 (28.0)
Subsequent Anti-cancer Therapy without Documented PD	5 (17.2)	2 (8.0)
Documented PD or Death after Subsequent Anti-cancer Therapy	0	0
Discontinued from Study without Documented PD or Death	2 (6.9)	1 (4.0)
Death or PD after 2 or More Missed Disease Assessments	1 (3.4)	1 (4.0)
Duration of Response (months), n (%)		
<6	19 (65.5)	16 (64.0)
6 to <9	8 (27.6)	7 (28.0)

	Phase 2 Analysis Set	
	IRC Assessment (N = 56)	**Investigator Assessment (N = 56)**
9 to <12	0	0
12 to <18	2 (6.9)	2 (8.0)
≥18	0	0
Duration of Response (months)		
Median	7.46	6.93
95% Confidence Interval for Median	3.71, NE	2.69, NE
Range	1.41, 17.61+	1.41, 17.61+
Duration of Follow-up (months)		
Median	7.33	7.39
Q1, Q3	5.39, 8.21	5.78, 12.29

Abbreviations: IRC = Independent Review Committee; N = number of participants; n = number of participants in the specified category; NE = not estimable; PD = progressive disease

Table 33. Overall survival in study LOXO-BTK-18001 Phase 2 analysis set

Status	Phase 2 Analysis Set (N = 56)
Survival Status, n (%) [1]	
Died	21 (37.5)
Censored	35 (62.5)
Reason of Censored, n (%)	
Alive	27 (48.2)
Discontinued from study	8 (14.3)
Duration of Overall Survival (months), n (%)	
<6	17 (30.4)
6 to <9	11 (19.6)
9 to <12	15 (26.8)
12 to <18	9 (16.1)
≥18	4 (7.1)
Duration of Overall Survival (months)	
Median	14.75
95% confidence interval for median	9.66, NE
Minimum, Maximum	0.46, 20.17+
Duration of Follow-up (months)	
Median	10.78
Q1, Q3	9.13, 14.72
Rate (%) of Overall Survival	
6 months or more	79.4
95% confidence interval	65.8, 88.0
9 months or more	66.1
95% confidence interval	51.0, 77.5
12 months or more	56.5
95% confidence interval	39.7, 70.2
18 months or more	48.4
95% confidence interval	28.0, 66.1

Abbreviations: N = number of participants; n = number of participants in the specified category; NE = not estimatable.

ITT analysis

An intention-to-treat (ITT) sensitivity analysis was performed for PFS (**Table 42**) and DOR (**Table 43**), respectively, by an Independent Review Committee (IRC) assessment for the PAS, without censoring for subsequent anticancer therapy, or 2 or more missed disease assessments.

Table 34. Progression-free survival in study LOXO-BTK-180010 Primary analysis set main analysis versus ITT sensitivity analysis based on IRC assessments

Data Cutoff Date	31 January 2022	
	Main Analysis (N = 90)	ITT Sensitivity Analysis (N = 90)
Progression Status, n (%)		
Disease progression	35 (38.9)	38 (42.2)
Died (no disease progression beforehand)	10 (11.1)	18 (20.0)
Censored	45 (50.0)	34 (37.8)
Reason Censored, n (%)		
Alive without documented PD on or before data cutoff	18 (20.0)	27 (30.0)
Subsequent anticancer therapy without documented PD	9 (10.0)	0
Documented PD or death after subsequent anticancer therapy	7 (7.8)	0
Discontinued from study without documented PD or death	7 (7.8)	7 (7.8)
Death or PD after two or more missed assessments	4 (4.4)	0
Duration of Progression-Free Survival (months), n (%)		
<6	58 (64.4)	50 (55.6)
6 to <9	9 (10.0)	13 (14.4)
9 to <12	7 (7.8)	7 (7.8)
12 to <18	5 (5.6)	8 (8.9)
≥18	11 (12.2)	12 (13.3)
Duration of Progression-Free Survival (months)		
Median	7.36	7.89
95% confidence interval for median	5.32, 12.45	5.32, 11.30
Range	0.03+, 31.11+	0.03+, 31.11+
Duration of Follow-Up (months)		
Median	9.23	19.09
Q1, Q3	5.03, 22.11	7.62, 23.03
Rate (%) of Progression-Free Survival		
6 months or more	51.9	53.3
95% confidence interval	39.8, 62.7	41.9, 63.4
9 months or more	44.7	42.7
95% confidence interval	32.5, 56.1	31.5, 53.5
12 months or more	40.0	37.1
95% confidence interval	27.7, 52.0	26.0, 48.3
18 months or more	34.4	26.7
95% confidence interval	21.9, 47.1	16.2, 38.4

Abbreviations: IRC = Independent Review Committee; ITT = intention-to-treat; PD = progressive disease; N = number of participants; n = number of participants in the specified category.

Table 35. Duration of response in study LOXO-BTK-18001 primary analysis set main analysis versus ITT sensitivity analysis based on IRC assessments

Data Cutoff Date	31 January 2022	
	Main Analysis (N = 90)	ITT Sensitivity Analysis (N = 90)
Number of Responders	52	52
Response Status, n (%)		
Disease progression	15 (28.8)	17 (32.7)
Died (no disease progression beforehand)	4 (7.7)	6 (11.5)
Censored	33 (63.5)	29 (55.8)
Reason Censored, n (%)		
Alive without documented PD on or before data cutoff	18 (34.6)	27 (51.9)
Subsequent anticancer therapy without documented PD	9 (17.3)	0

Data Cutoff Date	31 January 2022	
	Main Analysis (N = 90)	**ITT Sensitivity Analysis (N = 90)**
Documented PD or death after subsequent anticancer therapy	3 (5.8)	0
Discontinued from study without documented PD or death	2 (3.8)	2 (3.8)
Death or PD after two or more missed assessments	1 (1.9)	0
Duration of Response (months), n (%)		
<6	27 (51.9)	23 (44.2)
6 to <9	10 (19.2)	11 (21.2)
9 to <12	1 (1.9)	2 (3.8)
12 to <18	5 (9.6)	6 (11.5)
≥18	9 (17.3)	10 (19.2)
Duration of Response (months)		
Median	21.59	16.10
95% CI for median	7.46, NE	7.46, NE
Minimum, Maximum	0.03+, 24.71+	0.99, 24.71+
Duration of Follow-Up (months)		
Median	11.93	12.52
Q1, Q3	5.55, 20.34	5.78, 20.76
Rate (%) of Duration of Response		
6 months or more	73.6	75.4
95% CI	58.0, 84.2	60.7, 85.3
9 months or more	57.1	58.1
95% CI	39.3, 71.5	41.3, 71.7
12 months or more (95% CI)	57.1	54.9
95% CI	39.3, 71.5	37.9, 69.0
18 months or more (95% CI)	52.4	47.1
95% CI	33.9, 67.9	29.7, 62.6

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; ITT = intention-to-treat; PD = progressive disease; N = number of participants; n = number of participants in the specified category; NE = not estimable.

- **Summary of main efficacy results**

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

Table 36. Summary of efficacy for trial LOXO-BTK-18001

Title: 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)		
Study identifier	Protocol No.: LOXO-BTK-18001 (Study 18001; BRUIN) EudraCT No.: 2018-003340-24	
Design	Open-label, multicentre study of oral pirtobrutinib to evaluate safety and efficacy as monotherapy and as part of combination therapy in patients with CLL/SLL and NHL who have failed or are intolerant to standard of care. This study includes monotherapy and combination treatment parts. The monotherapy part includes Phase 1 dose escalation and dose expansion, as well as a Phase 2 component.	
	Duration of main phase:	The study is ongoing. Patients are to be treated until there is an evidence of PD, unacceptable toxicity, or other reasons for treatment discontinuation as outlined in the protocol.

Hypothesis	*For Patients with MCL Previously Treated with a BTK Inhibitor* • A true ORR of ≥40% is hypothesised when pirtobrutinib is administered to patients with MCL who have received a prior BTK inhibitor. • A sample size of 65 patients is estimated to provide approximately 92% statistical power to achieve a lower boundary of a 2-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. • Ruling out a lower limit of 20% for ORR is considered clinically meaningful for patients with MCL who have discontinued prior BTK inhibitor therapy. • A cutoff date of 31 January 2022 was chosen, with the sample size in the PAS of 90 patients, to ensure that the vast majority of responders in the PAS will have at least 9 months of follow-up from the onset of response.		
Treatments groups	Pirtobrutinib		Phase 1 dose escalation: 25 mg QD to 300 mg QD pirtobrutinib Phase 2 (Cohorts 1 to 7): 200 mg QD pirtobrutinib Eligibility criteria, methods for disease assessment, and response criteria were consistent across Phase 1 and Phase 2. The PAS, the primary population to support the proposed MCL indication, pools patients across Phase 1 and Phase 2 and includes the first 90 patients with MCL enrolled and treated with pirtobrutinib monotherapy from either Phase 1 or Phase 2, irrespective of pirtobrutinib starting dose, that have received a prior BTK inhibitor-containing regimen and had no known central nervous system involvement, and with at least 1 site of radiographically assessable disease as determined by investigator. As a sensitivity analysis, a Phase 2 analysis set was generated; this analysis set has the same criteria as the PAS; however, only Phase 2 patients were included.
Endpoints and definitions	Primary endpoint	ORR according IRC.	ORR according to IRC assessment is defined based on the Lugano Treatment Response Criteria. ORR will be estimated as the proportion of patients with BOR of CR or PR. BOR is defined as the best response designation for each patient that is recorded between the date of the first dose of pirtobrutinib and the earliest of • the date of documented PD per the Lugano Treatment Response Criteria • the date of subsequent anticancer therapy, or • the data cutoff date.

