RANDOMIZED, OPEN LABEL, MULTICENTER, PHASE III STUDY OF ENTRECTINIB VERSUS CRIZOTINIB IN PATIENTS WITH LOCALLY-ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER HARBORING ROS1 GENE REARRANGEMENTS WITH AND WITHOUT CENTRAL NERVOUS SYSTEM METASTASES

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Main Information

Primary registry identifying number
LBCTR2025035706

Protocol number
MO41552

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
30/09/2022

Primary sponsor
F. Hoffmann-La Roche Ltd

Primary sponsor: Country of origin
USA

Date of registration in primary registry
19/06/2025

Date of registration in national regulatory agency
30/09/2022

Public title
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Acronym
Entrectinib study

Scientific title
RANDOMIZED, OPEN LABEL, MULTICENTER, PHASE III STUDY OF ENTRECTINIB VERSUS CRIZOTINIB IN PATIENTS WITH LOCALLY-ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER HARBORING ROS1 GENE REARRANGEMENTS WITH AND WITHOUT CENTRAL NERVOUS SYSTEM METASTASES

Acronym
Entrectinib study

Brief summary of the study: English

This is a randomized, open-label, multicenter, Phase III trial. The general purpose of the study is to compare the efficacy and safety of entrectinib compared with crizotinib in patients who have advanced or metastatic NSCLC harboring ROS1 gene rearrangements with and without CNS metastases. In addition to primary and secondary efficacy and safety objectives the study will be evaluating additional exploratory efficacy and safety objectives as well as exploratory biomarker objective and health status utility objective.The study will consist of a 28-day Screening Period, a Treatment Period, a Post-Treatment Follow-Up Visit occurring 4 weeks after the end of study treatment, and a Follow-Up Period. Approximately 220 patients with ROS1 rearrangement-positive, advanced or
recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC will be enrolled in this study at approximately 80 study sites in multiple countries.

Brief summary of the study: Arabic

هذة دراسة عشوائية، مفتوحة التسمية ، متعددة المراكز، في المرحلة الثالثة. الهدف العام من هذه الدراسة مقارنة فعالية وسلامة انتركتينيب مقابل كريزوتينيب لدى مرضى مصابين ببسرطان الرئة ذي الخاليا غير الصغيرة المتقدم موضعيًا او النقيلي المتضمن اعادة ترتيب جين ROS1 ،مع او بدون انتشار في الجهاز العصبي المركزي. بالإضافة إلى أهداف الفعالية وأهداف السلامة الأولية والثانوية ، ستقوم الدراسة بتقييم أهداف الفعالية الاستكشافية الإضافية وأهداف السلامة بالإضافة إلى هدف المرقم الحيوي الاستكشافي وهدف مرفق الحالة الصحية. ستتألف الدراسة من فترة فحص مدتها28 يومًا ، وفترة علاج ، وزيارة متابعة ما بعد العلاج بعد 4أسابيع من نهاية علاج الدراسة ، وفترة متابعة . سوف يشارك / سيتم تسجيل ما يقرب من220مريضًا يعانون من إعادة ترتيب ROS1 إيجابية أو متقدمة أو متكررة (المرحلة IIIB / C غير قابلة للعلاج الجذري) أو النقيلي (المرحلة الرابعة NSCLC في هذه الدراسة في حوالي80موقعًا للدراسة في بلدان متعددة .

