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A study to evaluate the effects of various degrees of reduced kidney function on how the study drug (RO7223280) is broken down and eliminated from the body

Submission date
14/04/2023

Recruitment status
No longer recruiting

Registration date
19/04/2023

Overall study status
Completed

Last Edited
04/12/2023

Condition category
Infections and Infestations

[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
RO7223280 is an experimental drug that is being tested in this clinical study for the treatment of a disease (infection) caused by a germ (bacteria) called Acinetobacter baumannii. RO7223280 is an experimental drug, which means it is not approved by the Health Authorities for the treatment of bacterial infection caused by Acinetobacter baumannii or for any other disease. The aim of this study is to find out how different severity levels of kidney damage will affect the breakdown and removal of the study drug (RO7223280) from the body (this is called pharmacokinetics [PK]).

Who can participate?
People who are 18 to 82 years of age (inclusive), with normal kidney function, or mild, moderate, severe kidney damage or have end-stage kidney disease (ESRD) requiring their blood to be purified using a machine at regular intervals (hemodialysis).

What does the study involve?
Participants with normal kidney function, or mild, moderate, or severe kidney damage will have to be a part of this study for around 5 weeks. The study will be conducted as follows:
1. Screening visit: Participants will have one screening visit. This will take place up to 28 days before the study drug administration to see if participants are eligible for the study.
2. Treatment (residential) period: Participants will have to report to the clinic 2 days before the study drug administration (Day –2) and stay in the clinic up to Day 4.
3. Follow-up visit: To check on the participant after the study treatment is finished. This visit will take place between 5 to 9 days after the study drug administration.
Participants with end-stage renal disease will have to be a part of this study for around 9 weeks. The study will be conducted as follows:
1. Screening visit: Participants will have one screening visit. This will take place up to 28 days before the study drug administration to see if participants are eligible for the study.
2. Treatment (residential) Periods 1 and 2: Participants will have to report to the clinic 1 day

before the first study drug administration (Day –1) and stay in the clinic until Day 2, when they will be discharged during Period 1. After a period of 7-21 days wherein no drug will be given (washout period) the participants will have to report back to the clinic for Period 2, one day before the second study drug administration (Day –1) and stay in the clinic until Day 2.
3. Ambulatory visit in Periods 1 and 2: Participants will have to visit the clinic on Day 4 (±1 day) and Day 7 (±1 day) after the first study drug administration in Period 1 and again on Day 4 (±1 day) and Day 7 (±1 day) of Period 2 after the second study drug administration.
4. Follow-up visit in Period 2: To check on the participant after the study treatment is finished. This visit will take place 11 to 15 days after the second study drug administration.

What are the possible benefits and risks of participating?
Participants will not receive any benefit from 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.
RO7223280 has had limited testing in humans and 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:
1. Allergic reactions due to administration of RO7223280, which can be in the form of itching, difficulty breathing, a rash, and/or drop in blood pressure.
2. There may be some changes in liver and kidney functions.
3. Participants may experience symptoms like chills, fever, nausea, headache, high or low blood pressure, fast heart rate, and shortness of breath, itching at the site of injection
Iohexol is a dye (contrast media) which helps in measuring kidney function. The dose of iohexol being administered is significantly low and therefore the risk of side effects is also significantly lower.
There may be a risk in exposing an unborn child to the study drug, and not all potential risks are known at this time. Women and men must take precautions to avoid exposing an unborn child or a breastfed baby to the study treatment. Participants who are pregnant, or breastfeeding cannot take part in this study.

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

When is the study starting and how long is it expected to run for?
February 2023 to January 2024

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

Who is the main contact?
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Contact information

Type(s)
Public

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
BP43628

Study information

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

Study objectives
The main purpose of this study is to assess the effect of different levels of renal impairment on the pharmacokinetics (PK) of RO7223280 in plasma and urine compared with demographically matched participants with normal renal function, following a single intravenous (IV) dose of RO7223280.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/02/2023, Salus IRB (2111 W.Braker Lane, Suite 100, Austin, Texas, 78758, USA; +1 (0)512 380 1244; salus@salusirb.com), ref: not applicable

Study design
Phase I multiple-center single-dose non-randomized open-label four-part study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Bacterial infection

Interventions
Part 1, 2 and 3: Participants with normal, mild, moderate, and severe renal impairment will receive a single dose of RO7223280, 600 mg, administered as an IV infusion on Day 1.