	Secondary endpoint	ORR according to INV	ORR according to INV assessment is defined based on the Lugano Treatment Response Criteria. ORR will be estimated as the proportion of patients with BOR of CR or PR.
	Secondary endpoint	BOR by IRC and INV	BOR is defined as the best response designation for each patient that is recorded between the date of the first dose of pirtobrutinib and the earliest of • the date of documented PD per the Lugano Treatment Response Criteria • the date of subsequent anticancer therapy, or • the data cutoff date.
	Secondary endpoint	DOR by IRC and INV	DOR will be calculated for patients who achieve a response of CR or PR as a BOR. DOR is defined as the number of months from the start date of the first documented response to the earlier of either the documentation of PD or death from any cause. Patients who are alive and without documented PD as of the data analysis cutoff date will be censored.
	Secondary endpoint	TTR by IRC and INV	TTR is defined as the number of months elapsed between the date of the first dose of pirtobrutinib and the first documentation of overall response (CR or PR, whichever occurs earlier).
	Secondary endpoint	TTBR by IRC and INV	TTBR is defined as the number of months elapsed between the date of the first dose of pirtobrutinib and the first documentation of CR (if patient's BOR is CR) or PR (if patient's BOR is PR).
	Secondary endpoint	PFS by IRC and INV	PFS is defined as the number of months from the date of the first dose of pirtobrutinib to the earlier of either documentation of PD or death from any cause. Patients who are alive and without documented PD as of the data analysis cutoff date will be censored.
	Secondary endpoint	OS	OS is defined as the number of months from the date of the first dose of pirtobrutinib to the date of death from any cause. Patients who are alive or lost to follow-up as of the data cutoff date will be censored.
Database lock	09 March 2022 (based on a data cutoff date of 31 January 2022)		
Results and Analysis			
Analysis description	**Primary Analysis - Overall Response Rate (ORR)**		
Analysis population and time point description	*Patients with MCL Previously Treated with a BTK Inhibitor - Primary Analysis Set* *Data cutoff date: 31 January 2022*		
Descriptive statistics and estimate variability	Treatment group		Pirtobrutinib
	Number of patients		90
	ORR by IRC: % (95% CI)		57.8 (46.9, 68.1)
Analysis description	**Secondary Analysis – Key Secondary Endpoints**		
Analysis population and time point description	*Patients with MCL Previously Treated with a BTK Inhibitor - Primary Analysis Set* *Data cutoff date: 31 January 2022*		
	Treatment group		Pirtobrutinib

Descriptive statistics and estimate variability	Number of patients	90
	ORR by INV: % (95% CI)	52.2 (41.4, 62.9)
	DOR by IRC: median, months (95% CI)	21.59 (7.46, NE)
	TTR by IRC: median, months (range)	1.84 (1.0, 7.5)
	TTBR by IRC: median, months (range)	1.87 (1.0, 16.5)
	PFS by IRC: median, months (95% CI)	7.36 (5.32, 12.45)
	OS median, months (95% CI)	NE (14.75, NE)
Analysis description	**Other specify: Sensitivity Analysis**	
Analysis population and time point description	*Patients with MCL Previously Treated with a BTK Inhibitor - Primary Analysis Set – Phase 2 Only (Sensitivity Analysis)* *Data cutoff date: 31 January 2022*	
Descriptive statistics and estimate variability	Treatment group	Pirtobrutinib
	Number of patients	56
	ORR by IRC: % (95% CI)	51.8 (38.0, 65.3)
	DOR by IRC: median, months (95% CI)	7.46 (3.71, NE)
	TTR by IRC: median, months (range)	1.84 (1.0, 3.7)
	TTBR by IRC: median, months (range)	1.84 (1.0, 5.6)
	PFS by IRC: median, months (95% CI)	5.55 (5.32, 9.30)
	OS median, months (95% CI)	14.75 (9.66, NE)

Abbreviations: BOR = best overall response; BTK = Bruton's tyrosine kinase; CI = confidence interval; CLL = chronic lymphocytic leukaemia; CR = complete response; DOR = duration of response; INV = investigator; IRC = independent review committee; MCL = mantle cell lymphoma; NE = not estimable; NHL = non-Hodgkin lymphoma; ORR = overall response rate; OS = overall survival; PAS = Primary Analysis Set; PD = progressive disease; PFS = progression-free survival; PR = partial response; QD = once daily; SLL = small lymphocytic lymphoma; TTBR = time to best response; TTR = time to response.

2.5.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Non Controlled Trials	39/90	24/90	3/90

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.5.5.6. Supportive study

Not applicable.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The main study in support of this Conditional Marketing Authorisation (CMA) application is a phase 1/2 single arm, open-label study (LOXO-BTK-18001). In the cohorts of interest for the initially claimed indication of pirtobrutinib as monotherapy for the treatment of adult patients with mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor, subjects had received a median number of 3 prior lines of systemic therapy, with 1 prior BTKi. Discontinuation from previous BTKi was in most cases (81.1%) due to disease progression. Consequently, the CHMP requested, and the applicant accepted that the indication should be amended to better reflect the patient population of the pivotal study to treatment of adult patients with relapsed or refractory MCL who have been previously treated with a BTKi.

This single arm design of the study design leads to uncertainties due to the absence of any comparator and is further compounded from the relatively small sample size and the limited follow-up of the study. However, in the context of a CMA and given the rarity of the disease, the poor prognosis of the patient population and the lack of alternative treatments in this clinical setting the CHMP considered that these limitations would not preclude a conditional marketing authorisation.

Two SAPs were developed in parallel by the applicant: an interim CSR SAP and a SCE SAP which hinders interpretation of data since the 2 SAPs had different sample size considerations and analysis populations.

The interim CSR SAP referred to a sample size of 65 patients for Cohort 1 alone (Non-blastoid MCL BTK treated patients) with the Efficacy Analysis Set (EAS) including all MCL and CLL/SLL patients enrolled in the Phase 1 and Phase 2 portions of the study and who were treated with prior BTK inhibitor-containing regimen and received at least 1 dose of pirtobrutinib. According to this SAP all results were to be displayed by cohort (i.e. patients from Cohort 1 are analysed separately from other MCL patients from Cohort 7).

On the other hand, the SCE SAP mentioned 65 patients in the context of a pooling based on Cohort 1 and Cohort 7 (all MCL BTK treated patients). The decision to increase the SCE primary analysis set to the first 90 patients was described only in the SCE SAP.

Finally, the CSR SAP (and the study protocol) did not include a definition of subgroup analysis, as this was only defined during the development of the original SCE SAP Version 1.0 (20 April 2021).

Important modifications were made to the protocol which impacted the study design and the statistical approach. Phase 2 cohorts were redefined with protocol v6.0 to be disease specific rather than stratified by BTK mutational status. This amendment was made to support registration. Even though, limited impact on efficacy analysis could be expected from this change, results by BTK mutational status which would have been able to confirm the *in vitro* activity on C481 mutation were not provided.

It was also noted that the first version of each SAP was finalised when the study had already been ongoing for more than 2 years. Both SAPs were revised just before the interim analysis cut-off date. The cut-off date itself was modified from 16 July 2021 to 31 January 2022 in the revised version of the SCE SAP dated 13 January 2022. That means the cut-off was changed 6 months after the previously defined cut-off date had been reached, and only two weeks before the newly defined date. There were no clear predefined criteria for the determination of the cut-off date. Of note, the cut-off date appears

to be left undefined in the interim CSR SAP but the same date was selected as for the SCE (31 January 2022).

As both provided SAPs are relevant to the MCL application it is not possible to determine on what basis one should be considered primary and the other as supportive. This creates a multiplicity issue, which is of concern, particularly as no multiplicity adjustment had been planned in either SAP. The late changes in planned analyses in conjunction with the single arm nature of the study also raise bias concerns for the reported results.

The CHMP noted the consistency in the results that have been performed across the various analysis populations and cut-off dates which provides some reassurance on the robustness of ORR results in the MCL population, despite the methodological limitations.

Due to the potential for additional heterogeneity, the CHMP had previously warned against pooling patients from Phase 1 who fulfil eligibility criteria with patients from Phase 2 (EMA/CHMP/SAWP/470869/2020). This advice was not followed. Nevertheless, the applicant has provided sensitivity analyses based on the subset of patients from Phase 2 only (Phase 2 analysis set), i.e. excluding patients from Phase 1, which did not show important differences between the PAS and the Phase 2 analysis set.

If the applicant were to proceed with pooling, CHMP advised that the PAS should include only patients treated at the proposed 200mg QD dose. This recommendation was not followed either. The applicant provided additional demographic, baseline characteristics and primary / secondary efficacy results for the subset of patients treated at 200 mg QD dose in the PAS. As could be expected due to the large overlap between the full PAS population and its 200 mg QD subset, baseline characteristics and efficacy results were generally similar between the 200 mg QD PAS subset and the full MCL PAS and using both cut-off dates.

It was also noted that the PFS censoring rules were not in line with the Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/27994/2008/Rev.1). As requested, the applicant provided sensitivity PFS and DoR analyses more in line with the intent-to-treat principle (as per EMA guideline). The PFS sensitivity analysis results appear consistent with the main PFS analysis. It is noted that DoR rates beyond 12 months are numerically lower with the sensitivity analysis compared with the original analysis results, and similarly the median DoR is lower in the sensitivity results (16.10 months) in comparison with the original results (21.59 months). Nevertheless, it is difficult to draw any meaningful interpretation from these observed differences, especially as the censoring rate is high and the median follow-up is only around 12 months.

Efficacy data and additional analyses

Several analysis groups have been presented and analysed by the applicant. In this report, PAS will be considered as the main assessment population, as this is closer to the claimed indication and also provided the longest FU, despite the limitations discussed in the previous section. This analysis group includes the first 90 patients with MCL enrolled from either Phase 1 or Phase 2, irrespective of pirtobrutinib starting dose, who have received a prior BTK inhibitor-containing regimen. It should be noted that 6 patients started on a lower dose, up to the target 200 mg QD dose, while 2 and 5 patients started with 250 and 300 mg QD dose respectively.

Regarding protocol deviations, data were not provided for PAS analysis. However, major deviation only occurred for 7 and 1 patients in cohorts 1 and 7 respectively, without any anticipated impact of the reliability of the results.

In the PAS, median time on treatment is 5.24 months (range: 0.2 to 39.6 months). Patients in the PAS had a median time on study of 10.45 months (range: 0.5 to 34.4 months).

Demographics data for age, sex and weight are globally in line with targeted indication. In the PAS population, subjects had received a median number of 3 prior lines of systemic therapy, with 1 prior BTKi. Discontinuation from this previous BTKi was most of the time (81.1%) due to disease progression.

Primary endpoint: ORR

By IRC assessment, the ORR was 56.7% in PAS, including 18.9% of CR.