Health conditions/problem studied: Specify

Patients who have advanced or metastatic NSCLC harboring ROS1 gene rearrangements with and without CNS metastases

Interventions: Specify

Study MO41552 is a randomized, open-label, multicenter, Phase III trial. The general purpose of the study is to compare the efficacy and safety of entrectinib compared with crizotinib in patients who have advanced or metastatic NSCLC harboring ROS1 gene rearrangements with and without CNS metastases.
The investigational medicinal products (IMPs) for this study: Entrectinib (Test product) and Crizotinib (Comparator product)
The study will consist of a 28-day Screening Period, a Treatment Period, a Post-Treatment Follow-Up Visit occurring 4 weeks after the end of study treatment, and a Follow-Up Period. For each participating patient, the first day of treatment will be Day 1 (baseline). The overall study design is presented in Synopsis Figure 1 in the attached protocol. Patients who withdraw from the study will not be replaced A Schedule of Activities is provided in Appendix 1 in the attached protocol
Screening Period:
To be eligible, patients must have a histologically- or cytologically-confirmed diagnosis of advanced or recurrent (Stage IIIB/C, not amenable for radical treatment) or metastatic (Stage IV) NSCLC that harbors a ROS1 gene rearrangement. Documented positivity for ROS1 gene rearrangements must have been determined locally at CLIA-certified or equivalently-accredited diagnostic laboratories prior to enrolment. Patients with measurable and/or non-measurable CNS metastases that are neurologically stable will be allowed.
Treatment Period:
Following screening, eligible patients will be randomly assigned in a 1:1 ratio to receive open label treatment with either entrectinib (experimental arm) or crizotinib (control arm). Randomization will be performed centrally via an interactive voice or web-based response system (IxRS). To ensure balance among the treatment groups, randomization will be stratified according to CNS metastasis status (no CNS disease / measurable CNS disease / non measurable CNS disease) and prior brain radiotherapy within 2 months of randomization (yes / no). Enrolment caps will be used to ensure that at least 30% of enrolled patients will present with CNS metastases at baseline.
Patients assigned to the experimental arm will self-administer oral entrectinib at a dose of 600 mg once daily with or without food, i.e., three 200-mg capsules per day. Patients assigned to the control arm will self-administer oral crizotinib as described in local prescribing information, i.e., 250 mg twice-daily per os taken with or without food. Treatment in both arms will continue until progressive disease, unacceptable toxicity, death, or withdrawal from the study, whichever occurs first.
In case of isolated asymptomatic CNS progression (e.g., new CNS oligometastases), local therapy may be given (e.g., stereotactic radiotherapy or surgery), followed by continuation of either entrectinib (experimental arm) or crizotinib (control arm) until systemic disease progression and/or symptomatic CNS progression.
Investigators may choose, at their discretion, to continue entrectinib or crizotinib treatment beyond isolated asymptomatic CNS progression, and/or beyond systemic progression, in patients who meet all of the following criteria:
· Evidence of clinical benefit, as assessed by the investigator in consultation with the Medical Monitor
· Absence of symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease after an integrated assessment of radiographic data, biopsy results (if available) and clinical status
· No decline in ECOG performance status that can be attributed to disease progression
· No unacceptable toxicities associated with entrectinib or crizotinib administration Patients treated with entrectinib or crizotinib in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the above criteria. Tumor assessments will occur during the Screening Period, at baseline, every 8 weeks during the Treatment Period, and at the Post-Treatment Follow Up (see Appendix 1) in attached protocol. Primary and secondary efficacy endpoints will be assessed by a BIRC (see below) and by investigators according to RECIST v1.1. Additionally, as exploratory endpoints, the BIRC will assess efficacy in patients with baseline CNS metastases using RANO-BM criteria.
This study will also have an exploratory analysis examining biomarkers. These analyses will be conducted on archival (or freshly collected pre-treatment) tissue specimens, study plasma/blood samples, and tumor/plasma specimens collected at the time of progressive disease in patients
who consent to an optional biopsy (see Appendix 1) in attached protocol. Collected samples, as well as other potential markers, will be

