Can edoxaban and rivaroxaban be prescribed for breastfeeding mothers?

The New Horizons Study

Protocol Short Title/ Acronym: The New Horizons Study

Version 1.4 30/10/2023

Trial Identifiers

IRAS Number:	1005067
Other Trial Identifiers:	Sponsors Identifier: 3631

Sponsor

Name of organisation(s):	King's College Hospital
Sponsor contact:	Amy Holton
Address:	King's Health Partners Clinical Trials Office, Floor 16, Tower Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT
Telephone:	020 71885732
Fax:	n/a
Email:	amy.holton@kcl.ac.uk

Chief Investigator

Name:	Professor Roopen Arya
Address:	Department of Haematological Medicine, KCH
Telephone:	020 3299 3570
Email:	roopen.arya@nhs.net

Research Team:

Name:	Dr Jignesh Patel
Address:	Department of Haematological Medicine, King's College Hospital / Institute of Pharmaceutical Science, King's College London
Telephone:	07984 94 9011
Email:	jig.patel@kcl.ac.uk

Name:	Dr Lewis Couchman
Address:	Analytical Services International Ltd, Cranmer Terrace, London SW17 0RE
Telephone:	020 8725 2338
Email:	lewis.couchman@bioanalytics.co.uk

Name:	Dr Hua Xu
Address:	Analytical Services International Ltd, Cranmer Terrace, London SW17 0RE
Telephone:	020 8725 2338
Email:	hua.xu@bioanalytics.co.uk

Trial Protocol Version History Summary

Protocol Version Number	Issue Date	Summary of Significant Changes
1.2	26/07/2022	Initial submission
1.3	19/09/2022	Changes following feedback from REC and MHRA
1.4	30/10/2023	Extension of eligibility criteria for recruitment and reflection of this change in primary and secondary endpoints

1. Study Synopsis

Title of clinical trial	Can edoxaban and rivaroxaban be prescribed for breastfeeding mothers?
Protocol Short Title/Acronym	The New Horizon's Study
Trial Phase if not mentioned in title	IV
Sponsor name	King's College London
Chief Investigator	Prof Roopen Arya
IRAS number	1005067
Purpose of clinical trial	To determine whether it would be safe for breastfeeding mothers to be prescribed edoxaban or rivaroxaban during the postnatal period
Primary objective	To determine if edoxaban and rivaroxaban are excreted into breastmilk to clinical relevant concentrations when volunteer breastfeeding women take the IMP for 3 consecutive days within the 12 week postpartum period.
Secondary objective (s)	To describe the concentration-time profiles of edoxaban and rivaroxaban in the plasma and breastmilk of breastfeeding mothers within the 12 week postpartum period, following daily dosing for 3 consecutive days and therefore to establish the potential exposure of breastfed infants to edoxaban and rivaroxaban. To determine the extent of edoxaban transfer into human breastmilk within the 12 week postpartum period. To determine the extent of rivaroxaban transfer into human breastmilk within the 12 week postpartum period.
Trial design	Open-label, single-centre study of breastfeeding mothers within the 12 weeks post-partum period.
Endpoints	N/A
Sample size	12 (6 in the edoxaban arm, 6 in the rivaroxaban arm)
Summary of eligibility criteria	Women $\geq$18 years of age, within the 12 week postnatal period, who agree to stop breastfeeding their infant during the plasma and breastmilk sampling phase
IMP, dosage and route of administration	Edoxaban 60mg oral film coated tablets Rivaroxaban 20mg oral film coated tablets
Maximum duration of treatment of a participant	3 days
Version and date of protocol amendments	1.4 30th October 2023

2. Glossary of Terms

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

CONTENTS

Title The New Horizons Study

1. Study Synopsis 3

2. Glossary of Terms 4

3. Background & Rationale 7

4. Trial Objectives and Design 8

4.1. Trial Objectives 8

4.2. Primary endpoints 8

4.3. Secondary endpoints 8

4.4. Trial Design 8

4.5. Trial Flowchart 10

5. Trial Medication 13

5.1. Investigational Medicinal Product 13

5.2. Dosing Regimen 13

5.3. IMP Risks 14

5.4. Drug Accountability 14

5.5. Storage of IMP 14

5.6. Participant Compliance 15

5.7. Concomitant Medication 15

6. Selection and Withdrawal of Participants 15

6.1. Inclusion Criteria 15

6.2. Exclusion Criteria 16

6.3. Study Restrictions 17

6.4. Selection of Participants 17

6.5. Consent 17

6.6. Randomisation Procedure / Code Break 17

6.7. Withdrawal of Participants 17

6.8. Expected Duration of Trial 18

7. Trial Procedures 18

7.1. By Visit 18

7.1.1. Screening Visit 18

7.1.2 Day 1 (0hr) 18

7.1.3 Day 1 - 3hr, 12hr and 24hr visits 18

7.1.4 Day 2 19

7.1.5 Day 3 - 0hr, 3hr, 12hr and 24hr visits 19

7.1.6 Day 4 19

7.2. Laboratory Tests 19

8. Assessment of Safety 20

8.1. Specification, Timing and Recording of Safety Parameters 20

8.2. Procedures for Recording and Reporting Adverse Events 20

8.3. Adverse events that do not require reporting 21

8.4. Premature Termination of the Trial 21

9. Statistics 21

9.1. Sample Size 21

9.2. Randomisation 21
9.3. Analysis 21
10. Trial Management Group 22
11. Data Monitoring Committee and Trial Steering Committee 22
12. Direct Access to Source Data and Documents 22
13. Ethics & Regulatory Approvals 22
14. Quality Assurance 22
15. Data Handling 22
16. Data Management 23
17. Publication Policy 23
18. Insurance / Indemnity 23
19. Financial Aspects 23
20. Archiving 23
21. Signatures 23
REFERENCES 25