This is higher than the rates obtained with available R/R MCL post BTKi treatments such as bortezomib, lenalidomide, and temsirolimus but lower than those reported for brexucabtagene autoleuel (85%) and salvage therapies like R-BAC (83%) or Rituximab + Ibrutinib (88%), in the same setting, even though it is difficult to make comparisons across different studies. In any case, given the limited choice of treatments and the prognosis in this patient population, the reported results are considered clinically significant.

Differences between IRC and investigators assessments were observed even though the Kappa coefficient for overall response, was estimated as 0.843 (95% CI: 0.733, 0.954) indicates a good agreement between the 2 assessments. The applicant provided details of discrepancies between investigator and IRC assessment for the 25 patients presenting a different evaluation of best overall response, in the form of patient narratives. A variety of reasons for discrepancies were identified, such as different lesion selection, reader discrepancy and missing confirmatory bone marrow and in most cases do not impact on the overall response for the patient. The CHMP agreed that the impact of the discordant assessments in BOR have minimal impact on the overall evaluation of the efficacy of pirtobrutinib.

Secondary endpoints

At time of the latest data cut-off date, with a median FU of 12.68 months (5.78, 25.82) and based on IRC assessment, of 51 responding patients, the median duration of response was 17.61 months (7.29, 27.24). A DOR of less than 6 months was noted in 47% of the responders, and more than 18 months for 19.6% of the responders. Moreover, the Kaplan-Meier plot of duration response shows a stable DOR for about half of responders between 6 and 18 months. Considering the poor prognosis of this population once BTKi refractory, these data are promising.

Based on IRC, time to response and time to best response are 1.84 month and 1.87 month respectively, and less than 2 months for 80% of patients. This is consistent with others BTKi authorised and, regarding the rapid course of the disease, clinically significant.

PFS results for PAS are promising, despite a median of 7.36 month (IRC assessment). Rates of PFS are 40% at 12 months and 34% at 18 months.

Among the 90 patients included in the PAS analysis, 44 (57.1%) were censored, including 31 patients (40.3%) which were still alive. The median OS was 23.46 [14.72; NE]). It should be noted that an 18 months OS or more was reached in 58.7% of patients (45.5, 69.5).

These data, even taking into account methodological uncertainties with regards to interpretation of time to event endpoints, are encouraging and are clinically significant and support the efficacy of the product in the claimed indication.

Subgroups analysis

Despite limitations of subgroup analysis due to the study design, limited sample size of subgroups and short FU, it was noted that response rates appeared to be higher for low grade disease (Ann Arbor, MCL international prognostic index) or better prognosis (ECOG<2, Bulk<5cm, absence of bone marrow or gastrointestinal involvement). Of note no strong conclusion can be made between response rate and MCL histology due to the small sample size for pleomorphic and blastoid subtypes in the PAS population. Surprisingly, better response rates are observed for patients with >3 prior lines of systemic therapies; this observation is however tempered by a shorter DOR. Finally better responses are observed for patients who discontinued previous BTKi for toxicity instead of disease progression.

Additional efficacy data needed in the context of a conditional MA

The single arm, open-label study design limits the ability to make any direct comparisons against other available therapies which in the post-BTK inhibitor population is limited to CAR-T therapy and has limited utility for many patients with relapsed MCL. Another limitation is the interpretation of data, in particular with regards to assessment of time to event endpoints. These uncertainties will be addressed through the ongoing confirmatory Phase 3 Study in previously treated, but BTK inhibitor-naive, patient with MCL (Study 20019 [BRUIN-MCL-321]). This is a global, open-label, Phase 3 randomised study in previously treated, but BTK inhibitor-naive, patients with MCL, randomised 1:1 between pirtobrutinib experimental arm and the Investigator's choice of covalent BTK inhibitor. The proposed confirmatory study is for a different patient population with MCL who have not yet received a BTK inhibitor, in an earlier line of therapy than for which the initial marketing authorisation is sought. This is considered necessary for the feasibility of this confirmatory study.

The primary endpoint of the study is PFS as assessed by the IRC per the Lugano 2014 criteria (Cheson et al. 2014). PFS, as the primary endpoint for this study, serves as a surrogate for OS and is used because of the protracted duration of follow-up expected to reach an OS endpoint. Overall survival is a secondary endpoint for the study. At the time of the primary PFS analysis, the secondary OS analysis will seek to establish that there is no detrimental impact on survival, with a potential to observe a positive trend in OS.

The results from the study are expected to be available by 31 March 2026.

2.5.7. Conclusions on the clinical efficacy

The clinical efficacy data submitted in this MAA support the benefit of pirtobrutinib in the final agreed indication. The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The final study report of the phase 3 open-label, randomised Study of LOXO-305 versus investigator choice of BTK inhibitor in patients with previously treated BTK inhibitor-naive Mantle Cell Lymphoma (BRUIN-MCL-321) should be provided.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

The main safety analysis sets in support of this application comes from patients receiving pirtobrutinib monotherapy on Study 18001 (**Table 31**). This study includes a Phase 1 dose escalation and

expansion portion, as well as a Phase 2 part. The primary objective of Phase 1 was to determine the MTD and/or RP2D of pirtobrutinib through safety characterisation. From Phase 1, the RP2D of pirtobrutinib 200 mg QD was selected and used for Phase 2. The primary objective of Phase 2 was to assess the antitumor activity of pirtobrutinib based on ORR by IRC.

For the primary safety analysis, patient safety data from Phase 1, all dose levels, and Phase 2 monotherapy data are pooled. At least one dose of pirtobrutinib 200mg QD or above were received by 96% of patients in OMTSAS and 97% of patients in MSAS, while other patients received a lower dose (25mg to 150 mg).

Exposure fata from the two data cut-off dates for the safety data base are summarised in **Table *37***.

Table 37. Summary of cumulative exposure overall monotherapy safety analysis set study 18001

Time on Treatment, Months	Data Cut-off: 31 January 2022		Data Cut-off: 29 July 2022	
	MSAS N = 164	**OMTSAS N = 725**	**MSAS N = 166**	**OMTSAS N = 773**
	Proportion of Patients n (%)			
≥6	66 (40.2)	423 (58.3)	77 (46.4)	480 (62.1)
≥9	35 (21.3)	339 (46.8)	57 (34.3)	406 (52.5)
≥12	22 (13.4)	240 (33.1)	42 (25.3)	326 (42.2)
≥18	17 (10.4)	122 (16.8)	20 (12.0)	200 (25.9)
≥24	7 (4.3)	41 (5.7)	13 (7.8)	97 (12.5)

Abbreviations: MCL = mantle cell lymphoma; MSAS = MCL safety analysis set; N = number of patients; n number of patients in the specific subset; OMTSAS = overall monotherapy safety analysis set.

Dose intensity

The Study 18001 protocol allowed dose interruptions, reductions, and escalations at the discretion of the treating physician. Relative dose intensity was defined in the SCS SAP as the percentage of dose received relative to the planned dose through to treatment discontinuation. Mean dose intensity was high (>95%) for both OMTSAS and MSAS, and median dose intensity was 100% for MSAS and 99.68% for OMTSAS. Similar data were observed for patients who received the intended dose of 200 mg QD in OMTSAS.

Dose modification

Dose modifications were frequent and were primarily dose interruptions (51.7% in OMTSAS and 42.7% in MSAS) of which the main reason was AE (29.8% in OMTSAS and 26.6% in MSAS), patient error (19.0% in OMTSAS and 15.9% in MSAS) and procedure (16.7% in OMTSAS and 10.4% in MSAS). Most (80%) of dose interruptions due to patient error had a duration of one day.

Dose reductions were less frequent than dose interruptions (5.5% of patients in MSAS and 6.5% in OMTSAS) and were mainly related to AEs.

Finally dose increases were mainly related to intra-patient dose escalation during the phase I. In addition, some patients who had their dose-reduced and who could tolerate pirtobrutinib were allowed to re-escalate to the preceding dose level.

Patients Demographic

Demographic characteristics for patients in the main safety data sets are summarised in **Table 38**.

Table 38. Patient demographics in main monotherapy safety analysis sets - Data cut-off 31 January 2022

Parameter	MSAS (N = 164)	CSAS (N = 311)	OMTSAS (N = 725)
Sex, n (%)			
Male	128 (78.0)	206 (66.2)	482 (66.5)
Female	36 (22.0)	105 (33.8)	243 (33.5)
Race, n (%)			
White	129 (78.7)	286 (92.0)	628 (86.6)
Black or African American	3 (1.8)	12 (3.9)	22 (3.0)
Native Hawaiian or Other Pacific Islander	0	2 (0.6)	3 (0.4)
Asian	20 (12.2)	5 (1.6)	42 (5.8)
American Indian or Alaska Native	2 (1.2)	0	3 (0.4)
Other	10 (6.1)	5 (1.6)	26 (3.6)
Unknown	0	1 (0.3)	1 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	3 (1.8)	12 (3.9)	27 (3.7)
Not Hispanic or Latino	154 (93.9)	289 (92.9)	667 (92.0)
Unknown	7 (4.3)	10 (3.2)	31 (4.3)
Age group, n (%)			
< 50 years	1 (0.6)	10 (3.2)	31 (4.3)
50 - < 65	46 (28.0)	101 (32.5)	223 (30.8)
65 - < 75	70 (42.7)	138 (44.4)	294 (40.6)
75 - < 85	39 (23.8)	54 (17.4)	153 (21.1)
≥ 85 years	8 (4.9)	8 (2.6)	24 (3.3)
Age at Enrolment, years			
Mean (SD)	69.5 (8.60)	67.6 (8.87)	67.8 (9.88)
Median	70.0	68.0	68.0
Range	46, 88	36, 88	27, 95

At baseline, most patients in the OMTSAS had an ECOG score of either 0 (364 [50.2%]) or 1 (320 [44.1%]) The median time since initial diagnosis to first dose of study treatment was 97.95 months (range: 0.5, 739.4) in the OMTSAS, and was lower in the MSAS (72.38 [range: 4.5, 209.6]) and higher in the CSAS (133.95 [range: 8.2, 374.5]) than in the OMTSAS.

Prior cancer treatment

In OMTSAS and MSAS, the vast majority of patients received a prior BTK inhibitor (78.1% and 91.5% respectively), a prior anti-CD20 antibody (93.2% and 97.0% respectively) or a prior chemotherapy

(86.8% and 90.9% respectively). In addition, prior CART-therapy was received by 6.9% and 7.9% patients respectively in OMTSAS and MSAS and prior stem cell transplant by 9.2% and 24.4% of patients respectively.

