LIBRETTO-432: A Placebo-controlled Double-Blinded Randomized Phase 3 Study of Adjuvant Selpercatinib following Definitive Locoregional Treatment in Participants with Stage IB-IIIA RET fusion-Positive NSCLC

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This study has been transitioned to CTIS with ID 2023-506784-33-00 check the CTIS register for the current data. To compare EFS of participants in the primary analysis population with Stage II-IIIA RET fusion-positive NSCLC treated with...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55966

Source
ToetsingOnline

Brief title
LIBRETTO-432/J2G-MC-JZJX

Condition

- Other condition

Synonym
Lung cancer

Health condition

RET fusion-positive, Stage IB-IIIA NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Lung Cancer, NSCLC

Outcome measures

Primary outcome

Parameter:

- To compare Event-free survival (EFS) of participants in the primary analysis population with Stage II-IIIA RET fusion-positive NSCLC treated with selpercatinib versus placebo.

Outcome:

- EFS by investigator assessment in the primary analysis population.

Secondary outcome

Parameter:

- To compare EFS of participants in the overall population with Stage IB-IIIA RET fusion-positive NSCLC treated with selpercatinib versus placebo.

Outcome:

- EFS by investigator assessment in the overall population

- overall survival (OS)

- EFS by blinded independent central review (BICR)

- Time to distant disease recurrence in the central nervous system (CNS) by investigator assessment and BICR

- Progression-free survival on the next line of treatment (PFS2) by investigator assessment

Parameter:

- To evaluate the safety and tolerability of selpercatinib versus placebo in the primary analysis and overall populations.

Outcome:

- Safety per CTCAE v5.0 (including, but not limited to): incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities.

Parameter:

- To assess/evaluate performance of RET from investigator-identified laboratories compared to a single Lilly-designated RET test.

Outcome:

- The positive predictive value of RET tests from investigator- identified laboratories with respect to the Lilly-designated RET test

Parameter:

- To compare onset or worsening of NSCLC symptoms in participants treated with selpercatinib versus placebo.

Outcome:

- Mean change from baseline over time in NSCLC symptoms as measured by NSCLC

Symptom Assessment Questionnaire (NSCLC-SAQ).

- Time to onset or worsening of NSCLC symptoms as measured by NSCLC-SAQ.

Parameter:

- To compare physical functioning in participants treated with selpercatinib versus placebo.

Outcome:

- Mean change from baseline overtime in physical functioning as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-IL19) or Physical Functioning Scale (items 1-5) of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30).

- Time to deterioration of physical functioning as measured by EORTCIL19 or Physical Functioning Scale (items 1-5) of the EORTC QLQ-C30.

Study description

Background summary

Lung cancer is the most common type of cancer and the most common cause of cancer deaths worldwide, with 2 million new cases and 1.76 million deaths in 2018 (Ferlay et al. 2019). Approximately 30% of patients with non-small cell lung cancer (NSCLC) present with early- Stage (IB-IIIA) disease (Morgensztern et al. 2010). The standard of care options for these patients are definitive locoregional therapies with or without adjuvant therapy, followed by surveillance until disease progression or recurrence (NCCN 2020). Up to two-thirds of these patients develop recurrence and eventually die of metastatic disease (van den Berg et al. 2015; Grass et al. 2019; Schneider et al. 2020). As a result, there is a need for therapies that can further delay disease recurrence or progression following definitive treatment and adjuvant therapy currently available. In addition, while many adjuvant trials focus on

participants following complete surgical resection, they do not address the unmet medical need of early-stage patients who cannot or do not undergo resection and who instead receive definitive radiotherapy with a curative intent, including participants with lung cancer that has targetable mutations such as REarranged during Transfection (RET) fusion.

Participants with RET fusion-positive NSCLC have an identifiable oncogenic driver. However, in the adjuvant setting these participants still receive the same standard-of-care treatments as participants with NSCLC who do not have a driver alteration; that is, definitive therapy, with or without prior platinum-based chemotherapy, followed by surveillance until disease recurrence or progression.

Given the compelling activity of selpercatinib in metastatic RET fusion-positive NSCLC patients, a manageable safety profile, and the growing body of evidence that targeting the underlying driver of disease can improve outcomes regardless of stage of disease (Wu et al. 2020), it is hypothesized that treatment with selpercatinib during the surveillance period following completion of therapies with a curative intent; e.g., definitive locoregional therapy (such as surgery or radiotherapy) and applicable adjuvant chemotherapy, as determined by the investigator, will improve outcomes for patients with Stage IB-IIIA RET fusion-positive NSCLC.

Study objective

This study has been transitioned to CTIS with ID 2023-506784-33-00 check the CTIS register for the current data.

To compare EFS of participants in the primary analysis population with Stage II-IIIA RET fusion-positive NSCLC treated with selpercatinib versus placebo.

Study design

Study comparing the efficacy and safety of selpercatinib twice daily (BID) to placebo in participants with RET fusion-positive Stage IB-IIIA NSCLC following completion of therapies with a curative intent; e.g. definitive locoregional treatment (such as surgery or radiotherapy) and applicable adjuvant chemotherapy, as determined by the investigator.

