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Name of Sponsor/Company: Universitätsklinikum Heidelberg		**Sponsor-Code of Study:** K675	*(For National Authority Use only)*
Name of (Finished) Product:		**Name of Active Ingredient:**	
EudraCT-No.: 2019-001759-38	**CA Vorlage-No.:** 4043721	**IEC Antrags-No.:** AFmo-606/2019	

☒ **End of Trial Report** ☐ **Annual Safety Report**

SYNOPSIS

Title of Study:
Pharmacokinetics of a microdosed cocktail containing rivaroxaban, apixaban and edoxaban in children with congenital heart defects

Date of Approval / Vote:
BfArM: 04.12.2019 **Ethics Committee:** 08.10.2019

Amendments: None

Date of Approval / Vote:
BfArM: N/A **Ethics Committee:** N/A

Investigators:
Principal Investigator:
Prof. Dr. med. Matthias Gorenflo

Deputy Investigators:
Dr.med. Victoria Ziesenitz
Dr.med. Kristine Chobanyan-Jürgens

Study Centre(s):
Single-centre:
Heidelberg University Hospital
Centre for Child and Adolescent Medicine – Department of Paediatric and Congenital Cardiology
Im Neuenheimer Feld 430
69120 Heidelberg

Publication (reference):

Study period: **(date of first enrolment)** **(date of last completed)**	02.03.2020 22.06.2022	**Phase of development:**	Phase I (exploratory study)

Objectives:

Primary objective
To assess the pharmacokinetics of rivaroxaban, apixaban and edoxaban, when co-administered as a microdose cocktail (apixaban 25 µg, rivaroxaban 25 µg, edoxaban 50 µg) in children with congenital heart defect, aged 2-6 years.

Secondary objectives
To compare the pharmacokinetics in children with adults (healthy and patients from literature).
To characterise CYP3A activity by means of a midazolam microdose in children.
To characterise CYP2D6 activity by means of a yohimbine microdose in children.

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To evaluate tolerability and safety of this microdose cocktail in children.

Methodology:

Design: Phase I exploratory study.

The study procedure starts about 72 hours after end of surgery with the administration of the study drugs. All investigational medicinal products will be administered by feeding tube if available and necessary. Blood sampling will be obtained over a total duration of 25 hours after drug administration. This includes PK data and coagulation parameters that will be checked prior to study drug administration as well as 2 and 25 hours afterwards. The study participation ends with the first laboratory results and physical examination being performed daily within in the clinical routine after the 25 hour blood sampling.

Edoxaban, apixaban, rivaroxaban, midazolam, and yohimbine and metabolites of interest will be quantified by ultra-performance liquid chromatography – tandem mass spectrometry methods which are validated according to FDA standards.

Number of Volunteers (planned and analysed):

Planned: n = 20

Analysed: n = 14

Diagnosis and main criteria for inclusion:

- Age 2 – 6 years.
- Body weight ≥ 10 kg.
- Admitted as inpatient to the paediatric cardiac ward after congenital cardiac surgery
- Cardiac defects: non-cyanotic congenital heart defects such as atrial septal defect, ventricular septal defect, etc.
- Availability of a central vascular access.
- Otherwise healthy children as determined by medical assessment consisting of a medical history, physical examination, an ECG, and a laboratory evaluation, all performed within the clinical routine, that all show no clinically relevant abnormalities.
- Minor deviations of laboratory values from the normal range may be acceptable in the pre-operative assessment, if judged by the investigator to be of no clinical relevance for this trial. Criteria include, but are not limited to
    - ALT ≤ ULN x 1.1
    - AST ≤ ULN x 1.2
    - Bilirubin ≤ ULN x 1.2 (this will not apply to patients with Gilbert's syndrome)
    - Creatinine ≤ ULN + 0.1 mg/dl
    - Haemoglobin > 10 g/dl (pre- and postoperatively).

- Both parents (or legal representatives) have to be able to communicate well with the investigator, to understand and comply with the requirements of the trial.
- Voluntarily signed informed consent after full explanation of the trial to both parents (or legal representatives) of the participant. The informed consent will be obtained after the surgery but before any specific study procedures will be carried out.

Test product (IMP being tested), trade name, MA holder, MA number, dose and mode of administration, batch number(s):

All drugs were administered in single dose per patient as an oral solution. The microdose cocktail contained Xarelto® (Rivaroxaban) 25 µg, Eliquis® (Apixaban) 25 µg and Lixiana® (Edoxaban) 50 µg which resulted in a total amount of 100 µg. Midazolam and Yohimbine were given simultaneously in a dose of 10 µg and 25 µg. The investigational drugs were supplied by the Pharmacy of Heidelberg University Hospital.