The median number of line of prior systemic therapy was 3.0 in both OMTSAS and MSAS. The main reason for prior discontinuation from most recent BTK inhibitor was disease progression (58.6% in OMTSAS and 76.2% in MSAS) while toxicity was the reason for 13.1% of patients in OMTSAS and 9.1% of patients in MSAS.

Concomitant medication

Concomitant medications were recorded including those started 14 days prior to enrolment through the end of study. Overall, 96.3% of patients in the OMTSAS were treated with concomitant medications.

Medications used at a high incidence in patients in the OMTSAS tended to be supportive medications such as anti-bacterials (442 [61.0%]), antiviral agents (411 [56.7%]), and analgesics (342 [47.2%]). Other concomitant treatments supportive in B-cell cancers were widely used in the study, including anti-gout preparations (304 [41.9%]), immunostimulants (135 [18.6%]), blood substitutes and perfusion solutions (123 [17.0%]), and immune sera and immunoglobulins (90 [12.4%]). The concomitant medications used were in-line with standard clinical practice management of MCL, CLL/SLL and other NHL.

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%]).

2.5.8.2. Adverse events

Table 39. Overview of adverse events- monotherapy safety analysis sets -data cut-off: 29 July 2022

	MCL Safety MSAS (N=166)	CLL/SLL Safety CSAS (N=317)	Overall Monotherapy Safety OMTSAS (N=773)
Any TEAEs, n(%)			
Any TEAE	151 (91.0)	315 (99.4)	734 (95.0)
Grade 1-2	69 (41.6)	106 (33.4)	293 (37.9)
Grade 3-4	71 (42.8)	180 (56.8)	394 (51.0)
Grade 5	11 (6.6)	29 (9.1)	47 (6.1)
Any TEAE Related to Pirtobrutinib, n(%)			
Any TEAE	111 (66.9)	203 (64.0)	484 (62.6)
Grade 1-2	74 (44.6)	125 (39.4)	307 (39.7)
Grade 3-4	37 (22.3)	74 (23.3)	172 (22.3)
Grade 5	0	4 (1.3)	5 (0.6)
Any Serious TEAE, n(%)			
Any TEAE	62 (37.3)	151 (47.6)	314 (40.6)
Related to Pirtobrutinib	9 (5.4)	25 (7.9)	49 (6.3)
TEAE Action Taken, n (%)			
TEAE Leading to Study Drug Interrupted	54 (32.5)	147 (46.4)	299 (38.7)
Related TEAE Leading to Drug Interrupted	33 (19.9)	47 (14.8)	123 (15.9)
TEAE Leading to Dosage Reduction	9 (5.4)	19 (6.0)	42 (5.4)
Related TEAE Leading to Dosage Reduction	8 (4.8)	15 (4.7)	35 (4.5)
TEAE Leading to Study Drug Permanent Discontinuation	16 (9.6)	26 (8.2)	58 (7.5)
Related TEAE Leading to Study Drug Permanent Discontinuation	5 (3.0)	9 (2.8)	20 (2.6)
Fatal TEAE, n (%)			
Any Fatal TEAE	11 (6.6)	29 (9.1)	47 (6.1)
Related to Pirtobrutinib	0	4 (1.3)	5 (0.6)

Abbreviations: N = number of patients; n = number of patients in the specific subset; SAEs = serious adverse events; TEAE = treatment-emergent adverse events

Note: All adverse events reported during the treatment-emergent period are considered treatment-emergent adverse events (TEAEs); Patients with multiple severity ratings for a given AE are counted once under the maximum severity.

Common adverse events

For the purpose of specificity, incidences at the intended dose of 200 mg are specified in square brackets in this section.

In OMTSAS and MSAS respectively, common adverse events pertained primarily to SOC Gastrointestinal disorders (50.6% [47.8%] and 46.3%), General disorders and administration site conditions (47.9% [45.9%] and 50.0%) and Infections and infestations (46.9% [44.7%] and 50.0%).

Other frequent events were within SOC Musculoskeletal and Connective Tissue Disorders (39.2% [37.5%] and 32.3%), Respiratory, Thoracic and Mediastinal Disorders (38.2% [35.5%] and 36.0%), Skin and Subcutaneous Tissue Disorders (36.7% [35.0%] and 25.6%), Investigations (35.9% [34.2%] and 29.3%), Nervous System Disorders (32.7% [30.5%] and 24.4%), Injury, Poisoning and Procedural Complications (29.1% [28.1%] and 22.0%), Blood and Lymphatic System Disorders (28.0% [27.3%] and 24.4%), Metabolism and Nutrition Disorders (27.2% [26.4%] and 21.3%).

In OMTSAS, the most common adverse events by PT were fatigue (26.3% [24.1%]), diarrhoea (22.1% [20.2%]), and contusion (19.0% [18.6%]).

Other frequent adverse events in OMTSAS and MSAS respectively included, dyspnoea, cough, arthralgia, back pain, pyrexia, oedema peripheral, abdominal pain and headache, all of which have been described for other BTK inhibitors.

Treatment–related adverse event with an incidence ≥ 5% were related to gastro-intestinal events (diarrhoea), haematological events (neutrophil count decrease and neutropenia), contusion and fatigue.

Grade 3 or 4 adverse events

Grade 3/4 adverse events were mainly related to SOC Blood and Lymphatic System Disorders and infections and infestations.

In OMTSAS [at 200mg] and MSAS respectively, grade 3/4 PT related to haematological toxicity were neutrophil count decrease (10.6% [10.3%] and 8.5%), neutropenia (8.6% [8.3%] and 3.7%), anaemia (7.7% [8.0%] and 4.9%), platelet count decrease (4.8% [4.8%] and 5.5%), febrile neutropenia (2.2% [2.5%] and 1.2%), leucocytosis (1.9% [2.0%] and 3.7%) and thrombocytopenia (1.8% [2.0%] and 1.2%).

Grade 3/4 PT related to infections were, respectively for OMTSAS and MSAS: pneumonia (4.8% [4.8%] and 7.9%), COVID-19 pneumonia (4.8% [4.1%] and 2.4%), COVID-19 (2.3% [2.2%] and 2.4%), sepsis (2.2% [2.3%] and 3.0%).

Other grade 3/4 occurring in ≥1% of patients were fatigue, acute kidney injury, ALT increase, hypotension, atrial fibrillation and pleural infusion. In addition, grade 3/4 respiratory failure occurred at 1.6% in OMTSAS [1.3%] and 2.4% in MSAS, and dyspnoea occurred at 1.6% in OMTSAS [0.9%] and 3.6% in MSAS.

Adverse Drug Reactions

For the determination of adverse drug reactions (ADRs), the applicant used descriptive analytical criteria for the initial screening of the AE and abnormal categorical numerical safety data in the registration trial Study 18001. Scientific and medical judgment including incidence and severity of event, biological plausibility and known association with other Bruton's tyrosine kinase inhibitors was used to assess the relationship with pirtobrutinib and to determine whether the event was clinically significant and medically informative.

Events that met the initial screening criteria and/or were considered medically informative and clinically significant were designated as ADRs for single agent pirtobrutinib in patients with previously treated chronic lymphocytic leukaemia/ small lymphocytic lymphoma or non-Hodgkin lymphoma, including mantle cell lymphoma and are shown in with their associated all Grade and Grade ≥ 3 frequencies from the OMTSAS and for patients that received the intended 200mg dose QD as the starting dose and who did not subsequently dose escalate.

Table 40. ADRs of patients treated with pirtobrutinib monotherapy[a] at 200 mg QD

System organ class (MedDRA)	ADR	Frequency category (%) (All grades)	Grade≥ 3[c] (%)
Infections and infestations	Pneumonia	Common (8.2)	5.1
	Urinary tract infection	Common (6.9)	0.7
	Upper respiratory tract infection	Common (5.0)	0
Blood and lymphatic system disorders	Neutropenia[b]	Very common (22.1)	19.2
	Thrombocytopenia[b]	Very common (12.9)	7.0
	Anaemia[b]	Very common (14.4)	8.2
	Lymphocytosis[b]	Common (5.1)	3.1
Nervous system disorders	Headache	Common (9.8)	0.3
Cardiac disorders	Atrial fibrillation/Atrial flutter	Common (2.7)	1.0
Vascular disorders	Haemorrhage	Very Common (16.8)	2.4
	Haematuria	Common (3.1)	0.0
	Epistaxis	Common (3.8)	0.2
	Haematoma	Common (1.9)	0.2
	Bruising	Very Common (21.8)	0.0
	Contusion	Very Common (18.2)	0.0
	Petechiae	Common (4.6)	0.0
Gastrointestinal disorders	Diarrhoea	Very common (19.9)	0.9
	Nausea	Very common (14.1)	0.2
	Abdominal pain	Very common (10.3)	1.0
Skin and subcutaneous tissue disorders	Rash[b]	Very common (11.7)	0.3
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (12.2)	0.5
General disorders and administration site conditions	Fatigue	Very common (23.7)	1.2

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

[b] *Includes multiple adverse reaction terms*

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

2.5.8.3. Serious adverse event/deaths/other significant events

Deaths

In OMTSAS, up until the 31st January 2022 data cut-off, 6.2% (45 patients) had an AE with fatal outcome within 28 days of the last dose of pirtobrutinib. More than half of these fatal AEs pertained to SOC infections and infestations (64.4%) of which the half were related to COVID-19 (51.7%). Fatal AEs considered related to pirtobrutinib by the investigator were observed for 4/45 patients and were all of infectious nature (included COVID-19 pneumonia, pneumonia necrotising, respiratory failure, and *Enterococcus faecium*-related septic shock).

Other deaths that occurred within 28 days of last dose pertained to SOC General disorders and administration site conditions (4 patients), Cardiac disorders (1 patient with cardiac arrest), Vascular disorders (1 patient with septic shock and 1 patient with massive haemorrhage), Respiratory, thoracic

and mediastinal disorders (4 patients), Nervous system disorders (1 patient), Injury, poisoning and procedural complications (1 patient), Metabolism and nutrition disorders (1 patient).