analyzed at a Sponsor-approved testing laboratory to assess relationships between biomarker expression and patient outcomes, including but not limited to
response, cancer biology and disease progression.
To assess safety in this study, patients will be followed for AEs (including SAEs, AEs of special interest, and AEs leading to dose modifications/interruptions, study drug withdrawal or death), ECG readings and selected clinical laboratory test results. Safety assessments will occur at each study visit (see Appendix 1) in the attached protocol. An Internal Monitoring Committee (IMC) will review the safety data collected during the conduct of the study. Safety monitoring will be performed periodically. Further details will be outlined in the IMC Charter.
Patient-reported outcomes (PROs) will be evaluated using the patient self-administered EORTC QLQ-C30, EORTC QLQ-LC13, EORTC QLQ-BN20, the single-item EORTC IL46, and EQ-5D-5L questionnaires.
Post-Treatment Visit and Follow-Up Period
Patients will report to the clinic 4 weeks after their last dose of entrectinib or crizotinib for a Post-Treatment Visit, at which time disease progression, PRO questionnaires, safety, survival and subsequent NSCLC therapies will be evaluated. Following the Post-Treatment Visit, the patient will report for clinic visits and/or undergo telephone interviews every 8 weeks for 6 months and, then, every 12 weeks thereafter (or as appropriate), for evaluation of survival and subsequent NSCLC therapies, as described in the Schedule of Activities (Appendix 1) in attached protocol.
After entrectinib or crizotinib is discontinued, patients will continue to be treated with non-study anticancer therapies at the discretion of the investigator, according to local practice. Upon discontinuation of entrectinib, female patients of childbearing potential will complete one additional pregnancy test at the Post-Treatment Visit. Upon discontinuation of crizotinib, female patients of childbearing potential will complete a pregnancy test at the Post-Treatment Visit and at home once every 4 weeks for the following 8 weeks.

Key inclusion and exclusion criteria: Inclusion criteria

Patients must meet the following criteria for study entry:
- Signed Informed Consent Form
- Age ≥ 18 years at time of signing the Informed Consent Form
- Histologically- or cytologically-confirmed diagnosis of advanced or recurrent (Stage IIIB/C, not amenable for radical treatment) or metastatic (Stage IV) NSCLC that harbors a documented ROS1 gene rearrangement
For a patient to be considered for this study, documented positivity for ROS1 gene rearrangements must have been determined locally at CLIA-certified or equivalently accredited diagnostic laboratories using nucleic acid-based testing methods that rely on direct assessment of ROS1 gene rearrangements in tumor tissue. Examples of acceptable methods include next-generation sequencing (NGS), Sanger sequencing, reverse transcriptase-polymerase chain reaction (RT-PCR), NanoString and EdgeSeq. Fluorescence in situ hybridization (FISH) is also an acceptable method, with ROS1positivity defined as the detection of at least 15% of neoplastic nuclei with ROS1 gene rearrangements among a minimum of 50 total neoplastic nuclei. Immunohistochemistry (IHC) is not an acceptable method
- No prior treatment with a ROS1 tyrosine kinase inhibitor, chemotherapy or other systemic therapy for advanced or recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC
- Prior radiotherapy is allowed if more than 14 days have elapsed between the end of treatment and randomization. Patients who received brain irradiation must have completed whole brain radiotherapy at least 14 days prior and/or stereotactic radiosurgery at least 7 days prior to the start of entrectinib treatment
- Measurable systemic disease according to RECIST v1.1
- Patients with measurable and non-measurable CNS lesions per RECIST v1.1, including leptomeningeal carcinomatosis, are eligible, provided that the patient is neurologically stable for at least 1 week prior to the first dose of study treatment
Patients who are receiving corticosteroids must be on a stable or decreasing corticosteroid dose within 7 days prior to start of treatment. The use of seizure prophylaxis is allowed so long as patients are taking non-enzyme-inducing anti-epileptic drugs (non-EIAEDs) (Appendix 6). If patients were previously on EIAEDs (Appendix 6) and these have been discontinued, they must have been discontinued for at least 2 weeks prior to the start of entrectinib treatment
NOTE: Previously irradiated CNS lesions cannot be selected as target (measurable) lesions.
- Life expectancy of at least 12 weeks
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (see Appendix 4 in attached protocol)
- Adequate hematologic function:
Platelet count ≥ 75 x 109/L
Absolute neutrophil count (ANC) ≥ 1000 cells/µL
Hemoglobin ≥ 8.0 g/dL
- Adequate renal function:
An estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease equation of at least 45 mL/min/1.73 m2 (see Appendix 9 in attached protocol)
- Adequate liver function:
Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 3.0 × upper limit of normal (ULN); ≤ 5.0 × ULN if liver metastases are present
Total serum bilirubin ≤ 2.0 × ULN; patients with a known history of Gilbert's syndrome and/or isolated elevations of indirect bilirubin are eligible
- Patients must have recovered from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment
- Ability to comply with the study protocol, in the investigator's judgment
- Ability to swallow entrectinib and crizotinib intact without chewing, crushing, or opening the capsules
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for up to 5 weeks after the last dose of entrectinib or for at least 90 days after the last dose of crizotinib
A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (³ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
Systematically acting hormonal contraceptives used by female patients must be combined with a barrier method
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of