Up to approximately 170 participants will be randomized 1:1 to receive either selpercatinib or placebo, using the following stratification factors:
- disease stage (Stages IB, Stage II, Stage IIIA)
- prior definitive therapy (surgery, radiotherapy).

Study intervention (selpercatinib or placebo) will be administered twice a day in continuous 28-day cycles. Treatment will continue until disease recurrence

or progression, unacceptable toxicity, or another protocol-defined reason for study discontinuation, for a maximum treatment duration of 3 years. A placebo-controlled trial is considered appropriate for this population since the standard of care following definitive therapy and appropriate adjuvant therapy for each participant is surveillance. As a result, participants will not forego any proven active treatment by participating in this study.

Participants randomly assigned to Arm B who discontinue treatment for disease recurrence or progression (per RECIST v1.1 and/or histopathological confirmation) may be eligible for crossover to selpercatinib. Crossover treatment will be optional at the discretion of the investigator.

Intervention

Study intervention (selpercatinib or placebo) will be administered twice a day in continuous 28-day cycles. Treatment will continue until disease recurrence or progression, unacceptable toxicity, or another protocol-defined reason for study discontinuation, for a maximum treatment duration of 3 years. A placebo-controlled trial is considered appropriate for this population since the standard of care following definitive therapy and appropriate adjuvant therapy for each participant is surveillance. As a result, participants will not forego any proven active treatment by participating in this study.

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Study burden and risks

Selpercatinib was well tolerated across all tumour types studied in LIBRETTO-001 (n=702 participants), with a safety profile characterized by recognizable toxicities, which can be monitored, reversed with dose interruption, or addressed through dose reduction or concomitant medication. Any grade treatment-emergent adverse event (TEAE)s were reported in 20% or more of participants; most events were reported as low grade. The Grade 3 or 4 TEAEs that were reported in at least 5% of participants. A total of 5% of participants discontinued due to an adverse reaction.

Although the study procedures in Study JZJX are generally consistent with standard of care, increased monitoring of vital signs (including blood pressure), haematology, hepatic panels, and electrocardiograms (ECGs) occur in the initial cycles to monitor for potential toxicities of interest. Additionally, a data monitoring committee (DMC) will assess unblinded safety data during the trial on a regular basis. The DMC will evaluate all safety-related data provided for each meeting to determine whether a change in

the conduct of the trial is warranted for the safety of patients.

Given the high unmet need for additional therapies to treat RET fusion-positive NSCLC, the clinical safety profile of selpercatinib, and the clinical efficacy observed in patients with RET altered solid tumours (including NSCLC) in LIBRETTO-001, the risk/benefit assessment supports evaluation of selpercatinib in the proposed patient population.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

-Must have histologically confirmed Stage IB, II, or IIIA NSCLC. Staging will be according to the Tumour, Node, Metastasis staging system for lung cancer
-Must have an activating RET gene fusion in tumour based on polymerase chain reaction (PCR) or next generation sequencing (NGS)

-Must have received definitive locoregional therapy with curative intent (surgery or radiotherapy) for Stage IB, II, or IIIA NSCLC
-a. Participants must have undergone the available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it, based on the investigator's discretion.
-Patients must have completely recovered from definitive therapy (surgery or radiotherapy) as well as adjuvant therapy at the time of randomization
-Must have Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
-Adequate hematologic, hepatic and renal function
-Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 2 weeks after. Men must refrain from donating sperm and must agree to using condom. Women of child-bearing potential must not be breastfeeding during treatment and for at least 2 weeks after the last dose of study drug
-Written informed consent.

Exclusion criteria

-Additional oncogenic driver mutations of NSCLC, e.g., ALK fusion, or activating mutations of EGFR -Evidence of small cell lung cancer -Clinical or radiologic evidence of disease recurrence or progression following definitive therapy -Known or suspected interstitial fibrosis or interstitial lung disease or history of (non-infectious) pneumonitis that required steroids -Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of study treatment or prolongation of the QT interval corrected for heart rate using Fridericia*s formula (QTcF) >470 msec on more than 1 ECG obtained during the baseline period -Uncontrolled human immunodeficiency virus (HIV)-1/2 infection -Has known active Hepatitis B or C -Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment (e.g., hypertension, diabetes, clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, or peritoneal carcinomatosis, pericardial effusion, or pleural effusion). Screening for chronic conditions is not required -Major surgery, excluding placement of vascular access, within 4 weeks of study drug -Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug -Other malignancy unless nonmelanoma skin cancer, carcinoma in situ of the cervix or other in situ cancers, or a malignancy diagnosed >=2 years previously and not currently active -Have a known hypersensitivity to any of the excipients of selpercatinib -Prior treatment with selpercatinib or pralsetinib -Taking a concomitant medication that is known to cause QTc prolongation -Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study. -have participated, within the last 30 days; (3 months in the UK), in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (3 months in the UK) whichever is longer should have passed.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	30-06-2021
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Retsevmo
Generic name:	Selpercatinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-05-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-07-2021
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-11-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-02-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-06-2023
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-09-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-506784-33-00
EudraCT	EUCTR2020-005191-35-NL
CCMO	NL76609.091.21