ISRCTN16112706 https://doi.org/10.1186/ISRCTN16112706

A study to investigate the lung penetration of RO7223280 following intravenous administration in healthy participants

Submission date	**Recruitment status**	[X] Prospectively registered
28/03/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
28/03/2022	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
28/03/2022	Other	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Antibiotic-resistant bacterial infections are an urgent global threat to public health. Antibiotic resistance happens when germs such as bacteria develop the ability to defeat the drugs designed to kill them. The treatment of the multi-drug resistant (MDR) bacteria Acinetobacter baumannii is extremely challenging because of high rates of resistance to multiple antibiotics. This is a clinical study of a new (novel) drug called RO7223280 which is being developed for the possible treatment of infections caused by the bacterium Acinetobacter baumannii. RO7223280 is an experimental drug and is not yet approved by health authorities like the U.S. Food and Drug Administration for the treatment of bacterial infections.
The main purposes of this study are:
1. To measure the amount of RO7223280 that gets into the lungs and how quickly the body processes it (also called pharmacokinetics [PK])
2. To assess the safety of RO7223280 and determine how well the participants tolerate it.

Who can participate?
Healthy volunteers who are between 18 to 55 years of age, inclusive

What does the study involve?
Participants will need to be a part of this study for about 5 weeks. This study will have three parts:
1. Screening period: Up to 4 weeks before the start of study treatment administration. During this period, the study doctor (also called an Investigator) will conduct certain tests and/or procedures, to make sure that the participants are eligible to participate in this study.
2. Treatment (residential) period: During this period, the participants will have to report to the clinic 1 day before the treatment administration (Day -1) and stay in the clinic for 4 nights. The participants will receive a single dose of 1000 mg RO7223280 over 1 hour through a tube put into a vein in the arm (intravenous infusion) on Day 1.
Each participant will then have a procedure called bronchoalveolar lavage (BAL) to measure the amount of study drug that goes into the lungs. This procedure will be scheduled up to 8 hours after the end of the study drug infusion. A bronchoalveolar lavage involves a flexible tube

inserted through the participant's mouth into one of their lungs. A small amount of fluid (made up of salt and water) will be sprayed into the lung from the tube and then immediately suctioned back to collect lung fluid and cells for examination. During this procedure, a local numbing drug (anaesthetic), such as lidocaine, will be sprayed into the participant's mouth and throat to numb the mouth, nose, and gag reflex.
The participants will have to fast for at least 2 hours before study drug administration and at least 4 hours before undergoing the BAL procedure.
Follow-up period: This will take place about 7 days after the study treatment administration to check on the participant after treatment completion. The participant will have to visit the clinic for the follow-up procedures.

What are the possible benefits and risks of participating?
Participants will be administered RO7223280 only for research purposes and it is not intended that the participants will receive any benefit from it. However, the information learned in this study may help future patients suffering from Acinetobacter baumannii infection.
Participants will be compensated for taking part in this research study. Participants will be compensated for each part of the study they complete up to a total amount of $2700. All study participants will be issued their compensation within 21 days of the completion of their participation in the study.
Participants may experience side effects from the treatments or procedures in this study. Side effects can vary from mild to serious and may be different from person to person. As RO7223280 is a new experimental drug with limited exposure in humans, not all the side effects that could occur are known at this time. The known side effects, as well as potential side effects of this drug based on human and laboratory studies, or knowledge of similar drugs, are listed below:
Allergic reactions: these can be in the form of itching, difficulty breathing, a rash, and/or a drop in blood pressure. In very rare cases, participants could have a life-threatening allergic reaction.
Infusion-related reactions: these side effects are related to the administration of the study drug as an intravenous infusion. Symptoms may include itching, flushing, and shortness of breath.
Other common side effects, seen were headache and side effects associated with either patches from the device used to record the heart’s activity (electrocardiogram [ECG]) or the infusion needle (e.g., skin inflammation (swelling), skin bruising).
As the study treatment is given through a needle placed in the participant's arm, they may experience mild discomfort during the procedure, and there is a small chance of infection from placing the needle in their arm.
Spirometry is a common test used to assess how well the lungs work by measuring how much air is breathed in and out and how quickly air is breathed out. Spirometry is generally a safe test, though it may require some exertion. Participants may feel short of breath or dizzy for a moment after they perform the test.
During the bronchoalveolar lavage (BAL) procedure participants may experience coughing or gaging as the bronchoscope will be inserted through their mouth. The coughing or gagging will stop as the numbing drug begins to work. Potential risks associated with BAL include irritation of the airways (bronchospasm), irritation of the vocal cords (laryngospasm), cough, temporary fever, temporary chills, and muscle pain, and there may be some short-lived difficulty with breathing. Less frequent risks include bleeding, infection, a hole in the airway (bronchial perforation), air in the space between the lung covering (pleural space) that causes the lung to collapse (pneumothorax). Participants may have an allergic reaction to the local numbing drug (e.g., lidocaine). Common side effects of lidocaine are feeling hot or cold, nausea and vomiting, drowsiness, dizziness.
There may be a risk in exposing an unborn child or a baby to the study treatment, and not all

potential consequences are known at this time. Participants must take precautions to avoid exposing an unborn child or breastfeed a baby during the study treatment. Women who are pregnant or are currently breastfeeding cannot take part in this study.

Where is the study run from?
F. Hoffmann-La Roche Ltd (USA)

When is the study starting and how long is it expected to run for?
December 2021 to September 2022

Who is funding the study?
F. Hoffmann-La Roche Ltd (USA)

Who is the main contact?
global-roche-genentech-trials@gene.com

Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
BP43629

Study information

Scientific Title
A non-randomized, open-label, single-dose study to investigate the intrapulmonary penetration of RO7223280 following intravenous administration in healthy participants

Study objectives
The purpose of this study is to investigate the intrapulmonary penetration of RO7223280 following administration of a single intravenous (IV) dose of RO7223280 in healthy participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/02/2022, Salus IRB (2111 West Braker Lane, Suite 100, Austin, Texas 78758; +1 (0) 512 380 1244; +1 (0)855 300 0815; clientservices@salusirb.com), ref: not applicable

Study design
Non-randomized open-label single-dose study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not applicable

Health condition(s) or problem(s) studied
Intrapulmonary penetration of RO7223280 following intravenous administration

Interventions
Participants will receive a single dose of RO7223280, 1000 milligrams (mg), as an IV infusion over a period of 1 hour on Day 1.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO7223280

Primary outcome measure
1. Concentrations of RO7223280 in epithelial lining fluid (ELF) (CELF) measured using bronchoalveolar lavage (BAL) and plasma samples collected at a specific timepoint, up to 8 and 12 hours post-dose on Day 1 respectively
2. ELF-to-Plasma ratios of RO7223280 in ELF measured using BAL and plasma samples collected

at a specific timepoint, up to 8 hours post-dose on Day 1
3. Concentrations of RO7223280 in alveolar macrophages (AM) measured using BAL and plasma samples collected at a specific timepoint, up to 8 and 12 hours post-dose on Day 1 respectively
4. AM-to-Plasma ratios of RO7223280 in AM measured using BAL and plasma samples collected at a specific timepoint, up to 8 hours post-dose on Day 1