3. Background & Rationale

VTE in the postpartum period

It is well established that there is an elevated risk of VTE during pregnancy, which continues during post-partum period (Treffers, *et al.* 1983; Ray and Chan, 1999; Simpson, *et al.* 2001; Soomro, *et al.* 2002; Heit, *et al.* 2005; James, *et al.* 2009). The risk of post-partum VTE is as much as 5 times higher than during pregnancy and 2.5 to 84 times greater than in non-pregnant women (Heit, *et al.* 2005; Salonen Ros, *et al.* 2001; Sultan, *et al.* 2012; Tepper, *et al.* 2014), and PE has been and remains a leading direct cause of maternal death in the UK for over 20 years (Centre for Maternal and Child Enquiries, 2011). The duration of the increased VTE risk after childbirth varies based on the type of risk factors and the risk can extend up to the first 3 to 6 weeks post-partum (Sultan, *et al*. 2014).

LMWH is commonly prescribed as thromboprophylaxis during both pregnancy and the post-partum period because it does not cross placenta and is reported to be safe during breastfeeding. Although warfarin use in pregnancy is restricted, it is reported to be safe to use during breastfeeding (Bates, *et al.* 2012).
In the UK, the timing of initiation and duration of post-partum thromboprophylaxis depends on the type of and the number of existing risk factors of postnatal VTE. Anticoagulation treatment for the management of VTE should be initiated immediately once DVT or PE is clinically suspected, until the diagnosis is excluded by objective testing. The maintenance of therapeutic doses of subcutaneous LMWH should be continued until at least 6 weeks postnatally, and the continuing risk of thrombosis should be assessed before discontinuing treatment. In place of LMWH, warfarin can be prescribed following birth in breastfeeding women.
Although direct oral anticoagulants (DOACs) offer many advantages, they have not been tested in breastfeeding women, thus have not been recommended in breastfeeding women who need treatment for post-partum VTE (Royal College of Obstetricians and Gynaecologists, 2015b).

Direct oral anticoagulants
DOACs, including direct anti-Xa inhibitors (rivaroxaban, apixaban and edoxaban) and the thrombin inhibitors (dabigatran), directly inhibit coagulation proteins in the coagulation cascade. Apixaban, rivaroxaban and edoxaban selectively and reversibly bind to factor Xa, competitively inhibiting both free and clot-bound factor Xa and prothrombinase activity, inhibiting thrombin formation. Dabigatran blocks the procoagulant activity by competitively and reversibly binding to the active site of free and fibrin-bound thrombin, preventing the conversion of fibrinogen into fibrin during the coagulation cascade. These four DOACs are currently available in the UK, for the treatment and prevention of VTE.

A number of clinical trials and post-marketing studies have demonstrated that fixed doses of edoxaban and rivaroxaban have improved or similar efficacy and non-inferior safety compared to warfarin or LMWH for prevention and treatment of arterial and venous thrombotic diseases, because of their predictable pharmacokinetic profile (Agnelli, *et al.* 2013; Hokusai-VTE Investigators, *et al.* 2013). The most severe side effect of edoxaban and rivaroxaban is major bleeding.

Previous non-clinical and clinical studies/case reports on DOACs in breastmilk
Previous preclinical animal studies indicate that DOACs are secreted into rat milk. The excretion of dabigatran into milk varies from 0.08 to 0.13% of the dose administered to the lactating rats (European Medicines Agency, 2008). A single oral dose of apixaban administered to lactating rats was extensively secreted into rat milk with a high milk to maternal plasma ratio (Cmax M/P about 8, AUC M/P about 30) (Wang, *et al.* 2011). Similarly, rivaroxaban and edoxaban were excreted into the milk of rats although the maternal plasma ratio has not been published (Xarelto 10 mg - Summary of Product Characteristics (SPC) - (EMC), 2015; Lixiana - Summary of Product Characteristics (SPC) - (EMC), 2015).

There are a few published clinical case reports describing the use of DOACs in postpartum women. A recent case reported that a patient was prescribed rivaroxaban 15 mg twice daily on the fifth day after delivery and demonstrated that a small amount of rivaroxaban passes into human breastmilk (M/P about 0.4), while the safety of rivaroxaban in nursing mothers and their breastfed infants remains to be verified (Wiesen, *et al*. 2016). A recently completed small clinical study indicated that small amount of dabigatran was excreted in breast milk, although the Cmax M/P and AUC M/P varied significantly between the two breastfeeding women involved in this study (0.04 vs. 0.12 for Cmax M/P; 0.02 vs. 0.1 for AUC M/P) (EU Clinical Trials Register, 2017).

The work completed by our group (Zhao *et al*. 2020) was the first clinical trial formally investigating apixaban and rivaroxaban's distribution into human breastmilk. Results obtained from three breastfeeding women who were > 6 months post delivery suggested that a small amount of rivaroxaban (milk to plasma ratio (M/P) = 0.26, estimated relative infant dose (RID) = 1.63%) transfers into breastmilk, in contrast to apixaban, which accumulates in milk to significant concentrations (M/P = 2.61, RID = 12.78%).

4. Trial Objectives and Design

4.1. Trial Objectives

Primary objective

To determine if edoxaban and rivaroxaban are excreted in breastmilk to clinical relevant concentrations when volunteer breastfeeding women are administered IMP for 3 consecutive days within the 12 week postpartum period.