For Rivaroxaban, Apixaban and Edoxaban the Pharmacy of Heidelberg University Hospital initially prepared stock solutions. Then, the respective amounts of the solutions were combined in a plastic cup and diluted in non-sparkling water up to 100 ml total volume for administration to the patients.

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IMP 1: Edoxaban
Trade name: Lixiana®
Manufacturer: Pharmacy of Heidelberg University Hospital
MA holder: Daiichi Sankyo Europe GmbH, Zielstattstrase 48, 81379 München, Germany
MA number: EU/1/15/993/001
Dose and mode of administration: 50 µg, oral use
Batch numbers: K675EDOX/202204 (stock solution)
K675EDOX/201939 (concentrate)
K675EDOX/202008 (concentrate)
K675EDOX/202033 (concentrate)
K675EDOX/202112 (concentrate)

IMP 2: Apixaban
Trade name: Eliquis®
Manufacturer: Pharmacy of Heidelberg University Hospital
MA holder: Bristol-Myers Squibb/Pfizer EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irland
MA number: EU/1/11/691/002
Dose and mode of administration: 25 µg, oral
Batch numbers: K675APIX/202204 (stock solution)
K675APIX/201939 (concentrate)
K675APIX/202008 (concentrate)
K675APIX/202033 (concentrate)
K675APIX/202112 (concentrate)

IMP 3: Rivaroxaban
Trade name: Xarelto®
Manufacturer: Pharmacy of Heidelberg University Hospital
MA holder: Bayer AG, 51368 Leverkusen, Germany
MA number: EU/1/08/472/041
Dose and mode of administration: 25 µg, oral
Batch numbers: K675RIVA/202204 (stock solution)
K675RIVA/201939 (concentrate)
K675RIVA/202008 (concentrate)
K675RIVA/202027 (concentrate)
K675RIVA/202048 (concentrate)
K675RIVA/202116 (concentrate)

IMP 4: Midazolam
Trade name: Dormicum V® 5 mg/5 ml Lösung
MA holder: Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen
MA number: 41118.00.00
Dose and mode of administration: 10 µg, oral
Batch numbers: F0002F02
F003F02
F1128F02

IMP 5: Yohimbinum hydrochloricum D 4
Trade name: Yohimbinum hydrochloricum D 4®
MA holder: Deutsche Homöopathie-Union-Arzneimittel GmbH & Co. KG, 76202 Karlsruhe, Germany
MA number: 2503755.00.00

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Dose and mode of administration: 25 µg, oral
Batch number: 0160419

Duration of treatment:
The trial duration will be approximately 48 hours (including Screening Visit and End of Trial Visit) for each participant.

Criteria for evaluation: (efficacy, safety)
As this is a microdosing study there is no expected therapeutic effect of the administered test products.
The general safety laboratory consists of: Red blood cell count, haematocrit, haemoglobin, white blood cell count, mean corpuscular volume, mean corpuscular haemoglobin, red cell distribution width, platelets, hypochromic erythrocytes, electrolytes (sodium, potassium, calcium, chloride, magnesium), creatinine, urea, blood glucose, CK, Creatine kinase myocardial bound (CK-MB), TNT, LDH, AST, ALT, γ-GT, phosphate, total protein, albumin, C-reactive protein (CRP), quick, INR, aPTT, AT3, D-dimer, thrombin time, fibrinogen, and PCT.

Statistical methods:
This is an explorative study. There are no data available which could be used for analytic considerations and comparison. Standard PK parameters ($AUC_{0-\infty,}$ Cl, Cl/F, C_{max}, $t_{1/2}$, T_{max}, V_{ss}, and V_{ss}/F) of the FXaI, MDZ, and yohimbine will be evaluated by non-compartmental analyses and its results will be presented by descriptive statistics.
Seriousness, severity, relationship, and frequency of AEs during the treatment period will be tabulated and summarized.

Summary – Conclusions:

Efficacy Results:
The application of the FXaI microdose cocktail together with highly sensitive UHPLC MS/MS analytical methods appears to be a safe and effective methodology to establish the PK of narrow therapeutic index drugs such as DOACs in young pediatric populations without approved pediatric indication The plasma concentration time profiles of all DOACs examined could be quantified over 24 hours, and were well comparable between subjects for each of the DOACs examined

Safety Results:
There were no adverse events during the period of observation

Conclusion:
This small heterogenic cohort delivers first preliminary information on the PK of DOACs in young children up to 6 years of age. The study was terminated prematurely at the end of 2022 due to insufficient patient recruitment, which was significantly impacted by the COVID-19 pandemic.

Date of report:
03.09.2026