Part 4: Participants with end-stage renal disease (ESRD) requiring haemodialysis will receive a single dose of RO7223280, 600 mg, administered as an IV infusion shortly after the completion of haemodialysis or on a non-dialysis day on Day 1 of Period 1. After a washout period of 7 to 21 days participants with will then receive a single dose of RO7223280, 600 mg, administered as an IV infusion prior to haemodialysis session on Day 1 of Period 2.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
1. Parts 1, 2 and 3: Observed maximum plasma concentration (Cmax) of RO7223280 (and its metabolite(s), as appropriate) measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay from plasma samples collected at multiple time points from Day 1 to Day 4
2. Parts 1, 2 and 3: Area under the plasma concentration-time curve extrapolated to infinity (AUCinf) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS /MS assay from plasma samples collected at multiple time points from Day 1 to Day 4
3. Parts 1, 2 and 3: AUC from zero to the last measurable concentration (AUClast) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 4
4. Parts 1, 2 and 3: Time to maximum plasma concentration (Tmax) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 4
5. Parts 1, 2 and 3: Percentage of extrapolated area under the plasma concentration-time curve extrapolated to infinity (AUC%extra) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 4
6. Parts 1, 2 and 3: Terminal rate constant (λz) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 4
7. Parts 1, 2 and 3: Total body clearance (CL) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 4
8. Parts 1, 2 and 3: Volume of distribution (Vss) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 4
9. Parts 1, 2 and 3: Amount of RO7223280 excreted into urine (Ae) measured using validated LC-MS/MS assay from urine samples collected at multiple time points from Day 1 to Day 3

10. Parts 1, 2 and 3: Fraction of the dose of RO7223280 administered excreted into urine (Fe) measured using validated LC-MS/MS assay from urine samples collected at multiple time points from Day 1 to Day 3
11. Parts 1, 2 and 3: Renal clearance of RO7223280 (CLr) measured using LC-MS/MS assay from urine samples collected at multiple time points from Day 1 to Day 3
12. Parts 1, 2 and 3: Molecular weight adjusted metabolite-to-parent ratio for Cmax and AUC parameters calculated using non-compartmental method of analysis from plasma samples collected at multiple timepoints from Day 1 to Day 4
13. Parts 1, 2 and 3: Fraction of RO7223280 unbound in plasma calculated using non-compartmental method of analysis from plasma samples collected at multiple timepoints from Day 1 to Day 4
14. Parts 4: Cmax of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
15. Parts 4: AUCinf of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points Day 1 to Day 7 in both Period 1 and Period 2
16. Parts 4: AUC from zero to the last measurable concentration (AUClast) of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
17. Parts 4: Tmax of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
18. Parts 4: AUC%extra of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
19. Parts 4: λz of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
20. Parts 4: CL of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
21. Parts 4: Vss of RO7223280 (and its metabolite(s), as appropriate) measured using validated LC-MS/MS assay from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
22. Parts 4: Amount of RO7223280 excreted into urine (Ae) measured using validated LC-MS/MS assay from urine samples collected on Day 1 in both Period 1 and Period 2
23. Parts 4: Fraction of the dose of RO7223280 administered excreted into urine (Fe) measured using validated LC-MS/MS assay from urine samples collected on Day 1 in both Period 1 and Period 2
24. Parts 4: CLr of RO7223280 measured using LC-MS/MS assay from urine samples collected on Day 1 in both Period 1 and Period 2
25. Part 4: Arterial (predialyzer/inflow to dialyzer) plasma concentration of RO7223280 (Cinlet) measured using a qualified LC-MS/MS assay from the dialysate collected at multiple time points on Day 1 of Period 2
26. Part 4: AUC from start of dialysis (t2) until the end of dialysis (t1) based on Cinlet (AUCinlet_t0-t1) measured using a qualified LC-MS/MS assay from the dialysate collected at multiple time points on Day 1 of Period 2
27. Part 4: Venous' (post dialyzer/outflow from dialyzer) plasma concentration of RO7223280 (Coutlet) measured using a qualified LC-MS/MS assay from the dialysate collected at multiple time points on Day 1 of Period 2
28. Part 4: AUC from start of dialysis (t2) until the end of dialysis (t1) based on Coutlet