the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of entrectinib or for at least 90 days after the last dose of crizotinib. Men must refrain from donating sperm during this same period
With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of entrectinib or for at least 90 days after the last dose of crizotinib to avoid exposing the embryo
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

100

Key inclusion and exclusion criteria: Exclusion criteria

- Current participation in another therapeutic clinical trial
- Prior treatment with a ROS1 tyrosine kinase inhibitor, chemotherapy or other systemic therapy for advanced or recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC
- NCI-CTCAE v5.0 Grade 3 or higher toxicities due to any prior therapy (excluding alopecia, fatigue, nausea and lack of appetite), which have not shown improvement and are strictly considered to interfere with current study medication
- History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction ≤ 50% observed during screening for the study
- History of prolonged QTc interval (e.g., repeated demonstration of a QTcF interval > 450 milliseconds from ECGs performed at least 24 hours apart) (see Appendix 10)
- History of additional risk factors for torsades de pointes (e.g., family history of long QT syndrome)
- Peripheral sensory neuropathy ≥ Grade 2
- Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis
Note: Radiation-induced lung disorders are not included in this exclusion criterion
- Previous malignancy within the past 3 years (other than curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have no impact on PFS and OS for the current NSCLC)
- Incomplete recovery from any surgery prior to the start of study treatment that would interfere with the determination of safety or efficacy
- Active GI disease (e.g., Crohn's disease, ulcerative colitis or short gut syndrome) or other malabsorption syndrome that would reasonably impact drug absorption
- History of prior therapy-induced pneumonitis
- Any condition (in the past 3 months) that would interfere with the determination of safety or efficacy of study treatments, e.g., myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack, stroke, symptomatic bradycardia, or uncontrolled arrhythmias requiring medication
- Known active infections that would interfere with the assessment of safety or efficacy of study treatments (bacterial, fungal or viral, including human immunodeficiency virus positive)
- History of hypersensitivity to any of the additives in the entrectinib and/or crizotinib drug formulations
- Pregnant or lactating women
- Known human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS)-related illness
- Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial entry

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Other

Trial scope: Specify scope

Study design: Allocation

Randomized controlled trial

Study design: Masking

Open (masking not used)

Study design: Control

Study phase

Active

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

Yes, Worldwide

IMP has market authorization: Specify

USA

Name of IMP

Entrectinib

Year of authorization

2019

Month of authorization

Type of IMP

Others

Pharmaceutical class

Entrectinib is an inhibitor of tyrosine receptor kinases tropomyosin receptor kinases

Therapeutic indication

Non-small cell lung cancer with ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) gene rearrangements

