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Application of *in vitro* studies to predict the pharmacokinetics of rivaroxaban tablets

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Abstract

Introduction. The most important stage of pharmaceutical development of a generic drug is a clinical trial involving humans – a bioequivalence study. Considering the importance of finding rivaroxaban drugs in the list of vital and essential drugs, as part of ensuring technological sovereignty, the use of scientific robust and effective methods for determining the quality of its dosage form is required.

Aim. Conduct a study of rivaroxaban tablets on a physiologically relevant tester to predict pharmacokinetic profiles.

Materials and methods. The objects of the study are "Xarelto®, film-coated tablets, 10 mg" (series BXJS871, with an expiration date of October 31, 2024, Bayer AG, Germany), "Xarelto®, film-coated tablets, 20 mg" (series BXKDF32, with an expiration date of May 17, 2026, Bayer AG, Germany) and "Rivaroxaban, film-coated tablets, 10 mg" and "Rivaroxaban, film-coated tablets, 20 mg", domestically produced, with valid expiration dates. During the study, reagents were used to prepare dissolution media and perform quantitative determination. The physiologically relevant test was performed on the SC PRT-6 device (LLC "Scientific Compliance", Russia). The quantitative content of released rivaroxaban within the comparative dissolution kinetics test in a medium of 0.1 in a medium of 0.1 % sodium lauryl sulfate solution in a phosphate buffer solution pH 6.5 was carried out on a SF-2000 spectrophotometer (LLC "OKB Spektr", Russia). The quantitative content of released rivaroxaban within the comparative dissolution kinetics test in biorelevant dissolution media and physiological relevance test was assessed on a high-performance liquid chromatograph "Chromatec-Crystal HPLC 2014" (JSC "Chromatec", Russia). Pharmacokinetic profiles were modeled in the PK-Sim® (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Germany) program based on the data obtained within the physiologically relevant test. The clinical study of rivaroxaban tablets was a prospective, open-label, randomized, crossover, two-stage comparative study in two groups of volunteers with a single dose of drugs on the fast condition. The study randomized 30 healthy male volunteers aged 18–45 years.

Results and discussion. A complex of *in vitro* tests was conducted, profiles were obtained that allow us to evaluate the dynamics and degree of release of the studied drugs in various parts of the human gastrointestinal tract. A comparison of the sequential and hybrid schemes for conducting the physiological relevance test was carried out. Within the framework of the set of tests,

qualitative and quantitative correlation with the clinical trials data was observed only for the hybrid physiological relevance test scheme. Based on the results of physiological relevance test using different schemes, pharmacokinetic profiles for a pair of drugs were predicted and the prediction error was assessed.

Conclusion. A set of scientific *in vitro* tests was conducted for the drugs "Xarelto®, film-coated tablets, 10 mg and 20 mg", "Rivaroxaban, film-coated tablets, 10 mg and 20 mg". Based on the physiological relevance test results, pharmacokinetic profiles for a pair of drugs were predicted with low error and high reliability. As part of the comparison of data obtained during clinical trial and modeling, the smallest prediction error was noted when performing physiological relevance test using a hybrid scheme.

Keywords: rivaroxaban, FaSSIF, FaSSGF, BCS

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Andrey M. Poluyanov, Eugenia A. Malashenko, Alla Yu. Savchenko and Igor E. Shohin conceived and developed the experiment. Alexandra V. Suvorova and Polina A. Losenkova performed comparative dissolution kinetics test and physiological relevance test, Yuri V. Medvedev performed quantitative release assessment by high-performance liquid chromatography and supervised the work. Ksenia K. Karnakova and Natalia S. Bagaeva performed statistical processing of the data. All authors participated in writing the text of the article and discussing the results.

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Применение *in vitro* исследований для предсказания фармакокинетики таблеток ривароксабана

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Резюме

Введение. Важнейшим этапом фармацевтической разработки воспроизведенного лекарственного средства (ЛС) является клиническое исследование с участием человека – исследование биоэквивалентности. Учитывая важность нахождения препаратов ривароксабана в перечне жизненно необходимых и важнейших лекарственных препаратов (ЖНВЛП), в рамках обеспечения технологического суверенитета требуется использование научных робастных и эффективных методов определения качества готовой лекарственной формы.

Цель. Провести исследование таблеток ривароксабана на физиологически релевантном тестере с целью предсказания фармакокинетических профилей.