(AUCoutlet_t0-t1) measured using a qualified LC-MS/MS assay from the dialysate collected at multiple time points on Day 1 of Period 2
29. Part 4: Dialysis clearance (CLd) of RO7223280 measured using a qualified LC-MS/MS assay from the dialysate collected at multiple time points on Day 1 of Period 2
30. Part 4: Molecular weight adjusted metabolite-to-parent ratio for Cmax and AUC parameters of RO7223280 calculated using non-compartmental method of analysis from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2
31. Part 4: Fraction of RO7223280 unbound in plasma calculated using non-compartmental method of analysis from plasma samples collected at multiple timepoints from plasma samples collected at multiple time points from Day 1 to Day 7 in both Period 1 and Period 2

Key secondary outcome(s))
Number of participants with adverse events collected using electronic case report form (eCRF) from study initiation up to follow-up visit (approximately 9 weeks)

Completion date
29/01/2024

Eligibility

Key inclusion criteria
1. Male and female participants aged 18 to 82 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 at screening and admission to the clinic

Criteria for participants with normal renal function only:
1. Participants must be in reasonably good health for their age group as determined by the Investigator
2. Estimated glomerular filtration rate (eGFR) at screening using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (based on serum creatinine) of ≥90 mL/min. The stability of renal function will be confirmed by 2 determinations of serum creatinine separated by at least 7 days. Renal function is considered stable if the two serum creatinine values differ by ≤20%
3. Matched to participants with mild, moderate, or severe renal impairment in sex, age (± 10 years), and BMI (± 15%) at screening

Criteria for participants with renal impairment only:
1. eGFR at screening and admission to the clinic using the CKD-EPI equation (based on serum creatinine) of: For mild renal impairment: ≥60 to <90 mL/min (Part 1); moderate renal impairment: ≥30 to <60 mL/min (Part 2); severe renal impairment: <30 mL/min (participants must not be on dialysis and in the opinion of the Investigator will not require dialysis during the study) (Part 3)
2. Stable renal function (Parts 1, 2, and 3). The stability of renal function will be confirmed by two determinations of serum creatinine separated by at least 7 days. Renal function is considered stable if the two serum creatinine values differ by ≤20%

Criteria for participants with ESRD requiring haemodialysis:
1. Reduced renal function with a clinical diagnosis of ESRD requiring renal replacement therapy
2. Requiring haemodialysis for more than 3 months at the time of the screening visit

Participant type(s)

Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
82 years

Sex
All

Key exclusion criteria
1. History or evidence of any medical conditions potentially altering the absorption, distribution, metabolism, or elimination of RO7223280, except those conditions associated with the primary renal disease
2. History of malignancy within the last year
3. Suffering from an active symptomatic infection (such as influenza, urinary tract infection, or gastrointestinal infections) within 2 weeks prior to treatment administration
4. Evidence of human immunodeficiency virus (HIV) infection and/or positive result for human HIV antibodies
5. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result
6. History of hypersensitivity to any of the excipients in the formulation of RO7223280 or OmnipaqueTM

Criteria for participants with normal renal function only:
1. Significant history or clinical manifestation of renal disorder, as determined by the Investigator
2. History or presence of renal disease or renal injury as indicated by any clinically significant deviations from normal reference ranges in renal function tests, unless approved by the Investigator

Criteria for participants with renal impairment or ESRD requiring haemodialysis only:
1. Nephrotic syndrome (defined as plasma albumin <2 g/dL combined with proteinuria >3 g/day)
2. Participants with renal impairment due to hepatic disease (hepatorenal syndrome)
3. Presence of a renal carcinoma, or an acute renal disease caused by infection or drug toxicity
4. Subjects with a functioning renal transplant or who are active on the transplant waiting list
5. Values outside the normal range for renal and liver function tests that are not consistent with their renal condition, as determined by the Investigator.
6. Blood potassium concentration <3 mmol/L or > 6.5 mmol/L at screening or admission to the clinic
7. Hyponatremia (<120 mmol/L) or hypernatremia (>150 mmol/L) at screening or admission to the clinic
8. Clinically significant liver disease, e.g., hepatitis, cirrhosis, and/or confirmed liver enzymes
9. Haemoglobin concentration <8.5 g/dL at screening or admission to the clinic

Date of first enrolment

04/05/2023

Date of final enrolment
27/11/2023

Locations

Countries of recruitment
New Zealand

United States of America

Study participating centre
New Zealand Clinical Research
New Zealand
8011

Study participating centre
Nucleus Network
United States of America
55114

Study participating centre
Orlando Clinical Research Center
United States of America
32809

Study participating centre
Advanced Pharma CR, LLC
United States of America
32809

Sponsor information

Organisation
F. Hoffmann-La Roche

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes