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The effect of body weight on rivaroxaban disposition in healthy human volunteers

Submission date
29/01/2023

Recruitment status
No longer recruiting

Registration date
08/02/2023

Overall study status
Completed

Last Edited
18/10/2024

Condition category
Other

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a condition that occurs when a blood clot forms in a vein. Treating at-risk patients with the proper anticoagulants (blood thinners) is a cornerstone in decreasing the risk of illness and death which result from these thromboembolic events. Novel direct oral anticoagulants, such as rivaroxaban, are viable treatment options and have obvious advantages over traditional agents. However, their optimal dosing in special patient populations such as people who are obese is a source of therapeutic dilemma and clinical controversy. On the other hand, obesity is highly prevalent worldwide and it represents an independent risk factor for the development of VTE. Clinical studies and practice guidelines provide conflicting data regarding the effect of weight on rivaroxaban. This places clinicians in a dilemma in decision-making regarding the use of standard doses of rivaroxaban in patients with VTE who are obese. The aims of the study are to compare the disposition of rivaroxaban in obese healthy volunteers with normal-weight healthy volunteers, and to compare the action of rivaroxaban in obese healthy volunteers with normal-weight healthy volunteers.

Who can participate?
Healthy volunteers who are between 18 and 60 years old and who have a body mass index 18.5 to 25 kg/m² or ≥35 kg/m²

What does the study involve?
Participants take a single dose of rivaroxaban film-coated tablet and blood samples are taken before taking rivaroxaban and after 1, 2, 4, 8, 12, 18, 36 and 48 hours. A total of nine urine samples are collected before and after taking rivaroxaban.

What are the possible benefits and risks of participating?
Taking part in this research will help answer an important clinical question, from which a lot of real-world patients will benefit. Most of the effective available alternatives of rivaroxaban either require multiple injections daily or require frequent clinic visits and blood withdrawal for monitoring, in addition to a long list of interactions with other drugs and food products. If this research answers the question regarding the effectiveness of rivaroxaban among obese participants in comparison to the control group, patients will be saved from these frequent visits

or the frequent injections. This study does no harm to participants other than possible complications that may result from the use of rivaroxaban, such as bleeding complications, but these possibilities are few because the study includes taking only one dose of the drug.

Where is the study run from?
Qatar University (Qatar)

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

Who is funding the study?
Qatar University (Qatar)

Who is the main contact?
Dr Ahmed Awaisu, aawaisu@qu.edu.qa

Contact information

Type(s)
Principal Investigator

Contact name
Prof Ahmed Awaisu

ORCID ID
https://orcid.org/0000-0002-9029-8925

Contact details
Qatar University
PO Box 2713
Doha
Qatar
2713
+974 (0)4403 5596
aawaisu@qu.edu.qa

Type(s)
Scientific

Contact name
Dr Ousama Rachid

ORCID ID
http://orcid.org/0000-0002-2364-3848

Contact details
Qatar University
Doha
Qatar

PO Box 2713
+974 (0) 4403 5631
orachid@qu.edu.qa

Type(s)
Public

Contact name
Mrs Majdoleen Alalawneh

ORCID ID
http://orcid.org/0000-0002-6597-1647

Contact details
Qatar University
Doha
Qatar
P.O. Box 2713
+974 (0)7765 4300
ma1903150@student.qu.edu.qa

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RESH-012

Study information

Scientific Title
Pharmacokinetic and pharmacodynamic study of a single dose of rivaroxaban under fed conditions in healthy obese vs non-obese subjects

Acronym
RIVOBESE-PK

Study objectives
Rivaroxaban pharmacokinetic and pharmacodynamic profiles change in obese individuals compared to non-obese individuals.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 25/07/2022, Evaluation Unit of Bioavailability and Bioequivalence Studies for Human Pharmaceuticals (21 Abdel Aziz Al Saud St., Manial Al-Rawda, Cairo, Egypt; +202 (0) 25354100 ext: 1806; hdr.bioequivalence@edaegypt.gov.eg), ref: Not Applicable
2. Approved 17/08/2022, Qatar University IRB (P.O. Box 2713, Qatar; +974 (0)4403 5307; QU-IRB@qu.edu.qa), ref: QU-IRB 1741-E/22
3. Approved 29/06/2022, the International Centre for Bioavailability, Pharmaceutical and Clinical Research IRB (North Industrial Zone, El Obour City, Cairo, Egypt; +20 (0)2 44891734; ahmed.ismail@hu.edu.eg), ref: FORM04/SOP: QA-034 – RESH-012