Other serious adverse events

In study 18001, SAEs were experienced by a third of the patients (**Table *41***) and were mainly related to infections which is expected both in the intended population and in the context of neutropenia-induced AEs.

Table 41. Serious adverse events occurring in ≥ 1% of patients by preferred term in order of decreasing incidence in the OMTSAS-Data cut-off: 31 January 2022

	MSAS (N = 164)		**CSAS (N = 311)**		**OMTSAS (N = 725)**	
PT, n (%)	**All**	**Related**	**All**	**Related**	**All**	**Related**
Any SAE	55 (33.5)	8 (4.9)	120 (38.6)	26 (8.4)	255 (35.2)	41 (5.7)
Pneumonia	13 (7.9)	3 (1.8)	17 (5.5)	5 (1.6)	34 (4.7)	8 (1.1)
COVID-19 pneumonia	5 (3.0)	0	16 (5.1)	2 (0.6)	28 (3.9)	2 (0.3)
COVID-19	2 (1.2)	0	11 (3.5)	0	17 (2.3)	0
Febrile neutropenia	1 (0.6)	1 (0.6)	9 (2.9)	5 (1.6)	13 (1.8)	8 (1.1)
Anaemia	1 (0.6)	0	7 (2.3)	2 (0.6)	12 (1.7)	2 (0.3)
Pyrexia	1 (0.6)	0	3 (1.0)	0	11 (1.5)	1 (0.1)
Sepsis	3 (1.8)	1 (0.6)	4 (1.3)	1 (0.3)	11 (1.5)	2 (0.3)
Acute kidney injury	2 (1.2)	0	4 (1.3)	0	10 (1.4)	0
Bacteraemia	1 (0.6)	0	2 (0.6)	1 (0.3)	7 (1.0)	1 (0.1)
Pleural effusion	3 (1.8)	0	2 (0.6)	0	7 (1.0)	0
Respiratory failure	2 (1.2)	0	3 (1.0)	1 (0.3)	7 (1.0)	1 (0.1)
Urinary tract infection	0	0	6 (1.9)	0	7 (1.0)	0

Abbreviations: CLL = chronic lymphocytic leukaemia; CSAS = CLL/SLL Safety Analysis Set; COVID-19 = coronavirus disease 2019; MCL = mantle cell lymphoma; MSAS = MCL Safety Analysis Set; N = number of patients; n = number of patients in the specified category; OMTSAS = Overall Monotherapy Safety Analysis Set; PT = preferred term; SAE = serious adverse event; SLL = small lymphocytic lymphoma

Only 4.9% of SAE in MSAS and 5.7% of SAE in OMTSAS were considered related to pirtobrutinib and were within SOC infections and infestations and blood and lymphatic system disorders events.

Adverse events of special interest

Adverse events of special interest (AESI) were identified based on the known safety profile of covalent BTK inhibitor therapies, non-clinical toxicology, and emerging safety data during the conduct of the

study. Aggregate analysis was conducted as part of the analysis of AESI to characterise the safety profile of these events and included the following composite terms: cytopenia (specifically, neutropenia, anaemia, and thrombocytopenia), infections, bleeding (including bruising and haemorrhage), and atrial fibrillation and atrial flutter. A summary of the cumulative incidence of adverse events of AESIs per exposure duration is presented in **Table *42***.

Table 42. Summary of treatment-emergent adverse events of special interest by exposure duration overall monotherapy safety analysis set study 18001 data cut-off: 29 July 2022

Adverse Event of Special Interest	Time on Treatment (N = 773)					
	<12 Months		<18 Months		<24 Months	
	Any TEAEs n (%)	Grade ≥3 n (%)	Any TEAEs n (%)	Grade ≥3 n (%)	Any TEAEs n (%)	Grade ≥3 n (%)
Anaemia	111 (14.4)	61 (7.9)	118 (15.3)	67 (8.7)	120 (15.5)	68 (8.8)
Neutropenia	172 (22.3)	149 (19.3)	186 (24.1)	161 (20.8)	191 (24.7)	164 (21.2)
Thrombocytopenia	103 (13.3)	52 (6.7)	110 (14.2)	57 (7.4)	115 (14.9)	62 (8.0)
Infections	367 (47.5)	125 (16.2)	408 (52.8)	145 (18.8)	421 (54.5)	158 (20.4)
Infections without COVID-19	317 (41.0)	96 (12.4)	346 (44.8)	108 (14.0)	356 (46.1)	116 (15.0)
Bleeding	257 (33.2)	11 (1.4)	268 (34.7)	15 (1.9)	273 (35.3)	16 (2.1)
Bruising	171 (22.1)	0 (0.0.)	176 (22.8)	0 (0.0)	179 (23.2)	0 (0.0)
Haemorrhage	123 (15.9)	11 (1.4)	141 (18.2)	15 (1.9)	144 (18.6)	16 (2.1)
Haemorrhage/Haemtoma	69 (8.9)	9 (1.2)	83 (10.7)	13 (1.7)	87 (11.3)	14 (1.8)
Atrial Fibrillation and Atrial Flutter	19 (2.5)	9 (1.2)	20 (2.6)	9 (1.2)	20 (2.6)	9 (1.2)

Abbreviations: COVID-19 = coronavirus disease 2019; N = number of patients; n = number of patients in the specific subset.

Adverse events of potential clinical significance (data cut-off 31 January 2022)

Second primary malignancies

In OMTSAS, second primary malignancies occurred in 6.6% (48 patients) of patients with 33/48 being non melanoma skin cancer, of which 35/48 were grade 2, 8 grade 3 events and 1 grade 4 event. These SPM were in majority non melanoma skin cancers. None of these skin cancer event was fatal or considered as SAE.

In MSAS, 6 patients (3.7%) had a second primary malignancy (1 anal squamous cell carcinoma not resolved, 3 basal cell carcinomas, 2 melanomas, 1 recurrent urothelial carcinoma). 4 patients had a grade 2 event and the two other patients had each a grade 1 and grade 3. 1/6 events was considered as SAE (recurrent urothelial carcinoma) but none was considered related to pirtobrutinib. One event on the 6 required pirtobrutinib discontinuation (squamous cell carcinoma) which was the only dose modification; to be noted, in MSAS, the median time to first onset was 57.43 weeks which is far above the median treatment duration of 4.5 months.

Tumour lysis syndrome

In study 18001, tumour lysis syndrome occurred in 4 patients of which 1 patient with CLL received pirtobrutinib in association with venetoclax and had two event of TLS. In OMTSAS, on the 3 remaining patients who received pirtobrutinib monotherapy, one patient had a MCL and 2 patients had B-cell prolymphocytic lymphoma.

In addition, as reported by the applicant, there was 1 case of a fatal TLS event in a patient with follicular lymphoma that was assessed as being related to pirtobrutinib. This case was reported in a separate ongoing trial conducted in China not part of the safety dataset (the OMTSAS) for this application.

Lymphocytosis

The applicant analysed lymphocytosis as a composite event of leucocytosis, lymphocyte count increase, lymphocytosis and white blood cell count increase. In OMTSAS and MSAS, 4.8% and 6.1% of patients respectively experienced lymphocytosis with the majority that were grade 3 and with one patient experiencing a grade 4 event. Furthermore, the majority (8/10) was considered related to pirtobrutinib and 3/10 were considered as SAE. Lymphocytosis was managed with treatment interruption in 3 patients. Time to first onset was short in general, within the first 4 weeks and with a median time to first onset of 1.14 week which is consistent with safety profile of other BTK inhibitors.

Cardiovascular events

Hypertension was the most frequent cardiac event (9.5% in OMTSAS with 2.8% of grade 3 and no grade ≥ 4, and 3.7% in MSAS with only grades 1 or 2) and approximately a third of these events were considered related to pirtobrutinib. None of the events of hypertension was considered serious. Median time of onset was 23.71 weeks in OMTSAS and 18.14 weeks in MSAS, with the majority of events occurring after 12 weeks but early time of first onset occurred also. Overall, events of hypertension were managed with pirtobrutinib interruption only in few cases.

Supraventricular tachyarrhythmia (excluding cases of atrial fibrillation and atrial flutter) occurred at 2.9% in OMTSAS with 0.6% ≥ grade 3, and at 2.4% (4 patients) in MSAS with only grades 1/2 of which 2 events were considered related to pirtobrutinib. Events were considered serious in 0.6% of patients in OMTSAS and none in MSAS. Median time to first onset was 7.29 weeks in OMTSAS and 3.14 weeks in MSAS. No pattern of time to first onset can be observed. Overall, most of events of supraventricular tachyarrhythmia were managed without dose modification, only one patients in OMTSAS had pirtobrutinib interruption.

Heart failure occurred in 1.4% of patients in the OMTSAS with half of the cases being grades 1/2 and the other half being grade 3/4. In MSAS, heart failure occurred in 1 patient (0.6%, grade 2) that was considered related to pirtobrutinib. No grade 5 events was observed. Events were considered serious in 0.6% of patients in OMTSAS and none in MSAS. Median time to first onset was approximately 12 weeks in both analysis set and all events occurred after 8 weeks. Overall, heart failure was managed with dose reduction for the patient in MSAS and with drug interruption (2 patients, 0.3%) or dose reduction (0.1%, 2 patient) in OMTSAS.

Ventricular arrhythmia occurred in 0.7% (5 patients) in OMTSAS and in 0.6% (1 patient) in MSAS. All events were of grade 1/2. 2 events in OMTSAS and the event in MSAS were considered related to pirtobrutinib. None of the events was considered serious and no grade 5 event occurred. Median time of onset was approximately 16 weeks in both analyses sets and most events occurred after 12 weeks. All the events of ventricular arrhythmia were managed without dose modification.

Rash

Rash is a known ADR of other BTK inhibitors (ibrutinib, zanubrutinib, acalabrutinib) with a very common frequency. Overall, the assessment of the applicant stating that rash did not translate into a clinically significant safety finding for pirtobrutinib can be followed.

Events of rash occurred in 12.3% of patients in OMTSAS and in 8.5% of patients in MSAS. The majority of events were grade 1 or 2 with only 3 patients in OMTSAS and 1 patient in MSAS who experienced a grade 3 event. Approximately half of the cases were considered related to study treatment. None of the events was considered serious and no grade 4 or 5 event occurred. Most of the time, rash events were managed without dose modification and in some cases with dose interruption or dose reduction in fewer cases. One event led to permanent discontinuation (non-serious related AE of maculo-papular rash in a patient with SLL).
Median time of first onset was approximately 6 weeks for both analysis set with events occurring as soon as within the first 4 weeks of treatment or after 12 weeks of treatment.