Therapeutic benefit

with NSCLC is currently being studied in 3 ongoing clinical studies in adults (ALKA [GO40783], STARTRK-1 [GO40784] and STARTRK-2 [GO40782]) and one study in a pediatric population (STARTRK-NG [CO40778]). Across the three adult studies, 94 patients with ROS1 rearrangement-positive NSCLC were assessed by BICR for efficacy following treatment with entrectinib (clinical cutoff date, 1 May 2019).
Results of this integrated analysis are summarized below:
· ORR was 73.4% (95% CI: 63.3, 82.0), including 11 patients (11.7%) with complete responses and 58 (61.7%) with partial responses. At a median follow-up of 20.3 months, the majority of patients were still in response (69 of 94, 73.4%)
· Median DOR was 16.5 months (95% CI: 14.6, 28.6)
· Median PFS was 16.8 months (95% CI: 12.0, 21.4)
Among the 94 patients in this integrated analysis, 34 had BICR-confirmed CNS disease at baseline and were analyzed by BICR for efficacy (clinical cutoff date, 1 May 2019).
Results of this integrated analysis are summarized below:
· Intracranial ORR was 50.0% (95% CI: 32.43, 67.57), with 5 patients (14.7%) achieving a CR and 12 patients (35.3%) achieving PR. In patients with measurable CNS disease by BICR (n=18), the intracranial ORR was 77.8% (95% CI: 52.4, 93.6)
· Median time to event (radiographic CNS disease progression or death due to any cause) was 24.8 months (95% CI: 16.1, NE) with a median follow-up for progression or death of 15.5 months On the whole, response to entrectinib treatment was clinically meaningful and durable in
both patients with and without baseline CNS metastatic disease. Intracranial response was similar in magnitude to systemic response.
Please refer to the Entrectinib Investigator's Brochure for more detailed information on systemic and intracranial efficacy of entrectinib in patients with ROS1 rearrangement positive NSCLC.

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

Time perspective: Specify perspective

N/A

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples with DNA**

Biospecimen description

- Mandatory blood samples for laboratory tests will be collected during screening, at every visit during the Treatment Period, at every post-progression visit in cases of isolated CNS progression, and at the Post-Treatment / Safety Follow-Up Visit (Appendix 1 in the attached protocol). Please refer to attached protocol for the laboratory tests.
The samples will be sent to the study site's local laboratory for the following laboratory tests: · Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells) · Chemistry panel: bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH · Coagulation: INR, aPTT, and PT · Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) · Pregnancy test – All women of childbearing potential will have a highly sensitive serum pregnancy test at screening. Urine pregnancy tests will be repeated every cycle whilst on study treatment. After Cycle 2, when patients will only attend visits every 2 cycles, patients should be provided with pregnancy tests to perform at home to maintain monthly pregnancy testing, and site staff should contact the patient to record the results of the test. Upon discontinuation of entrectinib, female patients of childbearing potential will complete one additional pregnancy test at the Post-Treatment Visit. Upon discontinuation of crizotinib, female patients of childbearing potential will complete a pregnancy test at the Post-Treatment Visit and at home once every 4 weeks for the following 8 weeks.. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. All urine pregnancy tests will be provided by the Sponsor to female patients of childbearing potential
- Pre-Treatment Tumor Sample for Exploratory Biomarkers (Mandatory): A mandatory tumor tissue sample will be collected at baseline prior to the first study treatment (refer to Appendix 1 in attached protocol). The sample will be sent to a central laboratory or to the Sponsor or a designee for exploratory biomarker analyses.
Key goals of these biomarker studies will be to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility
to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety (see Section 3.3.8 in attached protocol for additional detail on biomarker analyses). In addition, these studies may be used to generate data to support registration of a ROS1companion diagnostic assay claim entrectinib. Please refer to Section 3.3.8 in attached protocol for additional information on biomarker analyses.
The pre-treatment tumor sample can be either archival or newly collected, although a newly collected sample is preferred. A

representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10-15 slides containing unstained, freshly cut, serial sections must be submitted within 1 month of enrolment ,along with an associated pathology report, to the central laboratory. If no sample or less than 10 slides are available, the patient may still be enrolled with Sponsor approval.
FFPE tumor tissue should be of good quality based on total and viable tumor content. A minimum of 20% tumor nuclei content that can yield a minimum of 22 ng of DNA is required. If sending a core biopsy, use 2-3 biopsies aligned and paraffin embedded in a single block. Fresh tissue, unembedded tissue samples, and frozen tissue samples are not acceptable. FFPE samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that has been decalcified is not acceptable.
Further details of sample handling procedures, sample storage and shipment will be described in a separate laboratory manual.
The pre-treatment tumor tissue sample may be analyzed by next-generation sequencing methodologies, including whole genome sequencing (WGS) and/or whole exome sequencing (WES). Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study, but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.
- Mandatory Plasma Biomarker Samples for Exploratory Biomarkers, Mandatory blood plasma samples will be collected at baseline, at Visit 2 (Week 8), at all subsequent visits (every 8 weeks), and at all post-progression visits in case of isolated CNS progression (Please refer to Appendix 1 in attached protocol). The samples will be sent to one or several central laboratories or to the Sponsor or a designee for exploratory biomarker analyses. The goal of these studies will be to analyze mutations in circulating tumor DNA, including mutations in ROS1 and other cancer-related genes, that may be involved in resistance to ROS1 inhibitors (refer to Section 3.3.8 in attached protocol). Results may also be used to assess correlations of mutations with clinical efficacy and to assess how mutations evolve over time with treatment and advancing disease pathology.
A total of 4 x 10 mL of blood will be collected at each of the visits designated above. All plasma biomarker samples should be collected prior to study treatment administration. Details of sample handling procedures, sample storage and shipment will be described in a separate laboratory manual.
On the basis of continuous analysis of the data in this study and other studies, or on the basis of data from literature, collection of plasma biomarker samples may be stopped at any time if they are deemed uninformative. If no sample is available, the patient may still be enrolled with Sponsor approval
- The optional Additional Tumor Tissue Samples, For patients who have signed the Optional Collection of Tissue Samples Informed Consent Form, on-study fresh biopsies and/or leftover tumor tissue may be collected or provided at any time per investigator discretion, preferably at the time of radiographic progression and/or response. If taken at the time of radiographic progression, the biopsy should be taken before the start of subsequent anti-cancer therapy.
The optional tumor tissue samples may be analyzed by next-generation sequencing methodologies, including whole genome sequencing (WGS) and/or whole exome sequencing (WES), as described above in Section 4.5.10.2 in attached protocol. Details

of sample handling procedures, sample storage and shipment will be described in a separate laboratory manual.
- Optional Research Biosample Repository Samples, For patients who consent to the optional collection of samples for the Research Biosample Repository (RBR), any leftover material from the above sample collections will be stored and used for exploratory analyses as indicated in Section 4.5.14 in the attached protocol.
- Storage Periods for Collected Biological Samples
Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.14 in attached protocol), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:
. Blood, plasma and tumor tissue samples, and associated derivatives, collected for exploratory biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements)
· For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first.
When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.
Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4 in attached Protocol.
Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.
Consenting patients will undergo an optional fresh tumor biopsy or provide leftover tissue from a local procedure, preferably at the time of radiographic disease progression (before the start of subsequent anti-cancer therapy) and/or response; optional biopsy should be done at the investigator's discretion and per local consenting policy/procedure (if deemed clinically feasible by the investigator). Samples collected via resection, core needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps
biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.
The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or
not the patient has given consent to participate and (if applicable) the date of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.
Samples may be used for exploratory biomarker research as described in Section 4.5.10. Refer to Section 4.5.10 in attached Protocol for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses
- The Research Biosample]Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.
Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives: · To study the association of biomarkers with efficacy

