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A study to investigate the effect of various degrees of liver damage on the processing by the body of a single dose of RO7223280 given through the vein

Submission date
27/10/2022

Recruitment status
No longer recruiting

Registration date
08/11/2022

Overall study status
Completed

Last Edited
08/11/2022

Condition category
Digestive System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] 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 like bacteria and fungi develop the ability to defeat the drugs designed to kill them. Acinetobacter baumannii is one such bacteria against which new antibiotics are required. RO7223280 is being developed for the possible treatment of such infections. RO7223280 selectively kills Acinetobacter and inhibits an essential bacterial process not targeted by currently available antibiotics. RO7223280 prevents the growth of Acinetobacter carrying all known antibiotic resistance mechanisms tested to date, including resistance to a drug called carbapenem (carbapenem-resistant Acinetobacter baumannii; CRAB). Based on these favorable properties, RO7223280 is being developed for the treatment of hospital-acquired (nosocomial) bacterial lung infection (pneumonia; HABP), a lung infection that develops in a person who is on a ventilator (ventilator-associated bacterial pneumonia; VABP), and bloodstream infection due to CRAB. Health authorities have not yet approved RO7223280 for the treatment of bacterial infection due to Acinetobacter baumannii. The main aim of this study is to measure how much of the drug gets into the bloodstream and how long it takes the body to get rid of it when given to participants with normal liver function or differing levels of liver problems (impairment). In addition, the safety and tolerability of the RO7223280 and any side effects that occur will also be evaluated.

Who can participate?
Male and female participants between 18 and 75 years of age with normal liver function or differing levels of liver impairment

What does the study involve?
Participants will need to be a part of this study for about 5 weeks. The study will include the following parts:
1. A screening part of up to 28 days to check the eligibility of participants to take part in the study

2. A dosing/treatment period of up to 1 day. Participants with normal liver function and mild, moderate, or severe liver damage will receive a single dose of RO7223280, through the vein (IV infusion) on Day 1. Participants will have to get admitted to the clinic 1 day before receiving the treatment and will have to stay in the clinic for 3 days after receiving the treatment.
3. A follow-up part during which participants will return to the clinic for a follow-up visit 7 (±2) days following drug administration.

What are the possible benefits and risks of participating?
Participants' health may or may not improve in this study, but the information that is learned may help other people suffering from similar conditions in the future. Participants will receive monetary compensation for taking part in the study.
Participants may have side effects from RO7223280, or procedures used in this study. These can be mild to severe and even life-threatening, and they can vary from person to person. There may be side effects that are not known at this time. The potential side effects associated with RO7223280, and other procedures are listed below:
Risks associated with RO7223280:
1. Allergic reaction: itching, difficulty breathing, rash, drop in blood pressure, and in rare cases life-threatening allergic reaction.
2. Potential side effects: chills, fever, nausea, high or low blood pressure, fast heart rate, itching, flushing, shortness of breath, headache.
Risks associated with study procedures:
1. Blood sampling: drawing blood can cause pain, bruising, or infection where the needle is inserted. Some people experience dizziness, fainting, or upset stomach when their blood is drawn.
2. Electrocardiograms (ECG): ECG patches may cause a skin reaction such as redness or itching. Participants may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.
There may be a risk in exposing an unborn child to the study drug, and all risks are not known at this time. Participants who become 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?
July 2022 to October 2023

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
Dr Clinical Trials

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-002272-36

Protocol serial number
BP43792

Study information

Scientific Title
A multiple-center, open-label, non-randomized study to investigate the effect of various degrees of hepatic impairment on the pharmacokinetics of a single intravenous dose of RO7223280

Study objectives
The main aim of the study is to evaluate the effect of different levels of hepatic impairment on the pharmacokinetics (PK), safety and tolerability of a single intravenous (IV) dose of RO7223280, compared with demographically matched participants with normal hepatic function.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/09/2022, Ethics Committee of the Bratislava Self-Governing Region, Sabinovska 19, 820 05, Bratislava, Slovakia; +421 (0)2 4826 4912; Mgr.Ivana.Vanacka@region-bsk.sk), ref: not applicable

Primary study design
Interventional

Study design
Phase I open-label multicenter parallel-group single-dose three-part study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Impaired hepatic function

Interventions

Participants with normal hepatic function and mild, moderate and severe hepatic impairment will receive a single dose of RO7223280, 600 mg, administered as an IV infusion on Day 1.