Secondary objectives

To describe the concentration-time profiles of edoxaban and rivaroxaban in the plasma and breastmilk of breastfeeding mothers within the 12-week postpartum period, following daily dosing for 3 consecutive days and therefore to establish the potential exposure of breastfed infants to edoxaban or rivaroxaban.

To estimate the milk:plasma ratio of edoxaban and rivaroxaban when taken within 12 weeks postpartum.

4.2. Primary endpoints

Edoxaban concentrations in plasma and breastmilk will be measured 3, 12, 24 hours after swallowing the first 60mg dose of edoxaban and then a second 60mg dose will be taken by volunteers on day 2. On day three, prior to the third 60mg dose being taken, edoxaban samples will be drawn, and repeated at 3, 12, 24 and 72 hrs post third dose.

Rivaroxaban concentrations in plasma and breastmilk will be measured 3, 12, 24 hours after swallowing the first 20mg dose of rivaroxaban and then a second 20mg dose will be taken by volunteers on day 2. On day three, prior to the third 20mg dose being taken, rivaroxaban samples will be drawn, and repeated at 3, 12, 24, 72 hrs post third dose.

4.3. Secondary endpoints

The following PK parameters for edoxaban and rivaroxaban in milk and plasma will be the endpoints: Area under the concentration-time curve (AUC) from zero to 24 hours ($AUC_{(0\text{-}24h)}$) on day 1 and day 3 for both breastmilk and maternal plasma.

4.4. Trial design

This is an open-label, single-center study designed to determine the excretion of three consecutive oral doses of edoxaban (EDX group) and three consecutive oral doses of rivaroxaban (RVX group) in the breastmilk of breastfeeding mothers within the 12 weeks post-partum period. The subject population for this study will comprise 12 healthy breastfeeding mothers (6 subjects in each group) who agree to stop breastfeeding their infants during the trial sampling period.
The allocation to the study drugs will be that volunteers will be allocated to the IMP on an alternate basis, e.g. first volunteer allocated to the rivaroxaban arm, second volunteer allocated to the edoxaban arm, with this sequence of allocation then repeated as the trial progresses. Both edoxaban and rivaroxaban are once daily medications. The assessment of concentration and PK profile of edoxaban and rivaroxaban in breastmilk will be conducted through home visits, as outlined in table 4-1 and figure 4-1.

As no human data on edoxaban transfer into breastmilk exists, the edoxaban arm of the trial, will have a ‘go – no go’ component. After two volunteers have completed the edoxaban arm, interim analysis will be conducted. If significant transfer of edoxaban into breastmilk is found, then the edoxaban arm will cease. However, if not, then recruitment will continue to trial pre-specified target.

4.5. Trial Flowchart

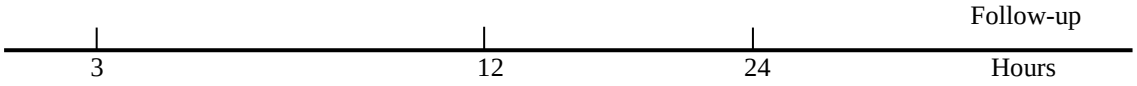
Table 4-1: Trial procedures during the clinical trial – EDX and RVX groups

	Pre-sampling		**Sampling**									**Post-sampling**
	Screening	**Randomisation**	**Visit 1 (day 1)**				**Visit 2 (day 2)**	**Visit 3 (day 3)**				**Final Visit (day 6)**
			0 hr	3 hr	12 hr	24 hr	0 hr	0 hr	3 hr	12 hr	24 hr	
Written informed consent	X											
Patient demographics	X											
Eligibility assessment, including vital signs	X	X										
Past medication, medical and social history	X											
Bloods (UEs, LFTs, FBC, coag screen) – safety bloods	X											X
Pregnancy test	X											
Randomisation (if applicable)		X										
Bloods reviewed and volunteer given all clear to take part. Date arranged with volunteer to do the study sampling		X										
IMP dispense		X										
Vital signs and then IMP administration			X				X	X				
Milk sampling (+/- 30min)				X	X	X		X (pre-dose)	X	X	X	X

Pharmacokinetic blood samples				X	X	X		X (pre-dose)	X	X	X	X
Adverse events			X	X	X	X		X	X	X	X	X
End of trial for patient												X

Figure 4-1. Milk and blood collection time points – EDX and RVX groups

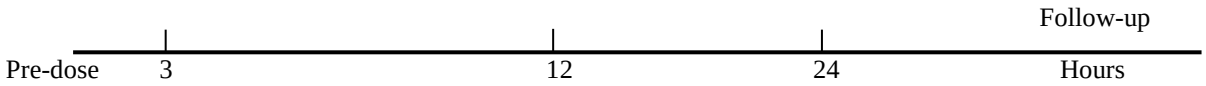
DAY 1



DAY 2

Second dose of EDX / RVX administered.

DAY 3



DAY 6

72 hours post day 3 dose.

5. Trial Medication

5.1. Investigational Medicinal Product

In this trial, subjects will be randomised to either edoxaban or rivaroxaban details of which are described in tables 5-1 and 5-2 below. The trial will use commercially available IMP which will be sourced by Clinical Trials Pharmacy at King's College Hospital. The IMP will be labelled in line with applicable national and local regulations and will be annex 13 compliant.

Table 5-1 Details of edoxaban

Brand name	**Lixiana®**
Product name	**Edoxaban**
Manufacturer	**Daiichi Sankyo**
Dosage Form	**Film-coated tablet**
Dose Mass	**60 mg**
Active ingredient	**Edoxaban**
Mode of administration	**Oral**

Table 5-2 Details of rivaroxaban

Brand name	**Xarelto®**
Product name	**Rivaroxaban**
Manufacturer	**Bayer plc**
Dosage Form	**Film-coated tablet**
Dose Mass	**20 mg**
Active ingredient	**Rivaroxaban**
Mode of administration	**Oral**

5.2. Dosing Regimen

The study drug will be orally administered as tablet (edoxaban or rivaroxaban) formulation once a day on days 1, 2 and 3. The IMP will be administered at subject's home under the guidance of the investigator with the date and time of administration recorded in the subject's CRF.

Table 5-3 Dosing regimen

<table>
<tr><td>Study Arm</td><td>Study Drug Dose</td><td>Subjects</td><td colspan="3">Duration for each subject*
(Day -28 to day 6)</td></tr>
<tr><td>Edoxaban (EDX)</td><td>60 mg (once daily)</td><td>6</td><td rowspan="2">Screening (day -28 to -3)</td><td>Treatment
(day 1 to 3 inclusive)</td><td rowspan="2">Safety review (day 6) & study closure</td></tr>
<tr><td>Rivaroxaban (RVX)</td><td>20 mg (once daily)</td><td>6</td><td>Treatment
(day 1 to 3 inclusive)</td></tr>
</table>

5.3. IMP Risks

As edoxaban and rivaroxaban have been marketed for many years and are widely prescribed, all effects can be reliably predicted in accordance with their Summary of Product Characteristics (SmPC). It is anticipated that the three single doses of edoxaban or rivaroxaban administered should not create emergencies. But in case there is, a member of the research team will be on call 24 hours a day (through mobile number).

Bleeding as a main risk due to healing of a raw area in the uterus (placental site), which could lead to postpartum haemorrhage with serious consequences, will be highlighted to women, before they consent into the trial.

As it has not been demonstrated if edoxaban or rivaroxaban are safe to prescribe during breastfeeding, study volunteers must stop breastfeeding their infants from the first dose until the follow-up period when the study drugs are undetectable in the maternal plasma.

Full details of AEs of edoxaban and rivaroxaban are listed in the respective SmPCs.

The Reference Safety Information (RSI) for all information pertaining to IMP risk for edoxaban and rivaroxaban are set out in the edoxaban and rivaroxaban SmPC.

Based on both the mechanisms described previously, and on clinical experience with edoxaban and rivaroxaban, the known and potential risks to human subjects can be summarised as follows:

It is recognized that the most common and severe side effect of edoxaban and rivaroxaban is bleeding, especially gastrointestinal bleeding, which may be potentially life threatening and require immediate medical attention. To minimize the risk to subjects, individuals with hepatic disease or history of liver problem associated with coagulopathy and clinically relevant bleeding risk, severe kidney disease or dialysis treatment, lesion or condition if considered a significant risk factor for major bleeding (e.g. gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, very high blood pressure or diabetes without medical control, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities) will be excluded from the study.

There have been uncommon or rare reports of hepatobiliary disorders (e.g. hepatic function abnormal and jaundice), and cardiac disorders (e.g. tachycardia) in patients taking edoxaban or rivaroxaban. Potential subjects will be tested for impaired liver functions as part of screening for eligibility.

Uncommon instances of allergic reactions such as pruritus and allergic oedema have been reported in patients treated with edoxaban or rivaroxaban. Individuals with a history of allergies to DOACs or/and with any history or current clinically significant hypersensitivity or allergic reactions (including known or suspected reactions to any components of the test products) will be excluded from the study. Subjects will also be monitored during the study for systemic hypersensitivity reactions.

The sponsor will immediately notify the chief investigator if any additional safety or toxicology information becomes available during the study. Subjects participating in this study will only be exposed to the IMP for up to 6 days, so the risks outlined in real terms, are extremely small.

5.4. Drug Accountability

Full drug accountability will be maintained.

The pharmacy clinical trials team will maintain full accountability records of the IMP. The pharmacy accountability logs will capture details of the subject to whom the investigational medicinal product was dispensed/prepared, the date, batch number, expiry date and quantity of the investigational product received, dispensed and unused.

5.5. Storage of IMP

IMP will be stored in the clinical trials pharmacy at King's College Hospital, according to the SmPC requirements. Both edoxaban and rivaroxaban do not require any special storage conditions and thus will not require temperature monitoring. The IMP will be stored under local hospital policy.

5.6. Participant Compliance

Subject's compliance with medication will be monitored by direct and real-time observation by the research team. The date and time of administration will be recorded.

5.7. Concomitant Medication

For management of concomitant therapies, please refer to the edoxaban and rivaroxaban Summary of Product Characteristics. A complete listing of all concomitant medication received during the treatment phase must be recorded in the relevant CRF.

Use of the following agents (prescription or non-prescription) presented in Table 5-4 and 5-5 is prohibited from the time points specified until completion of all study activities. More details are in the SmPC of edoxaban and rivaroxaban.

In the interests of subject safety and acceptable standards of medical care the Investigator will be permitted to prescribe treatment(s) at his/her discretion. All treatments must be recorded in the subjects' CRF (medication, dose, treatment duration and indication).