2.5.8.4. Laboratory findings

Analyses of data from clinical laboratory evaluations were consistent with the analyses of AEs reported in OMTSAS for Study 18001.

Haematology (neutrophils, haemoglobin, platelets, lymphocytes) laboratory abnormalities were present at baseline, while some worsened while on treatment, these changes were transient with most having returned to baseline or better as of the last post-baseline value recorded.

Chemistry laboratory values were also in accordance with the reported AEs. Blood creatinine increase was reported as an AE in 4.7% of patients in OMTSAS, even though laboratory findings suggest a higher incidence (26.5%). However, both reported AE and laboratory values suggest low grade events for creatinine increases and in approximately 90% of cases, values had return to their baseline grade or better at the last post baseline assessment.

No additional safety signals were identified from clinical laboratory evaluations.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

Table 43. Summary of selected adverse events by age interval in study LOXO-BTK-18001 (OMTSAS)-data cut-off 31 January 2022

	Age Interval			
	< 65 years (N = 254)	**65 – 74 years (N = 294)**	**75 – 84 years (N = 153)**	**≥ 85 years (N = 24)**
n (%)				
Total AEs	233 (91.7)	279 (94.9)	145 (94.8)	24 (100.0)
Serious AEs – Total	71 (28.0)	117 (39.8)	58 (37.9)	9 (37.5)
Fatal	13 (5.1)	25 (8.5)	6 (3.9)	1 (4.2)
Hospitalisation/prolong existing hospitalisation	65 (25.6)	109 (37.1)	57 (37.3)	9 (37.5)
Life-threatening	6 (2.4)	7 (2.4)	4 (2.6)	0 (0.0)
Disability/incapacity	0	2 (0.7)	0	0
Other (medically significant)	7 (2.8)	10 (3.4)	3 (2.0)	0 (0.0)
AE leading to drop-out	15 (5.9)	15 (5.1)	12 (7.8)	3 (12.5)
Psychiatric disorders	27 (10.6)	31 (10.5)	19 (12.4)	5 (20.8)
Nervous system disorders	90 (35.4)	93 (31.6)	45 (29.4)	9 (37.5)
Accidents and injuries	48 (18.9)	80 (27.2)	54 (35.3)	10 (41.7)
Cardiac disorders	32 (12.6)	41 (13.9)	20 (13.1)	4 (16.7)
Vascular disorders	40 (15.7)	40 (13.6)	36 (23.5)	3 (12.5)
Cerebrovascular disorders	3 (1.2)	7 (2.4)	2 (1.3)	1 (4.2)
Infections and infestations	112 (44.1)	151 (51.4)	68 (44.4)	9 (37.5)
Anticholinergic syndrome	60 (23.6)	87 (29.6)	43 (28.1)	4 (16.7)
Quality of life decreased	3 (1.2)	4 (1.4)	6 (3.9)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	30 (11.8)	50 (17.0)	27 (17.6)	3 (12.5)
Other AE appearing more frequently in older patients	10 (3.9)	18 (6.1)	19 (12.4)	1 (4.2)

Abbreviations: AE = adverse event; N = number of patients; n = number of patients in the specific category; OMTSAS = overall monotherapy safety analysis set.
Notes: All AEs reported during the treatment-emergent period are considered treatment-emergent adverse events; The reported AE term is coded using version 24.0 of the Medical Dictionary for Regulatory Activities; At each level of subject summarisation, a subject is counted only once if the subject reported 1 or more events. The results are presented in the descending order of incidence; Secondary primary malignancy is identified for other AE appearing more frequently in older patients.

2.5.8.7. Immunological events

Not applicable.

2.5.8.8. Safety related to drug-drug interactions and other interactions

Please see Clinical pharmacology section of this report.

2.5.8.9. Discontinuation due to adverse events

In the OMTSAS, 45 (6.2%) patients experienced an AE that led to permanent treatment discontinuation (Data cut-off 31 January 2022). 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%]) (SCS Table 14.4.12.1). No other SOCs had AEs leading to treatment discontinuation with incidences ≥ 1%.

There were 15 (2.1%) patients that 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.

The incidences of study treatment-related AEs that led to the treatment discontinuation were generally similar across analysis sets (MSAS: 5 [3.0%] patients; CSAS 8 [2.6%] patients; OMTSAS 15 [2.1%] patients).

2.5.8.10. Post marketing experience

Not applicable.

2.5.9. Discussion on clinical safety

The characterisation of the safety profile of pirtobrutinib is based on a single non-comparative phase 1/2 study. At the latest data cut-off (29 July 2022), 773 patients in total with MCL, CLL/SLL and other NHL received pirtobrutinib as monotherapy ("OMTSAS" analysis set). Among these, only 166 patients had MCL ("MSAS" analysis set) so the safety data of pirtobrutinib in the intended indication is limited. However, given the rarity of MCL and the safety information from the larger database, including other B-cell malignancies, the overall safety database is considered acceptable.

At the data cut-off, approximately half of the patients in OMTSAS and one third of the patients in MSAS were still on treatment. While this difference between both analyses sets was mainly attributed to the number of patients who discontinued the study due to progressive disease, the incidence of discontinuation due to AEs was comparable.

Both safety analysis sets include patients treated with other doses than the intended dose of 200mg. This is due to the inclusion of patients issued from the dose escalation part of the pivotal trial. Data of patients who received a different dose than 200mg (lower or higher) do not appear to alter the safety results, even though they represent a small percentage of the overall safety population. Nevertheless, the table of ADRs for inclusion in section 4.8 of the SmPC at the request of the CHMP is based only on data from patients who received the intended starting dose of 200mg QD and who did not subsequently dose escalate.

Adverse events

AEs were experienced by approximately 90% of patients in both analyses sets with 60% considered related to pirtobrutinib. Grade 3/4 AEs were experienced by 46.9% of patients in OMTSAS and 39.6% of patients in MSAS, of which half were considered related to pirtobrutinib. SAEs were experienced by one third of the patients but only 5% were considered related to pirtobrutinib.

Fatal AEs were experienced by 6.2% and 6.7% of patients in OMTSAS and MSAS respectively. Although 4 patients (0.6%) had a fatal AE considered related to pirtobrutinib in OMTSAS, none of the fatal AE was considered related to pirtobrutinib in MSAS.

Overall, common adverse events observed with pirtobrutinib monotherapy in pivotal study 18001 were consistent with the reported safety profile of the other authorised BTK inhibitors.

In OMTSAS and MSAS respectively, common adverse events pertained primarily to SOC of Gastrointestinal disorders (50.6% and 46.3% in OMTSAS and MSAS respectively), General disorders and administration site conditions (47.9% and 50.0%) and Infections and infestations (46.9% and 50.0%). Grade 3/4 adverse events pertained mainly to SOC Blood and Lymphatic System Disorders and Infections and infestations while gastro-intestinal events were of low grade in general.

In OMTSAS, the most common adverse events by PT were fatigue (26.3%), diarrhoea (22.1%), and contusion (19.0%) with similar profile in MSAS and have been included in section 4.8 of the SmPC. Other frequent adverse in OMTSAS and MSAS included arthralgia, back pain, oedema peripheral, abdominal pain and headache, which have been described for other BTK inhibitors. These have also been included in section 4.8 of the SmPC with the exception of back pain and oedema peripheral, due to the absence of ≥ grade 3 events and the absence of suggested mechanism of action.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

In addition, considering that fatigue was a very common adverse event, and that dizziness and asthenia were also reported in association with pirtobrutinib, the product information includes a warning that pirtobrutinib may have a minor influence on the ability to drive and use machines which should be considered when assessing a patient's ability to drive or operate machines.

Adverse event of special interest

Infections are known ADRs of BTK inhibitors, related to both the nature of the disease to be treated and to treatment induced of neutropenia. Serious infections, including fatal cases, have occurred in patients treated with pirtobrutinib. The most frequently reported Grade 3 or higher infections were pneumonia, COVID-19 pneumonia, COVID-19, and sepsis. The product information recommends prophylactic antimicrobial therapy in patients who are at increased risk for opportunistic infections. Based on the grade of infection and whether it occurs with neutropenia, dose interruption may be required.

Bleeding including fatal cases, have occurred in patients treated with pirtobrutinib, with and without thrombocytopenia. Major bleeding events of Grade 3 or higher, including gastrointestinal bleeding and intracranial haemorrhage were also observed. Warnings about the need to monitor patients for signs and symptoms of bleeding are included in the product information. Patients receiving anticoagulant or antiplatelet agents may be at increased risk of haemorrhage. The risks and benefits of anticoagulant or antiplatelet therapy should be considered when co administered with pirtobrutinib and consider additional monitoring for signs of bleeding. The use of pirtobrutinib has not been studied with warfarin or other vitamin K antagonists.

The benefit risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery should be considered depending upon the type of surgery and risk of bleeding. Serious haemorrhages and infections are both considered as important identified risks in the pirtobrutinib RMP.

Another class effect of BTK inhibitor is cytopenia. Grade 3 or 4 cytopenias, including neutropenia, anaemia and thrombocytopenia occurred in patients treated with pirtobrutinib. Complete blood counts should be monitored in patients during treatment as medically indicated. The SmPC of pirtobrutinib includes recommendations of dosing modification in section 4.2 in case of haematological toxicity with interruption in case of Grade 3 neutropenia associated with fever and/or infection, Grade 4 neutropenia lasting≥7 days, Grade 3 thrombocytopenia associated with bleeding and Grade 4 thrombocytopenia. Reintroduction at either original dose or a reduced dose is also recommended depending on the number occurrence. In addition, neutropenia, anaemia, and thrombocytopenia are listed in section 4.8.

Finally**,** atrial fibrillation or atrial flutter occurred in patients in both OMTSAS and MSAS. Almost one third of the patients had a grade 3/4 events and 5 cases were considered as SAE.