Study design
Interventional pharmacokinetic study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Pharmaceutical testing facility

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Rivaroxaban disposition in healthy human volunteers (obese vs non-obese population)

Interventions
A single dose of rivaroxaban (20 mg film-coated tablet) is given orally to the healthy participants in both groups (obese participants with BMI ≥35 kg/m² or weight more than 120 kg; the control group who are normal weight participants with BMI 18.5 to 25 kg/m²) under fed conditions. Nine blood samples are taken from all participants at the following timepoints: 0, 1, 2, 4, 8, 12, 18, 36, and 48 h from baseline. In addition, nine urine samples were obtained from all participants within the following time intervals: (-2 to 0) h, (0 to 3) h, (3 to 6) h, (6 to 9) h, (9 to 12) h, (12 to 15) h, (15 to 18) h, at 36 h, and at 48 h (all started from baseline time); study duration is 48 h. Analysis for all samples is carried out using ultra-performance liquid chromatography to obtain rivaroxaban concentrations (and other pharmacokinetic parameters) in these samples.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacodynamic

Phase
Not Applicable

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

Primary outcome measure
1. Rivaroxaban concentration in blood samples is measured using ultra-performance liquid chromatography - tandem mass spectrometer (UPLC MS/MS) at baseline, 1, 2, 4, 8, 12, 18, 36 and 48 hours
2. Rivaroxaban concentration in urine samples is measured using ultra-performance liquid chromatography - tandem mass spectrometer (UPLC MS/MS) at (-2 to 0), (0 to 3), (3 to 6), (6 to 9), (9 to 12), (12 to 15), (15 to 18), at 36, and at 48 hours
3. Area under the concentration-time curve (AUC), time for maximum concentration (Tmax), volume of distribution (Vd), clearance (Cl), and half-life (t1/2) are obtained using WinNonlin software (pharmacokinetic software) at baseline, 1, 2, 4, 8, 12, 18, 36 and 48 hours

Secondary outcome measures
1. Prothrombin time (PT) is measured using the standard quantitative method used in the medical laboratories at 0, 1, 2, 4, 8, 12, 18, 36, and 48 hours
2. Activated partial thromboplastin time (APTT) is measured using the standard quantitative method used in the medical care laboratories at 0, 1, 2, 4, 8, 12, 18, 36, and 48 hours

Overall study start date
30/01/2022

Completion date
26/09/2022

Eligibility

Key inclusion criteria
1. Healthy participants from the Egyptian general population
2. Age 18-60 years
3. Body mass index 18.5 – 24.9 kg/m² for normal-weight participants OR BMI ≥ 35 kg/m² for obese participants
4. The participant is fully aware of the study details and gave written informed consent
5. The physical examination is assessed and accepted by the attending physician
6. Oral body temperature within the normal range (35.9 – 37.6°C)
7. All laboratory screening results within the normal range for normal-weight volunteers and with some variation from the normal range for the obese participants
8. Normal coagulation tests at baseline of the study, i.e., international normalised ratio (INR) up to 1.1, prothrombin time (PT) 10 – 13 seconds, and activated partial thromboplastin time (aPTT) 30 – 40 seconds

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit

18 Years

Upper age limit
60 Years

Sex
Male

Target number of participants
36

Total final enrolment
36

Key exclusion criteria
Current participant exclusion criteria as of 18/10/2024:
1. History of hypersensitivity to the drug or similar compound
2. Having any known coagulation conditions (i.e., von Willebrand disease, haemophilia)
3. Having any known increased bleeding risk (i.e., haemorrhoids, peptic ulcer, or frequent nasal bleeding)
4. Having any chronic disease/condition (such as diabetes type 2, cardiovascular disease, hypertension, and cancer)
5. Known history or presence of food allergies or intolerability (e.g dairy product or gluten-containing food) or any condition is known to interfere with the absorption, distribution, metabolism or excretion of drugs
6. Vegetarian
7. Exhausting physical exercise in the last 24 hours (e.g. weight lifting).
8. History of serious illness that can impact the fate of drugs or clinically significant illness 3 weeks before the study
9. Obvious signs of serious renal, gastrointestinal, cardiovascular, hepatic, neurological, musculoskeletal, endocrine disorders as evidenced by physical
examination, and/or clinical laboratory tests
10. Participant HB