Table 5-4 Restricted Medications in EDX group of the Study

72 Hours Prior to Admission	24 Hours Prior to Admission
Prescription medications including anticoagulants and antiplatelet aggregation medicinal products; Significant CYP3A4 inhibitors and inducers; Significant P-gp inhibitors and inducers.	Nutraceuticals (e.g., St. John's Wort, ginseng, kava kava, Ginkgo biloba and melatonin)
Non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, diclofenac, naproxen, indomethacin).	Foods or beverages containing Seville-type (sour) oranges, or poppy seeds

Table 5-5 Restricted Medications in RVX group of the Study

72 Hours Prior to Admission	24 Hours Prior to Admission
Prescription medications including anticoagulants and antiplatelet aggregation medicinal products; Significant P-gp inhibitors and inducers; Significant CYP3A4 inhibitors and inducers.	Nutraceuticals (e.g., St. John's Wort, ginseng, kava kava, Ginkgo biloba and melatonin)
Non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, diclofenac, naproxen, indomethacin).	Foods or beverages containing grapefruit, seville-type (sour) oranges, or poppy seeds

6. Selection and Withdrawal of Participants

6.1. Inclusion Criteria

To be eligible to participate in this study all the following criteria must be met:

1. Subject is informed and given ample time and opportunity to think about her participation and has provided written informed consent for participation in the study before any study specific procedures take place.

2. Subject is considered reliable and capable of adhering to applicable protocol requirements, including the study drug being administered orally and visit schedule according to the judgement of the Investigator.

3. Women are aged ≥18 years.

4. Within the 12 weeks postpartum period.

5. Decision has been confirmed by the volunteer to hold breastfeeding their infant during the study period.

6. Negative pregnancy test.

7. Good physical and mental health, in the opinion of the investigator, determined on the basis of medical history and general clinical examination at screening.

8. Women have clinical laboratory test results within the reference ranges of the testing laboratory: normal renal and liver function, as judged by the chief investigator.

9. Women are not taking any medication interacting with edoxaban or rivaroxaban, as listed in table 5-4 and 5-5.

10. Women are available and permit the research team to make home visits to collect blood and milk samples.

11. Women agree to the study restrictions, as outlined in section 6.3.

6.2. Exclusion Criteria

Subjects are not permitted to enrol in the study if any of the following apply:

1. Low Molecular Weight Heparin (LMWH) thromboprophylaxis is indicated.
2. Increased risk of bleeding for any reason.
3. Known contra-indications to edoxaban or rivaroxaban.
4. On-going treatment with aspirin, NSAIDs (ibuprofen, diclofenac, naproxen, indomethacin) or other drugs that affect haemostasis.
5. Treatment with significant P-GP / CYP3A4 inducers or inhibitors.
6. Patients who have received an artificial heart valve, have had a heart attack or suffer an irregular heartbeat.
7. Known impaired renal function.
8. Known abnormal liver function tests.
9. Known hypersensitivity or allergy to edoxaban or rivaroxaban.
10. Use of other investigational study drugs within 7 days prior to study entry.
11. Women who are pregnant or of childbearing potential who refuse to use an acceptable effective form of contraception throughout the study. Acceptable forms of contraception include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, sexual abstinence.
12. Women who will not participate in study visits within a suitable distance from King's College Hospital NHS Foundation Trust, as judged by the research team.

6.3. Study Restrictions

Subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study:

Refrain from intake of grapefruit juice from 48 hours prior to dosing and until 24 hours post last dose of IMP;

Refrain from taking drugs of abuse during the study;

Refrain from taking medications during the study as outlined in Section 5.7;

Refrain from breastfeeding their infant during the study.

6.4. Selection of Participants

Participants will be recruited from an advertisement on www.mums.net, local mum's forums, and the outpatient clinic letters at the Hematology department of King's College Hospital NHS Foundation Trust. Volunteer women will be given £300 as a thank you for their time and participation. Should subjects fail at the screening they will receive reimbursement for their travel (up to £10). Subjects who voluntarily withdraw or are withdrawn from the trial on clinical grounds (CI decision), will receive 'part-payment' for their participation to the point of their involvement. This part-payment will be calculated on the basis of the number of pairs of breastmilk and plasma samples contributed by the volunteer. Each pair of samples contributed by volunteers will be paid £37.50p.

6.5. Consent

Volunteers will initially contact Dr Patel to express interest in taking part. A phone call will be arranged, where the trial PIL will be explained to the potential subject and any preliminary questions answered. The volunteer will then be encouraged to discuss with family / friends. Following a minimum of 24 hours, if the volunteer would like to proceed to screening, then a screening visit will be arranged, where the study information will be repeated and questions answered and bloods drawn. If patient is deemed suitable to take part following review of bloods, written informed consent will be obtained, following all the principles of Good Clinical Practice (GCP), and the Declaration of Helsinki.

6.6. Randomisation Procedure / Code Break

N/A – open label trial – volunteers and the research team are aware of which IMP a volunteer has been allocated to.

6.7. Withdrawal of Participants

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw participants from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a participant withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the participant.

A subject may be withdrawn in any of the following circumstances:

AE.

Protocol violation.

Withdrawal of consent.

Study drug administration may also be stopped for a subject due to a decision by the Investigator, see Section 9.4for further details.

The Investigator should as far as possible have the subject complete the scheduled discharge assessments and also have the subject attend a follow-up visit after 1 day (±1 day) following completion of the study. This could be modified where justified at the Investigator's discretion.

Investigators should attempt to obtain relevant information on subjects in the case of a subject withdrawal. For subjects considered as lost-to-follow-up, the Investigator should make an effort (at least one phone call and one written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal or discontinuation.