While it is acknowledged that the intended population for pirtobrutinib is at increased risk of atrial fibrillation (advanced age, cardiovascular co-morbidities), it is also a known ADR of other BTK inhibitors. Therefore, it is included in the RMP as an important identified risk and in section 4.8 of the SmPC together with a warning in section 4.4 that signs and symptoms of atrial fibrillation and atrial flutter should be monitored in patients and an electrocardiogram should be obtained as medically indicated. Based on the grade of atrial fibrillation/atrial flutter, dose interruption may also be required.

Additional events of clinical importance

Second primary malignancies were observed in both safety analysis sets, the majority of which were non-melanoma skin cancers.

The CHMP acknowledged that the included population is at increased risk of SPM and that previous treatments are also potentially confounding factors. Even though it is not possible to establish a direct causality with pirtobrutinib, patients should be monitored for the appearance of skin cancers and advise protection from sun exposure. In addition, second primary malignancies, non-melanoma skin cancer and other second primary malignancies have been included in the RMP as important potential risks and the applicant will conduct an analysis of the incidence of these events from ongoing clinical studies with pirtobrutinib with a 5-year follow-up.

Tumour lysis syndrome occurred in a small number of patients who received pirtobrutinib monotherapy in the pivotal trial with one fatal case reported in another trial which was not part of the safety dataset for this submission. TLS is uncommon in patients treated with ibrutinib and acalabrutinib. Furthermore, in the Study 18001 OMTSAS population, TLS occurred often in the context of disease progression particularly in patients with very high tumour burden. All cases except 1 (reported in a separate ongoing trial conducted in China not part of the safety dataset for this application) were assessed by the investigator to be not related to pirtobrutinib. Nevertheless, 2 cases had a suggestive chronology of TLS. Therefore, a direct causal role of pirtobrutinib cannot be ascertained at this stage. The product information, however, includes a warning that patients at high risk of TLS are those with high tumour burden prior to treatment and that patients should be assessed for possible risk of TLS and closely monitored as clinically indicated.

Lymphocytosis was analysed as a composite event of leucocytosis, lymphocyte count increase, lymphocytosis and white blood cell count increase. Most cases identified were grade 3 and one was a grade 4 event. Furthermore, the majority was considered related to pirtobrutinib and in some cases

was managed with treatment interruption. Lymphocytosis is listed in section 4.8 of the SmPC which is considered acceptable.

In addition to atrial fibrillation and atrial flutter other cardiovascular events were observed including some high grades in OMTSAS (for supraventricular tachyarrhythmia, heart failure and hypertension). These events were managed generally without dose modification and with dose interruption in some cases.

Whilst causality between the observed cardiovascular events and pirtobrutinib cannot be established based on the available data, cases of cardiac failure, cardiac arrhythmia and hypertension will be closely monitored in PSURs.

Events of rash were observed in the pivotal trial but were mainly low grade, non-serious reactions. Rash is a known ADR of other BTK with a very common frequency and inclusion in Section 4.8 with the same frequency is considered sufficient at this stage to manage this risk.

Additional safety data needed in the context of a conditional MA

As exposure to pirtobrutinib in MCL patients is still limited, additional data are expected in order to further characterise the important identified risks associated with its use from the ongoing comparative study in BTK inhibitor-naive, patients with MCL (Study 20019 [BRUIN-MCL-321]).

2.5.10. Conclusions on the clinical safety

Despite limitations arising from the limited exposure of pirtobrutinib in the intended target population which is a consequence of the rarity of the claimed indication and the non-comparative nature of the pivotal trial which hampers causality assessment, the overall safety profile of pirtobrutinib appears to be consistent with those of authorised BTK inhibitors. Main toxicities are related to high grade haematological toxicity and infections and low-grade gastrointestinal events. The inclusion of information on when to interrupt treatment in the product information is considered sufficient to manage these risks.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- The final study report of the phase 3 open-label, randomised Study of LOXO-305 versus investigator choice of BTK inhibitor in patients with previously treated BTK inhibitor-naive Mantle Cell Lymphoma (BRUIN-MCL-321) should be provided.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of Safety Concerns	
Important identified risks	Serious haemorrhage Serious infections Atrial fibrillation and atrial flutter
Important potential risks	Second primary malignancies other than non-melanoma skin cancer

Summary of Safety Concerns	
	Second primary non-melanoma skin cancer
Missing information	None

2.6.2. Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
LOXO-305 A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL) **Status:** ongoing	To integrate the analysis for SPM for a 5 year follow up	- Second primary malignancies other than non-melanoma skin cancer - Second primary non-melanoma skin cancer	An interim analysis is planned for submission to EMA by September 2025	final report by June 2028
LOXO-BTK-20019 A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN MCL-321 **Status:** ongoing				
LOXO-BTK-20020 A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321) **Status:** ongoing				
LOXO-BTK-20023 A Phase 3 Open Label, Randomized. Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-313) **Status:** ongoing				

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

2.6.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Serious haemorrhage	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 • Recommendation to monitor patients for signs and symptoms of bleeding is included in SmPC Section 4.4. • Recommendation to consider the benefit-risk of anticoagulant or antiplatelet therapy when co-administered with pirtobrutinib is included in SmPC Section 4.4. A statement is included in the same section that the use of pirtobrutinib has not been studied with warfarin or other vitamin K antagonists. • Recommendation to consider the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery depending on the type of surgery and risk of bleeding is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of the bleeding event and whether it occurs with thrombocytopenia is provided in SmPC Section 4.2. Additional risk minimisation measures: Not applicable
Serious infections	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 • Recommendation to consider prophylaxis in patients who are at increased risk for opportunistic infections is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of infection and whether it occurs with neutropenia is included in SmPC Section 4.2. Additional risk minimisation measures: Not applicable
Atrial fibrillation and Atrial flutter	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 • Recommendation to monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated is included in SmPC Section 4.4. • Guidance on dose interruption based on the grade of atrial fibrillation/atrial flutter is included in SmPC Section 4.2 Additional risk minimisation measures: Not applicable

Safety Concern	Risk Minimisation Measures
Second primary malignancies other than non-melanoma skin cancer	Routine risk minimisation measures: SmPC Sections 4.2 4.4, • Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4. Additional risk minimisation measures: Not applicable
Second primary non-melanoma skin cancer	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4, • Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4. Additional risk minimisation measures: Not applicable

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 27.01.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Jaypirca (pirtobrutinib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for pirtobrutinib is for the treatment of adult patients with mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

MCL is a rare and aggressive subtype of B-cell NHL and is incurable with current therapies. MCL accounts for 3% to 10% of all new NHL cases per year with a typical incidence of approximately 1 to 2 per 100,000 in Europe and the US. Prognosis for patients with MCL is poor, with OS of 3 to 5 years at diagnosis. 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. Indolent subtypes of MCL have been characterised, however, the typical presentation of MCL is usually aggressive and incurable requiring treatment at diagnosis for most patients.

3.1.2. Available therapies and unmet medical need

As per current guidelines, the following therapeutic options are available: lenalidomide, bortezomib, temsirolimus. To be noted, all these treatments were authorised before BTK arrival, but nevertheless remain an option after BTK treatment. Moreover, brexucabtagene autoleucel is now indicated after BTK treatment. In addition, for some patients, allogenic stem cell transplantation using reduced-intensity conditioning and the possible use or re use of first line chemotherapies are feasible. Despite these treatments, prognosis after BTKi is still poor and additional alternatives are needed.

3.1.3. Main clinical studies

The main 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 NHL", is an open-label, multicentre 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.

3.2. Favourable effects

The primary analysis set (PAS) which is one closest to the claimed indication and which provides the longest follow-up of patients, included the first 90 patients with MCL enrolled from either Phase 1 or Phase 2 of the study, irrespective of pirtobrutinib starting dose, who have received a prior BTK inhibitor-containing regimen. Demographics data for age, sex and weight are globally in line with

targeted indication. In the PAS population, subjects had received a median number of 3 prior lines of systemic therapy, with 1 prior BTKi.

The primary endpoint, ORR was 56.7% in PAS, by IRC assessment, of which 18.9% were reported as achieving complete response.

Median duration of response was 17.61 months (7.29, 27.24). The Kaplan-Meier plot of duration response shows a stable DOR for about half of responders between 6 and 18 months. Based on IRC assessment, time to response and time to best response are 1.84 month and 1.87 month respectively, and less than 2 months for 80% of patients. Rates of PFS are 40% at 12 months and 34% at 18 months. 18 months OS or more was reached in 59.3% of patients (46.1, 70.2).

Subgroup analysis by demographic did not show any discrepancy in term of ORR and DOR. Response rates appear to be higher for low grade disease or better prognosis, surprisingly, better response rates are observed for patients with >3 prior lines of systemic therapies.

3.3. Uncertainties and limitations about favourable effects

The single arm design of the pivotal study and the lack of a comparator leads in uncertainties especially in relation to interpretation of time to event endpoints such as PFS and OS. In addition, important modifications were made to the study protocol, and two analysis plans were developed in parallel with inconsistent specifications, and no plan for multiplicity adjustment. Moreover, the SAPs were finalised late and revised shortly before the conduct of the primary analysis, with critical updates made to the sample size and to the analysis cut-off date. Finally, the PAS included pooling of patients from Phase 1 and Phase 2 of the study and even a small number of patients that were not initiated on the target 200 mg QD dose.

Despite these limitations, the reported results were considered promising especially in view of the poor prognosis of the target population. Reassurance around the methodological limitations was provided by the consistency of the results from various additional analyses and across different subgroup populations. Further confirmation of these results is expected with the ongoing randomised study 20019 [BRUIN-MCL-321].

3.4. Unfavourable effects

In study 18001, AEs were experienced by approximately 90% of patients in both main safety analyses sets, the Overall Monotherapy Safety Analysis Set (OMTSAS) and MCL Safety Analysis Set (MSAS) with 60% considered related to pirtobrutinib. Grade 3 or 4 AEs were experienced by 46.9% of patients in OMTSAS and 39.6% of patients in MSAS, of which half were considered related to pirtobrutinib.

Overall, the adverse events observed with pirtobrutinib monotherapy in pivotal study 18001 were consistent with the known safety profile of the other authorised BTK inhibitors. The most common adverse events were fatigue, diarrhoea, and contusion. Grade 3/4 adverse events were reported mainly in the Blood and Lymphatic System Disorders and Infections and infestations SOCs while gastro-intestinal events were generally low grade.

Cytopenias which are known ADRs of BTK inhibitors, were frequently reported as grade 3/4 but rarely considered as SAE and were mainly managed with treatment interruption.

