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Clinical Trial identification Full trial title	**Phase 1/2 First-In-Human open-label trial to assess safety and efficacy of STX-241 in participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) resistant to EGFR tyrosine kinase inhibitors (TKIs) – STX-241 FIH study.**
Lay title	**A clinical trial to learn about the safety and effects of STX-241, a new oral anticancer drug for the treatment of patients with advanced lung cancer- "STX-241 FIH study"**
Registry ID	EU CT: 2023-510203-21-00 / CT.gov: NCT06567015
Rationale	In this clinical trial, we are testing a new drug called STX-241 for patients with a type of lung cancer called non-small cell lung cancer (NSCLC). This cancer often has mutations in a gene called *EGFR*, which make it grow. This type of cancer can be treated with a class of medicines, called EGFR tyrosine kinase inhibitors, such as osimertinib. However, these treatments may become ineffective because of a new mutation that is called C797X. There aren't approved treatments available for lung cancer when this C797X appears. STX-241 is a new kind of oral anticancer drug that targets both the original EGFR mutations and the C797X mutation. In tests done on cells and in mice with NSCLC, STX-241 has shown promise in stopping the cancer from growing. Now, researchers want to see how well it works in patients. This trial happens in two Phases. Phase I is designed to find out the right dose of STX-241 to use and check if it is safe for patients with NSCLC. Then in Phase II researchers will observe how well it works in patients with NSCLC that became resistant to other treatments such as osimertinib. This could be an important step in finding new ways to treat this type of lung cancer.

Trial Design

The clinical trial will be divided into three parts.
Parts 1 and 2 constitute the Phase 1 of the study and Part 3 corresponds to the Phase 2.

- The first part (Part 1) seeks to establish how safe and well tolerated STX-241 is, to find out more about its potential side effects and to determine the highest tolerated dose of STX-241, to identify at least 2 safe doses of STX-241 that will be tested in Part 2 of the study. Part 1 is split into 2 separate components:
  - Dose Escalation: this is the first component where patients with lung cancer that is not responding to third-generation treatments are given increasing doses of the new drug, STX-241. Researchers are looking for the highest dose that patients can handle without severe side effects, which is known as the Maximum Tolerated Dose (MTD), or the maximum administered dose (MAD) given if they can't find the MTD. They also watch how the drug affects the body and the cancer during this process.
  - Backfilling: the second component involves adding more patients to the study at doses that have already been tested and found to be safe during the dose escalation part. These patients also have lung cancer that hasn't responded to previous treatments, but specifically, they have certain genetic changes in their cancer cells that the drug is designed to target. The Data Review Committee, which is a group of experts monitoring the trial, will recommend which safe doses can be used for these additional patients. This helps the researchers gather more information about how the drug works in patients with these specific genetic changes.
- The second part (Part 2 - Dose Optimization) will determine the best dose of STX-241 within a range of doses identified in Part 1. It will further evaluate the side effects of STX-241 and will explore if STX-241 has some effect on lung cancer.
- The third part (Part 3 - Expansion Part or Phase 2) will find out if STX-241 at the dose selected in Part 2 works for lung cancer and will explore more about the side effects of STX-241 at this dose. Further details for Part 3 will be added when sufficient data from Parts 1 and 2 will be available.

For Part 1 and Part 2, approximately 135 participants aged 18 years and older, will enter the clinical trial around the world: approximately 45 in Part 1, at least 20 and up to 90 in Part 2. The number of participants in Part 3 will be determined at the end of the Part 2.

Participants will sequentially enter Part 1 of the trial in small groups of 3 to 6 participants. Each group will be treated with an increasing dose (called dose level) of STX-241, and the participants will be monitored closely for any medical problems. The doses tested in different group of participants will range from 10 mg to 180 mg of STX-241 given twice a day. Participants will take STX-241 every day, referring to cycles with a cycle lasting 28 days (28-Day cycles). In Part 2 of the clinical trial, all participants will receive a defined dose of STX-241 until their disease progresses or there are side effects requiring stopping treatment with STX-241.

Figure 1 below provides key steps for the trial.

Primary objectives for Part 1	
To characterize the safety and tolerability of STX-241 (*To make sure it's safe for people to use and to see if they can handle any side effects.)*	Assess any side effects associated with the drug STX-241, including changes in physical examination results, vital signs, laboratory values and heart function until 30 days after the end of the treatment to determine how well participants can receive treatment with STX-241 without experiencing severe or unacceptable side effects.
To determine the range of doses for Part 2, the optimal biologically active dose (OBD) and the maximum tolerated dose (MTD), of STX-241. *(To identify at least two safe doses of STX-241 between the maximum and the minimal effective dose.)*	To find the correct dose for the treatment, STX 241 will be given to successive small groups of participants, increasing the dose between groups. To increase the dose safely between groups the researchers need to know how many participants in each dose group will have Dose-limiting toxicities (DLT) during their first 28-days of treatment (a treatment cycle), and what the DLTs are. DLTs are certain types of toxicities caused by taking STX-241 which indicate that the current dose and higher doses may not be tolerated. When DLTs are observed depending on their number and nature, no higher dose may be tested, and lower doses may be considered for further studies of STX-241. The researchers need to define the Optimal Biological Dose (OBD) and the Maximum Tolerated Dose (MTD). The OBD will be determined by evaluating the occurrence of DLTs during the first cycle of treatment, as well as examining the drug's distribution in the body, tumor shrinkage and molecular signs of drug efficacy (ctDNA reduction) and any moderate or severe adverse events. The MTD will be determined by assessing the occurrence of DLTs during the first cycle of treatment.
Primary objectives for Part 2	
To determine the Recommended Phase II dose of STX-241 *(To assess which one of the doses identified in Part 1 might be the most adequate for Part 3.)*	For the selected doses (at least two) for Part 2 assess: - how STX-241 enters the body, circulates in the blood stream and is finally eliminated. - how well STX-241 works in shrinking or controlling the tumor (response to treatment).
To further characterize the overall safety	Further evaluate the number and types of side effects (See Part 1)