Subjects who voluntarily withdraw are termed dropouts. Dropouts may be replaced following discussion with the Investigator and Sponsor. Subjects withdrawn due to an AE will not be replaced.

6.8. Expected Duration of Trial

The beginning of the trial will be defined as first patient first visit and the end of trial will be defined as database lock.

Active participation in the trial for each volunteer is for 6 days and each individual participant will remain on trial until the morning of day 6 - final visit.

7. Trial Procedures

7.1. By Visit

Each participant will have pre-entry screening. For practical reasons, this may be conducted at the subject's home. Each home visit for the purposes of the trial will be conducted by a researcher and a chaperone. Following informed consent for the study has been obtained, the research team will check her medical history and physical health (including vital signs), as well as ask volunteers to have screening bloods. The procedures during each visit are detailed in Table 4-1.

7.1.1 Screening Visit

The following study evaluations will be performed/recorded during the course of the screening period (28 days):

- Signed informed consent
- Inclusion and exclusion criteria
- Record past medical and social history
- Record of concomitant medication usage, including contraindicated/restricted medication
- Participant demographics
- Pregnancy test
- Blood sampling (safety bloods)
- Vital signs

7.1.2 Day 1 (0hr)

- Record of concomitant medication usage, including contraindicated/restricted medication
- Vital signs
- IMP administration

7.1.3 Day 1 - 3hr, 12hr and 24hr visits

- Milk and blood sampling at 3hr, 12hr and 24hr
- Update of adverse events

7.1.4 Day 2

- Vital signs
- IMP administration
- Record any adverse events

7.1.5 Day 3 - 0hr, 3hr, 12hr and 24hr visits

- Vital signs
- IMP administration (0hr)
- Milk and blood sampling at 3hr, 12hr and 24hr
- Record any adverse events

7.1.6 Day 6 (study for participant ceases on morning of day 6)

- Record any adverse events
- 72 hr milk and blood sample
- Safety bloods

7.2. Laboratory Tests

According to the milk and blood collection time points and safety assessment schedule, the blood and milk volumes to be collected from any single subject are presented in Table 7-1.

Blood samples will be packed and transferred to King's College Hospital immediately after collection. Clinical samples (UEs/LFTs/FBC) will be handled by the Viapath, King's College Hospital. Pharmacokinetic blood samples will be cooled and centrifuged as soon as possible in the CI's laboratory at King's College Hospital. The separated plasma samples will be transferred to a clean tube and stored at -20°C.

Milk samples will be stored at -20°C in the CI's laboratory at King's College Hospital. Separated plasma samples and milk samples will then be transferred to ASI Bioanalytics (London, UK) within 56 days for the analysis. Detailed sample collection, handling, labelling, storage and shipment will be described in the Laboratory Manual at King's College Hospital and ASI Bioanalytics.

Table 7-1 Blood and Milk Volumes to be Collected in a single subject in EDX/RVX group over the course of the volunteers involvement in the trial

Assessment	Sample Volume (mL)	No. of Samples	Total Volume (mL)
Safety			
Clinical Chemistry	5.0	2	10.0
Haematology (PT, APTT)	3.7	2	7.4
FBC	2.0	2	4.0
Pregnancy test	3.5	1	3.5
Pharmacokinetic			
Plasma Samples	2.0	8	16.0
Milk Samples	10.0	8	80.0
Total (mL)			Blood: 41.0 Milk: 80.0

FSH: Serum Follicle-stimulating Hormone
Sample volumes are based on direct venepuncture.
Milk sample to be collected at any breast (10ml) by manual expression or breast pump.

Additional samples may be collected as required at the Investigator's discretion. However, the total volume of blood collected per subject during the study will not exceed 100 ml. Individual venepunctures for each time point will be performed. The exact date/time of the milk and blood sample collection will be recorded in the subject's CRF.
Time windows for the collection of the PK blood and milk samples are as follows:
±30 minutes for all sampling time points (with the exception of the pre-dose sample).

8. Assessment of Safety

8.1. Specification, Timing and Recording of Safety Parameters

The safety assessments will be relative to those risks identified in section 5.3.
Sample collection times are included in the schedule of visits and assessments.
AEs and SAEs will be reported from first dose until 24 hours following the final (third consecutive) dose.

8.2. Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- **Adverse Event (AE)**: Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
- **Adverse Reaction (AR):** Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- **Unexpected Adverse Reaction (UAR)**: An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

  The summary of product characteristics (SmPC) for that edoxaban and rivaroxaban.
- **Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that**:**
  - results in death;
  - is life-threatening;
  - required hospitalisation or prolongation of existing hospitalisation;
  - results in persistent or significant disability or incapacity;
  - consists of a congenital anomaly or birth defect.
- **Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

Reporting Responsibilities

King's College Hospital has delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator (and certainly no later than 24hrs) to the KHP-CTO in accordance with the current Pharmacovigilance Policy.

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days;
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the sponsor), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

8.3. Adverse events that do not require reporting

Adverse events or reactions that are consistent in nature and severity with those listed in Section 4.8 of the relevant SmPC for edoxaban and rivaroxaban do not need to be reported.

8.4. Premature Termination of the Trial

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Trial Steering Committee regulatory authority or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed, and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

For the edoxaban arm, following the recruitment and sampling of 2 patients, interim analysis will be completed. If significant transfer of edoxaban into human breastmilk is found, this arm of the study will cease (go : no-go criteria).