Participants will need to be a part of this study for about 5 weeks. The study will include the following parts:
1. A screening part of up to 28 days to check the eligibility of participants to take part in the study
2. A dosing/treatment period of up to 1 day. Participants with normal liver function and mild, moderate, or severe liver damage will receive a single dose of RO7223280, through the vein (IV infusion) on Day 1. Participants will have to get admitted to the clinic 1 day before receiving the treatment and will have to stay in the clinic for 3 days after receiving the treatment.
3. A follow-up part during which participants will return to the clinic for a follow-up visit 7 (±2) days following drug administration.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
1. Maximum observed concentration (Cmax) of total and unbound RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
2. Area under the plasma concentration versus time curve- extrapolated to infinity (AUCinf) of total and unbound RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
3. AUC from zero to the last measurable concentration (AUClast) of total and unbound RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4

Key secondary outcome(s)
1. Time to maximum observed concentration (tmax) of RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
2. Percentage of extrapolated area under the plasma concentration versus time curve extrapolated to infinity (AUC%extra) of RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
3. Terminal rate constant (λz) of RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
4. Apparent terminal elimination half-life (t1/2) of RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
5. Total clearance (CL) of total and unbound RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken

at multiple timepoints from Day 1 up to Day 4
6. Volume of distribution at steady-state (Vss) of total and unbound RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
7. Molecular weight adjusted metabolite-to-parent ratio for Cmax and AUC of RO7223280 measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay using plasma samples taken at multiple timepoints from Day 1 up to Day 4
8. Number of participants with adverse events (AEs) recorded from screening to end of study (approximately 5 weeks)
9. Number of participants with severity of AEs determined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) from screening to end of study (approximately 5 weeks)

Completion date
30/10/2023

Eligibility

Key inclusion criteria
1. Male and female participants aged 18 to 75 years of age, inclusive, at screening
2. Participants must have a body weight of at least 50 kg and a body mass index (BMI) within the range of 18 to 40 kg/m² (inclusive)

Additional inclusion criteria for participants with normal hepatic function:
3. Participants must be in reasonably good health as determined by the Investigator
4. Matched to participants with mild, moderate, or severe hepatic impairment in sex, age (± 10 years), and BMI (± 15%)

Additional inclusion criteria for participants with hepatic impairment only:
5. Documented chronic stable liver disease (Child-Pugh class A, B, or C, at screening); diagnosis of cirrhosis due to parenchymal liver disease. This will exclude biliary liver cirrhosis or other causes of hepatic impairment not related to parenchymal disorder
6. Anemia secondary to hepatic disease will be acceptable, if hemoglobin ≥9 g/dL and anemia symptoms are not clinically significant as judged by the Investigator (or designee), Sponsor and Medical Monitor
7. Participants must have a platelet count ≥25,000/µL

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Key exclusion criteria
1. History or evidence of any medical conditions (e.g., gallbladder removal, malabsorption syndromes) potentially altering the absorption, distribution, metabolism, or elimination of drugs
2. History or presence of clinically significant electrocardiogram (ECG) abnormalities based on the average of the triplicate ECG recordings (e.g., PQ/PR interval >210 ms), QT corrected for heart rate using the Fridericia's correction factor (QTcF) >480 ms or clinically significant cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease with recent myocardial infarction within the past 2 months, clinically significant cardiomyopathy, decompensated congestive heart failure, family history of congenital long QT syndrome, family history of sudden death)
3. History of unstable diabetes mellitus (as evidenced by hemoglobin A1c ≥9.0% [75 mmol/mol] at screening)
4. Vaccination is prohibited within 1 month prior to Day 1
5. Minimal smoking (up to 10 cigarettes/day) may be allowed at the discretion of the Investigator in discussion with the Sponsor and Medical Monitor. Participants will not be permitted to smoke within 2 hours prior to dose or 4 hours post-dose on Day 1
6. Evidence of human immunodeficiency virus (HIV) infection and/or positive result for human HIV antibodies.
7. Evidence of hepatorenal syndrome and estimated creatinine clearance range <60 ml/min or clinically significant abnormal sodium and potassium levels
8. Participants with insufficient venous access
9. History of hypersensitivity to any of the excipients in the formulation of RO7223280

Additional inclusion criteria for participants with normal hepatic function
10. Acute diseases or medical/surgical procedure with clinical significance (determined by the Investigator) within 2 weeks prior to screening, including gastrointestinal [GI] diseases and infections (such as respiratory or central nervous system infections)
11. Significant history or clinical manifestation of hepatic disorder
12. History or presence of liver disease or liver injury
13. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result

Additional inclusion criteria for participants with hepatic impairment only:
14. Acute diseases or medical/surgical procedure with clinical significance (determined by the Investigator) within 2 weeks prior to screening, including GI diseases and infections (such as respiratory, central nervous system infections, or spontaneous bacterial peritonitis)
15. Current functioning organ transplant or are waiting for an organ transplant
16. Evidence of severe ascites
17. Presence of a portosystemic shunt, except for participants with severe hepatic impairment
18. Participants in current need for paracentesis within 1 month, prior to Day 1
19. History of GI hemorrhage due to esophageal varices or peptic ulcers less than 6 weeks prior to screening
20. History within 90 days prior to the screening visit or current symptoms of hepatic encephalopathy Grade 2 or above
21. Worsening of hepatic encephalopathy within 1 month prior to Day -1
22. Use of rifaximin for the treatment of hepatic encephalopathy at any time during the study is permitted

Date of first enrolment

30/11/2022

Date of final enrolment
30/09/2023

Locations

Countries of recruitment
Germany

Poland

Slovakia

Study participating centre
Centrum Badan Klinicznych
Wroclaw
Poland
51-162

Study participating centre
APEX GmbH
München
Germany
81241

Study participating centre
Summit Clinical Research s.r.o
Bratislava
Slovakia
83101

Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

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

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