or disease progression · To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation · To increase knowledge and understanding of disease biology and drug safety · To study drug response, including drug effects and the processes of drug absorption and disposition · To develop biomarker or diagnostic assays and establish the performance characteristics of these assays
Sample collection:
The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to entrectinib, diseases, or drug safety:
· Blood sample (10 mL) collected at baseline
· Leftover blood, serum, plasma, peripheral blood mononuclear cell (PBMC), and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures
(e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study
The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.
Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.
For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.
RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC approved Informed Consent Formand applicable laws (e.g., health authority requirements).
For Additional Biospecimen information, Please refer to the attached protocol

Target sample size

220

Actual enrollment target size

Date of first enrollment: Type

Actual

Date of first enrollment: Date

24/09/2021

Date of study closure: Type

Actual

Date of study closure: Date

25/07/2029

Recruitment status

Recruiting

Recruitment status: Specify

Date of completion

IPD sharing statement plan

Yes

IPD sharing statement description

During this study, health and personal information ("information") about the subject will be collected. This section describes the protection, use, and sharing of subject's information, which consists of the following:
● Information in subject medical record, which is held by Hotel Dieu de France Hospital("study site")

● Information (including imaging data) that is collected or produced during this study ("study data"), which is held by the study site, Roche, Roche affiliates, and Roche's representatives (people and companies who work for Roche)
Subject's privacy is very important, and Roche uses many safeguards to protect subject's privacy, in accordance with applicable data privacy laws and laws related to the conduct of clinical trials.
The subjects study data and samples will be labeled with a patient identification (ID) number that is unique to subjects and not related to or derived from information their identifies (such as name, picture, or any other personally identifying information).
Roche, Roche affiliates, and Roche's representatives will only have access to study data and samples labeled with a patient ID number, except when accessing subjects medical record under certain circumstances, as described below:
Subjects information (including their medical record, which contains personal information that can identify subjects) may need to be reviewed to make sure the study is being done properly or to check the quality of the information. This information will be kept private.
The following people and groups of people may review this information:
● Study monitors of Roche and/or IQVIA, a company hired by Roche to perform certain study activities
● The Institutional Review Board or Ethics Committee (people responsible for protecting the rights and safety of people who take part in research studies)
● Regulatory authorities (government agencies involved in keeping research safe for people)
Roche, Roche affiliates, and Roche's collaborators and licensees (people and companies who partner with Roche) may use study data labeled with the patient ID number. Subjects study data may also be shared with researchers or government agencies, but only after personal information that can identify the subjects has been removed. the subjects study data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, testing, and
commercialization of products that treat or diagnose disease, or improve patient care.
These data will not include information that identifies subjects.
Subjects information will not be given to their insurance company or employer, unless required by law. If the results from this study are published in a medical journal or presented at a scientific meeting, subjects will not be identified.
Information from this study will be retained by the study site for 15 years after the end of the study or for the length of time required by applicable laws, whichever is longer. In addition, Roche will retain the study data for 25 years after the final study results have been reported or for the length of time required by applicable laws, whichever is longer.
If the subjects sign this consent form, they will give permission to the study site to use and/or share subjects information, which includes study data and information in subjects medical record.
Subjects study data may be used or shared for the purposes of this study and for research related to ROS1 rearrangement-positive NSCLC or other types of cancer, common pathways (links) among diseases, the use of experimental drugs in disease therapy,
and/or the development of tests or tools that help with detecting or understanding ROS1 rearrangement-positive NSCLC. Subjects do not have to sign this consent form, but if the subjects do not, they cannot take part in this study.
Subjects study data may be used by and/or shared with Roche, Roche affiliates, Roche's collaborators and licensees, the Institutional Review Board or Ethics Committee, and regulatory authorities. Subjects study data and samples may be analyzed in any country worldwide

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
EUDRACT NUMBER	2019-003859-11