9. Statistics

Descriptive statistics will be used to analyse the data and describe the study population.
Classical non-compartmental pharmacokinetic analysis will be conducted on the breastmilk and plasma samples. AUC (0-24 hours (day 1 and day 3) and milk to plasma ratio will be computed for each volunteer and then for the cohort as a whole.

9.1. Sample Size

12 subjects in total; 6 in the rivaroxaban arm and 6 in the edoxaban arm.

For the edoxaban arm, following the recruitment and sampling of 2 patients, interim analysis will be completed. If significant transfer of edoxaban into human breastmilk is found, this arm of the study will cease (go : no-go criteria).

9.2. Randomisation

This is an open label study.

9.3. Analysis

In addition to AUC computations, for each volunteer, the milk:plasma ratio will be calculated, along with an estimated infant dose. Mean values across the 6 volunteers in each group will finally be computed. The same will apply for the estimates for milk:plasma ratio.

Interim analysis in the edoxaban arm of the trial will be conducted following 2 volunteers completing sampling. If significant transfer of edoxaban is found, then this arm of the trial will cease. The decision to continue or cease the edoxaban arm of the trial will be taken by the trial steering committee, following a review of the data.

10. Trial Management Group

The trial management group will comprise of a thrombosis expert and study CI, a pharmacokinetic expert and an analytical expert who will review data generated from the study, to ensure no patient harm is resulting from the use of edoxaban and rivaroxaban in this study. The TMG will be responsible for the trial's day-to-day running and management. Chaired by the CI, the TMG will oversee the development and operation of the study, maintain recruitment rates and will be responsible for the day to day management of the trial activities and will meet on a regular basis to discuss any trial related activities or issues.

11. Data Monitoring Committee and Trial Steering Committee

This is a small pharmacokinetic study with a short duration and short follow-up. Safety and pharmacovigilance are important components of the study but costs of running these committees have to offset against the benefit in such a small trial, and also the minimal expected risk from previous published data where edoxaban and rivaroxaban has been used in healthy participants and patients. Therefore, there will be no data monitoring or trial steering committees for this study.

12. Direct Access to Source Data and Documents

The Investigator will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor, Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, breast milk assay reports etc.).

13. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to Health Research Authority (HRA), Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor) and the REC within the timelines defined in the Regulations. The KHP-CTO or delegate will upload the final report to a publicly registered database on behalf of the Sponsor.

14. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

15. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Participant data will be pseudo-anonymised.
- All pseudo-anonymised data will be stored on a password protected computer.

- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006, The General Data protection regulation (GDPR) and the Data Protection Act 2018 and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving Standard Operating Procedure (SOP).

16. Data Management

A paper case report form (CRF) will be used by the research team as source data for each subject, which is compliant with Medicines for Human Use (Clinical Trials) Regulations 2006. The majority of study data collected will be directly entered onto the paper CRF, and then transcribed onto the electronic Case Report Form (eCRF) produced within REDCap™ (Electronic Data Capture System) by the research team. Data will be available for Sponsor review via predefined reports extracted from the database at agreed intervals. The CRFs and eCRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

All source documents will be retained by the study centre. Photocopies of completed source documents will be provided only if essential (i.e., for regulatory purposes) at the request of the Sponsor.

Safety laboratory data are managed and stored within the KCH system and only the date and time of sampling are recorded on the paper CRF and eCRF.
The original informed consent form will be kept in the ISF with a with a copy filed in the patients notes and a copy given to the patient. Completed source documents will be filed in the appropriate source folder, or a note to indicate where the records can be located. All records will be kept in conformance to applicable national laws and regulations.

All CRF and eCRF entries, corrections and alterations must be made by the Investigator or other authorised study centre staffs. At the end of the study, essential documentation will be archived in accordance with sponsor and local requirements. The retention of study data will be the responsibility of the Chief Investigator.

17. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

18. Insurance / Indemnity

The sponsors - King's College Hospital NHS Foundation Trusts, declares to having insurance cover for the malpractice and/or negligence of their employees and agents. King's College Hospital NHS Foundation Trust indemnity insurance applies.

19. Financial Aspects

Funding to conduct the trial is provided by Professor Roopen Arya's (CI) research funding.

20. Archiving

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Sponsor Archiving Standard Operating Procedure (SOP).

21. Signatures

7th December 2023

Chief Investigator

Professor Roopen Arya

Date

REFERENCES

Agnelli, G., *et al.* (2013). Oral Apixaban for the Treatment of Acute Venous Thromboembolism. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. *The New England Journal of Medicine*, 369, 799-808.

Bates, S. M. (2012). VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest,* 141 (2 Suppl), e691S-736S.

Borght SV, Libbrecht L, Katoonizadeh A, Pelt J van, Cassiman D, Nevens F, *et al.* (2006). Breast Cancer Resistance Protein (BCRP/ABCG2) Is Expressed by Progenitor Cells/Reactive Ductules and Hepatocytes and Its Expression Pattern Is Influenced by Disease Etiology and Species Type: Possible Functional Consequences. *Journal of Histochemistry & Cytochemistry*, 54(9), 1051–1059.

Centre for Maternal and Child Enquiries (CMACE). (2011). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *British Journal of Obstetrics and Gynaecology,* 118 (Suppl. 1):1–203.

European Medicines Agency. (2008). CHMP ASSESSMENT REPORT FOR Pradaxa. [PDF] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000829/WC500041062.pdf/. [Accessed 19 July 2016]

EU Clinical Trials Register. (2017) Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004249-29/results. [Accessed 16 January 2018]

Frost C, Nepal S, Wang J, Schuster A, Barrett YC, Mosqueda-Garcia R, et al. (2013). Apixaban, an oral, direct factor Xa inhibitor: single-dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. *British Journal of Clinical Pharmacology*, 75(2):476-487.

