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Date: 07 Oct 2024

European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

Clinical Trial Application – J2N-MC-JZNX

Sponsor: Loxo Oncology Inc., Stamford, Connecticut, USA 06901

TITLE: A Phase 2, Open-label, Randomized Study Evaluating the Efficacy and Safety of 3 Doses of Pirtobrutinib in Participants with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor

EU CT Number: 2024-515689-15-01

UTN*:* U1111-1311-5780

Dear Sir or Madam,

Eli Lilly and Company Limited proposes to initiate the above study in patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor as part of phase 2 of the development plan for pirtobrutinib (LY3527727, LOXO-305).

Sponsor would like to draw your attention to the fact that this submission is a re-submission of the initial submission with the EU CT number 2024-515689-15-00. The initially submitted CTA was withdrawn due the Sponsor receiving comments from Global Health Authorities and has decided to incorporate those comments into the global protocol to ensure harmonization across geographies.
Due to the re-submission process in CTIS, the last two digits of the EU CT number from 00 to 01, therefore the EU CT number of this application is 2024-515689-15-01. According to the CTCG best practice guide naming of documents, version 2.0, dated 9 March 2023, there is no expectation that these numbers are immediately corrected within the documents during the ongoing procedure. The EU CT numbers will be updated at a later stage when the documentation is updated during a SM procedure.

The study does not include participants not able to give informed consent, minors, pregnant or breastfeeding women or a first administration of a new active substance to humans.

The Sponsor is Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly and Company, and therefore Eli Lilly is listed as Sponsor in CTIS. A statement of relationship between Loxo and Eli Lilly is also provided. The legal representative appointed by the Sponsor in the EU is Eli Lilly Cork Limited.

No CHMP scientific advice has been taken on this trial.

This trial is not part of a PIP.

Please find below a comprehensive table of all IMPs and AxMPs including their classification:

Substance/trade name	Source	Regulatory status	Classification	GMO status
Pirtobrutinib* (LY3527727, LOXO-305)	Central sourced	Not authorized	Substance is not a narcotic psychotropic or radiopharmaceutical	Substance does not contain a genetically-modified organism or organisms

* While (Jaypirca) pirtobrutinib 50 mg and 100 mg are newly authorized products in the EU 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 pirtobrutinib materials being provided for this study are clinical trial materials manufactured as per the Quality IMPD.

The Sponsor would like to highlight that the pirtobrutinib doses are considered CCI and have been redacted throughout core documents. To ensure the same level of CCI protection is maintained in the CTIS form, the "maximum daily dose" and "maximum total dose" have been given the value "0". Please find below this information:

- LY maximum daily dose allowed: 200 mg
- LY maximum total dose allowed: 219,000 mg

Eli Lilly has not obtained an orphan designation for pirtobrutinib for Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL).

The sponsor does not consider the above trial a low-intervention clinical trial.

The methodology of the above trial does not require that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products. As a consequence, informed consent will not be obtained by simplified means.

The Investigational Medicinal Product Dossier (IMPD) for pirtobrutinib includes a full quality dossier and safety and efficacy dossier (S&E IMPD) for the protocol. However, in order to avoid redundancy in this application, the non-clinical pharmacology and toxicology, clinical pharmacology, pharmacokinetics, and human exposure data are provided by cross-reference to the relevant sections of the pirtobrutinib Investigator's Brochure.

This submission contains a full part I and part II dossier. The following documents are included in part I. Redacted versions are provided where applicable.

- Protocol and synopsis (version a, dated 24-Sep-2024)
  - D1_Protocol_2024-515689-15-01
  - D1_Protocol synopsis_EN_2024-515689-15-00 (with translations where applicable)
- Investigator's brochure (version h, 30-May-2024)
  - E1_IB Pirtobrutinib
- Documentation relating to compliance with Good manufacturing practices for the IMP
  - F1_ Marketing-importing authorization MIA ELECTS
  - F1_ Marketing-importing authorization MIA Manufacturer 1
  - F1_ Marketing-importing authorization MIA Manufacturer 2
  - F1_ Marketing-importing authorization MIA Manufacturer 3

    - F2_QP GMP declaration JZNX ELECTS (version 1, dated 03-Sep-2024)
- IMP dossier (IMPD):
    - Safety & Efficacy IMPD (initial version, dated 23-Aug-2024)
        - G1_IMPD_E-S LY3527727 LOXO-305
    - Quality IMPD for pirtobrutinib (version 1.0, dated 30-Aug-2024)
        - G1_ IMPD_Q Pirtobrutinib
- Content of the labelling of the IMP:
    - J1_Label IMP 611743 L1 LY BTLE BK
    - J1_Label IMP 611744 L1 LY BTLE BK
    - J1_Label IMP 612110 L1 LY BTLE BK

The reference safety information for assessing whether an adverse reaction with pirtobrutinib (LY3527727, LOXO-305) is a suspected unexpected serious adverse reaction (SUSAR) is contained within the Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions, section 7 of the Investigator's Brochure dated 30-May-2024.

The reference safety information (RSI) in effect at the start of the development safety update report (DSUR) reporting period remains the RSI for the DSUR during the entire reporting period. Assessments in line listings and summary tabulations are based on the RSI at the beginning of the reporting period.

All relevant information regarding suspected unexpected serious adverse reactions which are fatal or life-threatening, will be recorded and reported to the Regulatory Authority as soon as possible and no later than 7 days after the sponsor is informed of such a suspected adverse reaction. Any other suspected unexpected serious adverse reactions will be reported no later than 15 days.

The intended submission date for the first ASR following trial authorization is 28-Mar-2025.

In line with local guidelines, the Sponsor wishes to propose the following Ethics Committees to participate in the review of Part II for the following Member States:

Italy

Comitato Etico Territoriale Regione Calabria
c/o l'Azienda Ospedaliero Universitaria "Renato Dulbecco"
Viale Europa SNC
88100 Catanzaro

Spain

CEIm Fundación Instituto Valenciano de Oncología
C/. Gregorio Gea, 31
Edificio D – 1ª Planta
46009 - VALENCIA
E-mail: ceim@fivo.org

For Italy: The stamp duty is virtually paid through the Authorisation of the Finance Office of FI no. 203563/79 of 14/08/79.

For Slovakia: Please send payment details to email cta@lilly.com.

For Germany: The Clinical Trial Application EU 2024-515689-15-01 in conjunction to being evaluated by the new CTR regulation 536/2014 (AMG), has been submitted to the German Bundesamt für Strahlenschutz (BfS) and will need to be considered for approval in accordance with radiation protection laws in Germany (Strahlenschutzgesetz).Hereby, we kindly request that the trial

package is evaluated by the Ethics committee with respect to § 36 Abs. 2, 3 StrlSchG, and to provide Lilly with signed favorable opinion in accordance to § 36 Abs. 2, 3 StrlSchG to be forward to the BfS to obtain approval for the aforementioned trial.

Yours Sincerely,

Local Applicant, Eli Lilly Cork Limited
For and on behalf of Eli Lilly and Company.