Sources of Monetary or Material Support

Name
F. HOFFMANN-LA ROCHE LTD

Secondary Sponsors

No Sponsors

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Fadi Karak	Hotel-Dieu De France, Achrafieh, Beirut Lebanon BP : 166830	Lebanon	+961 1 682666	felkarak@yahoo.com	Oncologist - Hotel-Dieu De France
Scientific	Fadi Karak	Hotel-Dieu De France, Achrafieh, Beirut Lebanon BP : 166830	Lebanon	+961 1 682666	felkarak@yahoo.com	Oncologist - Hotel-Dieu De France

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Hotel-Dieu De France	Dr. Fadi Karak	Oncologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Hotel Dieu de France	26/07/2021	Dr. Nancy Al Alam	nancy.alam@usj.edu.lb	00

Countries of Recruitment

Name
Brazil
China
Croatia
France
Germany
Greece
Italy
Jordan
Lebanon
Mexico
Netherlands
Spain
Turkey
Slovakia
Romania
Sweden
India
Thailand

Health Conditions or Problems Studied

Condition	Code	Keyword
PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER HARBORING ROS1 GENE REARRANGEMENTS WITH AND WITHOUT CENTRAL NERVOUS SYSTEM METASTASES	2-Propanol (T51.2)	NSCLC

Interventions

Intervention	Description	Keyword
oral entrectinib	at a dose of 600 mg once daily with or without food, e.g. three 200-mg capsules per day	Entrectinib
oral crizotinib	oral crizotinib as described in local prescribing information, e.g., 250 mg twice-daily per os taken with or without food	Crizotinib

Primary Outcomes

Name	Time Points	Measure
To evaluate the efficacy of entrectinib compared with crizotinib in patients who have ROS1 rearrangement-positive NSCLC with CNS metastases at baseline	End of Study	· Progression-free survival (PFS), defined as the time from randomization to the first documented disease progression (extracranial or intracranial) or death from any cause, whichever occurs first, as determined by a blinded independent review committee (BIRC) using RECIST v1.1

Key Secondary Outcomes

Name	Time Points	Measure
To evaluate the efficacy of entrectinib compared with crizotinib in patients who have ROS1 rearrangement-positive NSCLC in the whole study population (ITT)	End of Study	· Progression-free survival in the CNS (CNS-PFS), defined as the time from randomization to the first documented disease progression in the CNS or death from any cause, whichever occurs first, as determined by the BIRC using RECIST v1.1 · Overall response rate (ORR), defined as the percentage of patients who attain CR or PR, as assessed by the BIRC and the investigator per RECIST v1.1 · Duration of response (DOR), defined as the time from when response (CR or PR) is first documented to disease progression or death, whichever occurs first, as assessed by the BIRC and the investigator per RECIST v1.1 · Progression-free survival (PFS), defined as the time from randomization to the first documented disease progression (extracranial or intracranial) or death from any cause, whichever occurs first, as determined by the BICR and investigator using RECIST v1.1 · Overall survival (OS), defined as the time from randomization to death from any cause · Impact on functioning, including health related quality of life, using the Global Health Status/Quality of Life (GHS/QoL), the Physical Functioning (PF) and Role Function (RF) scores, as assessed by the EORTC QLQ-C30 and analyzed as a time to first and confirmed clinically meaningful deterioration · Impact on lung cancer-specific symptoms, as assessed by the EORTC QLQ-LC13
To evaluate the efficacy of entrectinib compared with crizotinib in patients who have ROS1 rearrangement-positive NSCLC with CNS metastases at baseline	End of Study	· Objective response rate in the CNS (CNS-ORR), defined as the percentage of patients who attain CR or PR for lesions in the CNS, as determined by the BIRC per RECIST v1.1 · Duration of response in the CNS (CNS DOR), defined as the time from when a CNS response (CR or PR) is first documented to disease progression in the CNS, as determined by the BIRC per RECIST v1.1

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files