Hale, T. W. (2004). Drug therapy and breastfeeding: pharmacokinetics, risk factors, and effects on milk production. Neoreviews, 5, pp. e164.

Heit, J. A. (2005). Trends in the incidence of venous thromboembolism during pregnancy or post-partum: a 30-year population-based study. *Annals of Internal Medicine,* 143(10), 697-706.

Hokusai-VTE Investigators, *et al.* (2013). Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *The New England Journal of Medicine,* 369 (15), 1406-15.

James, A. H. (2009). Venous Thromboembolism: Mechanisms, Treatment, and Public Awareness. Venous Thromboembolism in Pregnancy. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 29, 326-331.

Kearon, C., *et al.*, 2016. for The subcommittees on Control of Anticoagulation and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked VTE: guidance from the SSC of ISTH. *Journal of Thrombosis and Haemostasis,* 14, 1–4.

Kubitza, D., *et al.* (2005a). Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clinical Pharmacology & Therapeutics*, 78, 412–421.

Kubitza, D., *et al.* (2005b). Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939–an oral, direct Factor Xa inhibitor–after multiple dosing in healthy male subjects. *European Journal of Clinical Pharmacology*, 61, 873–80.

Lixiana Film-Coated Tablets - Summary of Product Characteristics (SPC) - (Emc). (2021). [ONLINE] Available at: https://www.medicines.org.uk/emc/medicine/30513 [Accessed 17 March 2021].

Wiesen MHJ, Blaich B, Müller C, Streichert T, Pfister R, Michels G. (2016). The Direct Factor Xa Inhibitor Rivaroxaban Passes Into Human Breast Milk. *Chest*, 150(1), e1-e4.

Meyer Zu Schwabedissen, H. E. & Kroemer, H. K., (2011). In vitro and in vivo evidence for the importance of breast cancer resistance protein transporters (BCRP/MXR/ABCP/ABCG2). *Handb Exp Pharmacol.* 201,325–371.

National Institute for Health and Care Excellence (2010). Venous thromboembolism: reducing the risk for patients in hospital. [ONLINE] Available at: https://www.nice.org.uk/guidance/cg92/. [Accessed 17 March 2016].

Patel, J. P., *et al.* (2012) Women's views on and adherence to low-molecular-weight heparin therapy during pregnancy and the puerperium. *Journal of Thrombosis and Haemostasis.* 10 (12), 2526-34.

Raskob, G. E., *et al.*, 2014. Thrombosis: a major contributor to global disease burden. Arteriosclerosis, *Thrombosis, and Vascular Biology,* 34 (11), 2363-71.

Ray, J. G. & Chan, W. S. (1999). Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. *Obstetrical & Gynecological Survey,* 54 (4), 265-71.

Royal College of Obstetricians and Gynaecologists. (2015). Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk (Green-top Guideline No. 37a). [ONLINE] Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37a/[Accessed 17 March 2016].

Royal College of Obstetricians and Gynaecologists. (2015). Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management (Green-top Guideline No. 37b). [ONLINE] Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37b/[Accessed 17 March 2016].

Salonen Ros, H. (2001). Increased risks of circulatory diseases in late pregnancy and puerperium. *Epidemiology,* 12 (4), 456-60.

Simpson, E. L. (2001). Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. *International Journal of Gynecology & Obstetrics*, 108 (1), 56-60.

Soomro, R. M., Bucur, I. J. & Noorani, S. (2002). Cumulative incidence of venous thromboembolism during pregnancy and puerperium: a hospital-based study. *Angiology,* 53(4), 429-34.

Sultan, A. A. (2012). Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. *British Journal of Haematology*, 156(3), 366-73.

Tepper, N. K. (2014). Post-partum venous thromboembolism: incidence and risk factors. *Obstetrics & Gynecology*, 123 (5), 987-96.

Treffers, P. E., *et al.* (1983). Epidemiological observations of thrombo-embolic disease during pregnancy and in the puerperium, in 56,022 women. *International Journal of Gynecology & Obstetrics*, 21 (4), 327-331.t

U.S. Department of Health and Human Services Food and Drug Administration. (2005). Guidance for Industry Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for

Labeling. [ONLINE] Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf). [Accessed 17 March 2016].

Vasios, G., *et al.* (2016). Simple physicochemical properties related with lipophilicity, polarity, molecular size and ionization status exert significant impact on the transfer of drugs and chemicals into human breast milk. *Expert Opinion on Drug Metabolism & Toxicology,* 12 (11): 1273-1278.

Wang, L., *et al.* (2011). Tissue distribution and elimination of [14C] apixaban in rats. *Drug Metabolism and Disposition,* 39, 256-64.

Weinz, C., *et al.* (2009). Schwarz T, Kubitza D, Mueck W, Lang D. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metabolism and Disposition*, 37, 1056-64.

Wells, P. S., Forgie, M. A. & Rodger, M. A. (2014). Treatment of venous thromboembolism. *Journal of the American Medical Association*, 311, 717–28.

Xarelto film-coated tablets - Summary of Product Characteristics (SPC) - (Emc). (2021). [ONLINE] Available at: https://www.medicines.org.uk/emc/medicine/21265 [Accessed 17 March 2021].

Zhao, Y., Arya, R., Couchman, L., Patel, J.P. Does apixaban and rivaroxaban distribute into human breastmilk to clinically relevant concentrations? *Blood* 2020; 136 (15): 1783–1785