Secondary objective for all parts*	
Assess the efficacy of STX-241	This clinical trial will also evaluate: - How long STX-241 will allow participant to live without the disease getting worse (Progression free survival: PFS) - The period of time from when a participants' tumor shrinks to when it grows again (Duration of response: DOR) -The period of time from the start of treatment until participants' tumor shrinks (time to response: TTR) -The period of time that participants continue to live after their initial diagnosis or treatment, regardless of whether the disease gets better or worse. (Overall survival: OS)

*Details for Part 3 objectives will be added when sufficient data from Parts 1 and 2 are available, via an amendment.

Trial Population	Patients over 18 years; with non-small cell lung cancer no longer responding to the anticancer treatment previously received and with no other available therapeutic option. In addition, for Backfilling component of Part 1 and Part 2 patients should have a specific alteration that occur in EGFR protein called C797X mutation. Patients must be able to perform their daily activities without much help and should have in particular normal or near to normal blood tests for liver, kidney, and bone marrow organs. Details for Part 3 trial population will be added when sufficient data from Parts 1 and 2 will be available.
Interventions	STX-241 will be given orally, two times daily on an empty stomach, without having eaten anything beforehand, until disease progression or there are side effects requiring stopping treatment with STX-241.
Ethical considerations	For dose escalation (Part 1) when further participants have to be enrolled at the current dose level and after each dose level, a committee formed of trial doctors (investigators) and Sponsor's representatives will review the data and decide whether to proceed to the next dose level depending on STX-241 tolerability. Up to 45 patients will participate in Part 1 (up to 30 in the dose escalation component and up to 15 in the backfilling component). A data review committee has been appointed for this trial. The data review committee is a group of independent physicians who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a trial for efficacy, for harms, or for absence of efficacy.
Benefit /risk	There may or may not be direct benefit to the participants receiving STX-241 treatment. Researchers hope that the information learned from this clinical trial will benefit other patients with cancer in the future. As with any experimental drug it is impossible to foresee all potential risks. Specific Risks and Burdens: As with all drugs, STX-241 can cause side effects. These effects can arise even if STX-241 has a positive action on controlling the disease. Each participant may or may not develop certain side effects listed below: - Gastrointestinal effects: diarrhea and decreased appetite - Skin and nail problems: rash, dry skin, itching, redness or infection around the nails of fingers and toes - Lung effects including sudden difficulty in breathing together with cough and fever, which may be a sign of inflamed lungs (a condition called "interstitial lung disease") - Heart effects including abnormal electric activity of the heart that affects its rhythm (QTc prolongation) - Effects on the menstrual cycle including changes in duration and/or usual character and decrease of the mammary gland for men. Even if estimated to be rare before initiating treatment by STX-241 as monotherapy, participants must be advised of signs and symptoms of Stevens Johnson Syndrome (life-threatening reaction with flu-like symptoms and painful rash).

Benefit /risk

(cont'nd)

Participation to this clinical trial implies more frequent visits, examinations and tests that patient would otherwise have undergone per routine standard surveillance. It implies additional procedures including invasive ones such as blood sampling or contrast imaging, which may be source of discomfort. For some patients participating to the trial, this closer follow-up might be a source of additional emotional stress. Other patients may find it reassuring to be followed-up more intensively than in normal conditions. In rare occasion fresh tumor biopsy will be requested (in case the archival tumor sample has not been collected after progression of the latest therapy, or in the absence of an archival tumor biopsy) to confirm the presence of C797X mutation. The clinical trial requires sampling of blood detailed in the Table below for each part. It is worth noting that the average amount for blood donation is 480 mL

There will be regular monitoring by imaging that will expose the participants to limited doses of radiation and the risk of an allergic reaction to the contrast agents used (CT-scan). **See Figure 1** below.

		Blood samplings						
	Trial Day	Screening	C1		C2	C3	≥C4*	End of treatment visit
			D1/D2	D15	D1	D1	D1	
Part 1	Volume total (mL)	49	83	58	79	43	19	39
Part 2	Volume total (mL)	49	79	58	75	43	19	39

*Depending on the number of cycles received and notably the number of odd cycles the volume provided might be higher

Figure 1 : Overview of the design