Infections occurred in 47.2% of patients in OMTSAS and 36% of patients in MSAS. A third of patients in OMTSAS and almost half patients in MSAS had grade ≥ 3 events or had a SAE. Infections were the main cause of death among patients who had a fatal AE (29/45 patients), representing more than half of these patients of which half were related to COVID-19.

Bleeding events occurred in approximately one third of patients (34.3% and 27.4% in OMTSAS and MSAS respectively) and were considered related to pirtobrutinib in more than half of the cases. In the majority of cases, these were of low grade.

Atrial fibrillation or atrial flutter occurred in 2.6% of patients in OMTSAS and 3.7% in MSAS. Almost one third were of grade 3/4 event but few cases were considered as SAE. Although the majority of patients had a history of atrial fibrillation or other cardiac event, it is a known ADR of other BTK inhibitors and are described in the product information and included in the RMP as an important identified risk.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of pirtobrutinib for the current application is based on a single non comparative phase 1/2 study. The safety data in the intended indication (MSAS at 200mg) is limited to 166 patients. It is reasonable to expect a similar safety profile in this population with the population of the larger OMTSAS which includes other types of B-cell malignancies, however this will be confirmed with the ongoing randomised study 20019 [BRUIN-MCL-321].

Second primary malignancies occurred in 6.6% of patients in OMTSAS which were mainly non-melanoma skin cancers in common with what has been observed with other BTK inhibitors. Although it is acknowledged that the target population is at increased risk of SPM and the lack of a comparator does not allow for an accurate calculation of the incidence, the product information includes warnings for the monitoring of patients for the appearance of skin cancers and advise protection from sun exposure. The applicant is also planning a long-term analysis to better estimate the incidence of SPM in association with pirtobrutinib use based on ongoing studies.

Tumour lysis syndrome occurred in a small number of patients in OMTSAS and uncertainties remain on whether these events were causally associated with pirtobrutinib. However, as this cannot be excluded the product information includes a warning in relation to this risk.

3.6. Effects Table

Table 44. Effects Table for Jaypirca for the treatment of adult patients with relapsed or refractory MCL who have been previously treated with a BTK inhibitor (data cut-off:29 July 2022).

Effect	Short description	Unit	Pirtobrutinib 200 mg QD	Uncertainties / Strength of evidence	References
Favourable Effects					
ORR	Proportion of patients with BOR of CR or PR based on Lugano Treatment Response Criteria for malignant lymphoma	%	56.7 (45.8, 67.1)	No control arm, Uncertainties over analysis plan CR: 18.9%	Study LOXOBTK-18001, PAS
Median DOR	Number of months from the start date of the first documented response to the earlier of the documentation of PD or death from any	months	17.61 (7.3, 27.2)	Median FU: 12.68 for responders	

Effect	Short description	Unit	Pirtobrutinib 200 mg QD	Uncertainties / Strength of evidence	References
cause.					
Unfavourable Effects					
Serious infection	≥Grade 3	%	5.8	Incidence based on population not entirely reflecting target population	Population treated with pirtobrutinib 200mg QD, starting dose, in Study LOXOBTK-18001 with no dose escalation
Serious haemorrhage		%	2.4		
Atrial fibrillation/ atrial flutter		%	1.0		

Abbreviations: QD: quaque die; ORR: objective response rate; BOR: best observed response; CR: complete response; PR: partial response; DOR: duration of response; PD: progressive disease; FU: follow-up

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pooled dataset from Phase 1 and Phase 2 shows the promising efficacy of pirtobrutinib in MCL patients with clinically significant overall response rate and meaningful duration of response, which in a rare type of lymphoma setting in patients with limited treatment options is highly favourable. The fact that one fifth of the subjects gained complete response is also meaningful for patients having an aggressive form of cancer.

The identification of the safety profile of pirtobrutinib, although limited by the single arm trial and the small size of the intended population appears nevertheless reasonably adequately characterised in the larger overall monotherapy safety database.

Overall, the safety profile of pirtobrutinib appears similar to the other marketed BTK inhibitors (cytopenia, infections, bleedings, gastrointestinal events, atrial fibrillation) and these are considered manageable with warnings in the product information. Further characterisation of the potential risk of second primary malignancies is planned through a cumulative analysis of ongoing studies.

3.7.2. Balance of benefits and risks

The population of the pivotal study in support of this application had a median 3 prior lines of systemic therapy, including 1 BTK inhibitor and is representative of the intended target population with limited therapeutic options. As most of these patients had discontinued BTK inhibitor treatment due to disease progression to better reflect the trial population, the CHMP requested that the initially proposed indication for pirtobrutinib is revised to relapsed and refractory MCL in patients previously treated with a BTK inhibitor.

The uncertainties arising from the explorative nature of the main study and the methodological issues limit the ability to comprehensively evaluate the balance of benefits and risks. Nevertheless, considering the promising efficacy results which appeared consistent across different analyses and the acceptable safety profile, the CHMP considered that in the context of a CMA the benefit risk balance for pirtobrutinib is positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

In the targeted indication for Jaypirca as monotherapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor, meaningful efficacy has been observed in patients receiving the proposed 200 mg QD dose in terms of response rates and the corresponding duration of responses.

The main uncertainties regarding the benefit assessment relate to the absence of a comparator which limits the interpretation of endpoints more directly linked to patient benefit such as PFS and OS, but also the limited sample size, and the duration of follow up.

Similarly, safety and tolerability were maintained in patients in the pivotal trial. As pirtobrutinib will be used for an extended period of time owing to the durable responses seen, patient safety surveillance remains ongoing and determination of safety findings following more chronic exposure remains under evaluation.

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Pirtobrutinib is designated as an orphan medicinal product for the treatment of MCL (EU/3/21/2450). Mantle cell lymphoma is a rare and aggressive subtype of NHL and, while indolent subtypes of MCL have been characterised, the classical presentation of MCL is typically aggressive and incurable, with treatment at diagnosis required for most patients. Frontline treatment selection is based on patient characteristics and candidacy for intensive chemoimmunotherapy (CIT) approaches, which yield high response rate including CRs with few however long-term remissions (Lenz et al. 2005; Flinn et al. 2014). OS at diagnosis is estimated at only 3 to 5 years (Dreyling et al. 2018).

Covalent BTK inhibitors are the most established therapy for relapsed MCL. Patients will eventually relapse with a poor outlook, as available data of patients with MCL post BTK inhibition has reported a median OS between 2.5 to 8.4 months (Martin et al. 2016; Cheah et al. 2015; Epperla et al. 2017).

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

  To confirm the positive benefit-risk profile established in Study 18001 the applicant has initiated a confirmatory Phase 3 Study in previously treated, but BTK inhibitor-naive, patients with MCL (Study 20019 [BRUIN-MCL-321]). Specifically, Study 20019 is a global, open-label, Phase 3 randomised study in previously treated, but BTK inhibitor-naive, patients with MCL, randomised 1:1 between pirtobrutinib experimental arm and the Investigator's choice of covalent BTK inhibitor. BTK inhibitors, ibrutinib, acalabrutinib or zanubrutinib, were selected according to local country availability in the comparative arm. Approximately 500 patients will be randomised 1:1 between pirtobrutinib and the Investigator's choice of BTK inhibitor therapy.

  The proposed confirmatory study is for a different patient population with MCL who have not yet received a BTK inhibitor; this could be acceptable from an efficacy and safety point of view. Feasibility of this confirmatory study is likely given the different patient population. The estimated study completion date is April 2025.

- Unmet medical needs will be addressed:

  Treatment alternatives in the indication niche for pirtobrutinib include lenalidomide, bortezomib +/- rituximab and temsirolimus. The activity (ORR) of these drugs is reported around 20-30% and thus nominally lower than that for pirtobrutinib (58%). Moreover, this data derives from the pre-BTK era. Even though there are no efficacy metrics for these treatments from the current treatment paradigm i.e. adult patients with relapsed or refractory MCL who have been previously treated with a BTK inhibitor, it would be reasonable to expect that the activity of these treatments in this setting would be even lower. Hence, even if this has not been demonstrated in a head-to-head comparison, pirtobrutinib is likely to provide a major therapeutic advantage over these products based on efficacy for adult patients with relapsed or refractory MCL who have been previously treated with a BTK inhibitor.

  While pirtobrutinib targets BTK, it is the first non-covalently binding agent. Data from the pivotal study clearly show that it retains activity also in patients who have developed resistance to first-generation BTK inhibitors. Moreover, as re-use of first-generation BTK inhibitors post progression on a BTK is not authorised or rational, pirtobrutinib provides a new mechanism of action for the treatment of patients with MCL that have progressed on a first generation BTK inhibitor.

  The CAR-T therapy brexucabtagene autololeucel has a CMA in the same indication as that sought for pirtobrutinib. While the reported ORR appears to be higher than that of pirtobrutinib, many patients will not be sufficiently fit for this treatment modality, whose side effects include CRS and ICANS (which is not associated with BTK inhibitors). Moreover, there is an important lag time between leukapheresis and administration of the CAR-T cells, whereas pirtobrutinib is "off the shelf". Thus, pirtobrutinib offers a meaningful therapeutic option for the larger population of patients with BTK inhibitor pretreated MCL, including those unable to receive CAR-T therapy or for whom CAR-T has been unsuccessful.

  Moreover, for patients that survive to more than one line of therapy after progression on a first BTK inhibitor, it provides a treatment alternative that is not cross resistant to other options. Thereby the novel mechanism of action constitutes a major therapeutic advantage.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  Given the epidemiology data presented, a substantial number of patients may potentially benefit from treatment with pirtobrutinib over the period between Conditional Marketing Authorisation and full approval. Taking into account the short life expectancy of the intended target population and the known manufacturing delays for the initiation of CAR-T therapy, pirtobrutinib immediate availability is considered of public health interest and outweighs the risks inherent to the fact that additional data are yet to be available for the Phase 3 confirmatory study.

3.8. Conclusions

The overall benefit/risk balance of Jaypirca is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Jaypirca is not similar to Tecartus within the meaning of

Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jaypirca is favourable in the following indication:

as monotherapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

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

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

Description	Due date
inhibitor in patients with previously treated BTK inhibitor naïve MCL should be submitted by	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that pirtobrutinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.