# Protocol SYNOPSIS

**Sponsor's protocol code number:** LOXO-BTK-20019

**Version date:** 22 October 2020

**Version number:** 2.0

**EudraCT number:** 2020-004553-72

**Phase: 3.**

**Sponsor’s name:** Loxo Oncology, Inc.

**Official title**

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)

**Abbreviated title:**

A Phase 3 Study of LOXO-305 Versus Investigator Choice of BTK Inhibitor in Patients With Previously Treated Mantle Cell Lymphoma

**Rationale for the clinical trial:**

Mantle Cell Lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL). Younger, healthy patients are usually given induction chemotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation, and finally rituximab as maintenance treatment. Induction chemotherapy followed by maintenance rituximab is an acceptable alternative in transplant-ineligible patients. Neither approach is considered curative, however, and relapse is virtually universal.

Ibrutinib has been approved in a number of countries and acalabrutinib and zanubrutinib, other covalent inhibitors of Bruton’s tyrosine kinase (BTK), have been approved in certain countries as rescue therapy in patients progressing after induction chemotherapy, with or without stem cell transplantation. A pooled analysis of three ibrutinib clinical trials on involving 370 patients with relapsed/refractory MCL revealed a stable median progression-free survival (PFS) of 12.5 months. Similar results have been reported for the other covalent BTK inhibitors. There is an urgent need for comparative data between these BTK inhibitors. You are a

LOXO-305 is an orally available, highly selective, adenosine triphosphate (ATP)-competitive BTK inhibitor, with single-digit nanomolar inhibitory activity against wild-type BTK. LOXO-305 differs from the approved BTK inhibitors (ibrutinib, acalabrutinib and zanubrutinib) in a number of key aspects, including selectivity, favorable pharmacokinetic (PK) and pharmacological properties, and non-covalent binding mechanism. Thanks to these properties, LOXO-305 achieves PK exposures in excess of the BTK minimum inhibitory concentration of 90% (IC90), thereby ensuring tonic on-target inhibition of BTK throughout administration, irrespective of the internal turnover of BTK. LOXO‑305 is also a highly selective molecule, offering BTK selectivity more than 300 times greater than 370 other kinases tested, with no statistically significant effects on non-kinase targets at a concentration of 1 µM, thereby limiting its non-target toxicity potential.

In a phase 1/2 trial (LOXO-BTK-18001, NCT03740529), LOXO-305 demonstrated potent, sustained anti-tumor activity for various B-cell malignancies, including MCL, in particular in patients with previously treated MCL who had received a prior BTK inhibitor. These results provide a basis to assume that the efficacy of LOXO-305 monotherapy in BTK inhibitor-naïve patients compares favorably with the efficacy of current covalent inhibitors. In view of this, the sponsor feels that a direct clinical evaluation should be conducted on LOXO-305. The proposed clinical trial design with investigator choice for a comparative study is feasible and the results will be broadly applicable.

The global clinical trial LOXO-BTK-20019 (BRUIN MCL-321) will be conducted on BTK inhibitor-naïve patients with previously treated MCL. The clinical trial will compare the efficacy and safety of LOXO-305 as continuous monotherapy with the investigator choice of approved covalent BTK inhibitor (ibrutinib, acalabrutinib, or zanubrutinib) as continuous monotherapy. The clinical trial will be conducted globally and the investigator's choice of BTK (ICB) will be based on local availability in the respective country.

This trial will generate important data, highlighting the differences in safety, tolerability, and efficacy between LOXO-305 and the covalent BTK inhibitors in this patient population.