Secondary outcome measures

1. Maximum observed concentration (Cmax) of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
2. Time to maximum observed concentration (Tmax) of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
3. Observed plasma concentration at the end of infusion (Cend) of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
4. Area under the plasma or blood concentration versus time curve from time zero to the last measurable concentration (AUClast) of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
5. Area under the plasma or blood concentration versus time curve from time zero extrapolated to infinity (AUCinf) of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
6. Apparent terminal elimination half-life (T1/2), computed as ln(2)/ λz of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
7. Terminal rate constant (λz) calculated by linear regression of the log-transformed terminal part of the concentration time curve of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
8. Total body clearance (CL), calculated as Dose/AUCinf of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
9. Volume of distribution at steady-state (Vss), estimated based on IV data calculated using mean residence time (MRT) and CL of RO7223280 and its metabolites, as appropriate, in plasma measured using blood samples at pre-dose and at multiple timepoints, up to 12 hours post-dose on Day 1 and thereafter on Days 2, 3 and 4
10. Percentage of participants with adverse events (AEs) measured from screening up to 7 days after last study drug administration (up to approximately 5 weeks)
11. Percentage of participants with severity of AEs assessed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE) from screening up to 7 days after last study drug administration (up to approximately 5 weeks)
12. Changes in vital signs values as assessed by measuring temperature (oral or temporal), pulse rate, respiratory rate, and blood pressure (systolic and diastolic) from screening up to 7 days after last study drug administration (up to approximately 5 weeks)
13. Changes in physical examination parameters as measured by assessment of cardiovascular, respiratory, gastrointestinal, dermatological, neurological, and musculoskeletal systems, in addition to head, eyes, ears, nose, throat, neck, and lymph nodes from screening up to 7 days after last study drug administration (up to approximately 5 weeks)
14. Changes in electrocardiogram (ECG) parameters, measured using 12-lead ECG from

screening up to 7 days after last study drug administration (up to approximately 5 weeks)
15. Changes in clinical laboratory safety parameters measured using blood or urine samples collected from screening up to 7 days after last study drug administration (up to approximately 5 weeks)

Overall study start date
17/12/2021

Completion date
02/09/2022

Eligibility

Key inclusion criteria
1. Male and female participants aged 18 to 55 years of age, inclusive, at screening
2. Healthy participants. Health status defined by the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, serology, coagulation, and urinalysis
3. Participants must weigh at least 50 kg and must have a body mass index (BMI) within the range of 18 to 32 kg/m², inclusive

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
1. History of any clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological, haematological, or allergic disease, metabolic disorder, cancer, or cirrhosis
2. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study
3. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs
4. History or presence of clinically significant ECG abnormalities
5. History of malignancy
6. Vaccination is prohibited within 2 months prior to Day 1
7. Use of glucocorticoids and other immunosuppressive medications is prohibited within 30 days

(or within 5 times the elimination half-life, whichever is longer) prior to Day 1
8. Currently enrolled in, have participated in, or plan to participate in any other clinical study involving an investigational medicinal product or medical device study from within 30 days directly preceding screening or within 5 times the elimination half-life, if known (whichever is longer), until completion of the follow-up visit
9. Normal lung function with forced expiratory volume in the first second (FEV1) predicted ≥80% and FEV1/forced vital capacity (FVC) >0.7.
10. Clinically significant abnormalities in laboratory test results (including complete blood count, chemistry panel, and urinalysis)
11. Evidence of human immunodeficiency virus (HIV) infection and/or positive result for human HIV antibodies
12. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result
13. Participants who may not tolerate a BAL or cannot undergo a BAL because of the presence of contraindications to a BAL including suspected intolerance to medications required for bronchoscopy
14. History of hypersensitivity to lidocaine (and other local anaesthetics of the amino amide type) or to any of its formulation ingredients
15. History of hypersensitivity to any of the excipients in the formulation of RO7223280
16. Participants with insufficient venous access.

Date of first enrolment
29/03/2022

Date of final enrolment
24/08/2022

Locations

Countries of recruitment
United States of America

Study participating centre
Pulmonary Associates Clinical Trials (PACT)
PA 3811 East Bell Road, Suite 107
Phoenix, AZ
United States of America
85032

Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

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Sponsor type
Industry

Website
http://www.roche.com/about_roche/roche_worldwide.htm

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/12/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement

IPD sharing plan summary
Not expected to be made available