Previous participant exclusion criteria:
1. History of hypersensitivity to the drug or similar compound
2. Having any known coagulation conditions (i.e., von Willebrand disease, haemophilia)
3. Having any known increased bleeding risk (i.e., haemorrhoids, peptic ulcer, or frequent nasal bleeding)
4. Having any chronic disease/condition (such as diabetes type 2, cardiovascular disease, hypertension, and cancer)
5. Known history or presence of food allergies or intolerability (e.g dairy product or gluten-containing food) or any condition is known to interfere with the absorption, distribution, metabolism or excretion of drugs
6. Vegetarian
7. Exhausting physical exercise in the last 24 hours (e.g. weight lifting).
8. History of serious illness that can impact the fate of drugs or clinically significant illness 3 weeks before the study
9. Obvious signs of serious renal, gastrointestinal, cardiovascular, hepatic, neurological, musculoskeletal, endocrine disorders as evidenced by physical
examination, and/or clinical laboratory tests

10. Participant HBsAg, HCV, and HIV positive
11. History of drug or alcohol abuse, smoking more than 10 cigarettes or equivalent per day
12. Regular use of medication
13. Use of any known enzyme inducers or inhibitors (e.g. barbiturates, rivaroxaban, phenytoin, rifampin) within 30 days prior to study entry.
14. Use of any prescription or non-prescription (OTC) medication within 3 weeks prior to the study
15. Donation of at least 400 ml of blood within 60 days, or more than 150 ml of blood within 30 days, or more than 100 ml blood plasma or platelets within 14 days before the study
16. Participation in another study within 60 days prior to the start of this study
17. Body mass index less than 18.5 kg/m²
18. Hemoglobin Hb less than 13 g/dl

Date of first enrolment
01/07/2022

Date of final enrolment
31/07/2022

Locations

Countries of recruitment
Egypt

Study participating centre
The International Center for Bioavailability, Pharmaceutical, and Clinical Research
Floor No. 2, Plot No.10, Block No. 12018
North Industrial Zone
El Obour City
Cairo
Egypt
00000

Sponsor information

Organisation
Qatar University

Sponsor details
University Street
Doha
Qatar
PO Box 2713
+974 (0)4403 3333
QUMCC@qu.edu.qa

Sponsor type
University/education

Website
http://www.qu.edu.qa/

ROR
https://ror.org/00yhnba62

Organisation
International Center for Bioavailability, Pharmaceutical, and Clinical Research

Sponsor details
Floor No.2, Plot No.10, Block
No. 12018, North Industrial Zone
El Obour City
Cairo
Egypt
00000
+20 (0)2 44891734
info@icbr.info

Sponsor type
Research organisation

Funder(s)

Funder type
University/education

Funder Name
Qatar University

Alternative Name(s)
QU

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Qatar

Results and Publications

Publication and dissemination plan
Publication is planned in a high-impact peer-reviewed journal shortly.

Intention to publish date
30/07/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Dr Ahmed Awaisu (aawaisu@qu.edu.qa):
1 All pharmacokinetic data obtained from plasma by using ultra-performance liquid chromatography (multiple time point rivaroxaban concentration in plasma, area under the concentration-time curve, volume of distribution, half-life, and clearance) will be available upon request.
2. Data obtained from urine samples using ultra-performance liquid chromatography (amount of rivaroxaban recovered in urine, and the average extraction rate) will also be available upon request.
3. All study consent forms are available (anonymous) upon request for all participants.
4. Case record forms for all participants will be available upon request (anonymous).
The raw data will be available from the results publication date, whenever requested. No time restrictions will be applied to the data availability. There are no ethical or legal restrictions on the data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/06/2024	18/10/2024	Yes	No