Материалы и методы. Объектами исследования являются «Ксарелто®, таблетки, покрытые пленочной оболочкой, 10 мг» (серия BXJS871, срок годности до 31.10.2024, Bayer AG, Германия), «Ксарелто®, таблетки, покрытые пленочной оболочкой, 20 мг» (серия BXKDF32, срок годности до 17.05.2026, Bayer AG, Германия), «Ривароксабан, таблетки, покрытые пленочной оболочкой, 10 мг» и «Ривароксабан, таблетки, покрытые пленочной оболочкой, 20 мг» отечественного

производства, с действующими сроками годности. Во время исследования использовались реактивы, необходимые для приготовления сред растворения и проведения количественного определения. Физиологически релевантный тест проводили на приборе СК ФРТ-6 (ООО «Сайнтифик Комплайнс», Россия). Определение количественного содержания высвободившегося ривароксабана в рамках теста сравнительной кинетики растворения (ТСКР) в среде 0,1%-го раствора натрия лаурилсульфата в фосфатном буферном растворе с pH 6,5 проводилось на спекторофотометре СФ-2000 (ООО «ОКБ Спектр», Россия). Количественное содержание высвободившегося ривароксабана в рамках ТСКР в биорелевантных средах растворения (БРС) и физиологически релевантного теста (ФРТ) оценивали на высокоэффективном жидкостном хроматографе «Хроматэк-Кристалл ВЭЖХ 2014» (ЗАО СКБ «Хроматэк», Россия). Фармакокинетические профили были смоделированы в программе PK-Sim® (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Германия) на основании данных, полученных в рамках проведения ФРТ. Клиническое исследование таблеток ривароксабана представляло собой проспективное открытое рандомизированное перекрестное в двух этапах сравнительное исследование в двух группах добровольцев с однократным приемом препаратов натощак. В исследовании были рандомизированы 30 здоровых добровольцев мужского пола в возрасте 18–45 лет.

Результаты и обсуждение. Был проведен комплекс испытаний *in vitro*, получены профили, позволяющие оценить динамику и степень высвобождения исследуемых ЛС в различных отделах ЖКТ человека. Осуществлено сравнение последовательной и гибридной схем проведения ФРТ. По результатам проведения ФРТ по разным схемам были предсказаны фармакокинетические профили для пары препаратов и рассчитана ошибка прогнозирования.

Заключение. Проведен комплекс научных испытаний *in vitro* для препаратов «Ксарелто®, таблетки, покрытые пленочной оболочкой, 10 мг и 20 мг», «Ривароксабан, таблетки, покрытые пленочной оболочкой, 10 мг и 20 мг». В рамках сравнения данных, полученных при проведении клинического исследования и при моделировании наименьшая ошибка прогнозирования была отмечена при выполнении ФРТ по гибридной схеме.

Ключевые слова: ривароксабан, FaSSIF, FaSSGF, БКС

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. А. М. Полуянов, Е. А. Малашенко, А. Ю. Савченко и И. Е. Шохин придумали и разработали эксперимент. А. В. Суворова и П. А. Лосенкова провели ТСКР и ФРТ. Ю. В. Медведев проводил количественную оценку высвобождения методом высокоэффективной жидкостной хроматографии и руководил работой. К. К. Карнакова и Н. С. Багаева проводили статистическую обработку данных. Все авторы участвовали в написании текста статьи и обсуждении результатов.

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INTRODUCTION

The crucial stage in the pharmaceutical development of a generic drug product is a clinical trial on human subjects – a bioequivalence study. The process of pharmaceutical development of a generic drug product involves selection and adjustment of production conditions, manufacturing and accumulating various production batches. The next stage is selection of the clinical batch for the bioequivalence study.

At this stage, *in vitro* testing of the pre-selected batches is required. The simplest of all tests for all solid dosage forms included in the regulatory documentation is the dissolution test [1, 2]. A logical continuation of this form of investigation is the dissolution kinetics comparison test (DKCT) [3].

There are also approaches that implement more complex models, such as testing in biorelevant media [4]. However, these tests are not mandatory, despite their importance for problematic drugs such as those in Subclass IIc of the Biopharmaceutical Classification System (BCS) [5, 6].

A typical example of BCS Class II drugs are the formulations of Rivaroxaban, containing a small molecule (M = 436 g/mol) as an active ingredient that is practically insoluble in water. Pharmacologically, Rivaroxaban is

a direct inhibitor of Factor Xa. The importance of its use was demonstrated in particular during the SARS-CoV-2 pandemic [7, 8].

Besides the importance of the drug in the treatment of a number of diseases, as well as being on the list of vital and essential drugs, the task of ensuring technological sovereignty requires application of robust and effective scientific methods for determining the quality of its dosage form in addition to the mandatory regulatory studies.

MATERIALS AND METHODS

Objects of study

The objects of study were as follows: "Xarelto®, film-coated tablets, 10 mg" (batch serial no. BXJS871, expiration date 31.10.2024, produced by Bayer AG, Germany), "Xarelto®, film-coated tablets, 20 mg" (batch serial no. BXKDF32, expiration date 17.05.2026, produced by Bayer AG, Germany), "Rivaroxaban, film-coated tablets, 10 mg" (non-expired, produced by a domestic manufacturer), and "Rivaroxaban, film-coated tablets, 20 mg" (non-expired, produced by a domestic manufacturer).

Reagents and solutions

The following reagents were used in the study: purified water, type I; concentrated hydrochloric acid (HCl) (class "extra pure", produced by "Sigma Tec" LLC, Russia); concentrated orthophosphoric acid (H_3PO_4) (class "for HPLC", produced by Scharlau, Spain); sodium hydroxide (NaOH) (class "p.a.", produced by "Component-Reaktiv" LLC, Russia); sodium phosphate dibasic (Na_2HPO_4) anhydrous (class "extra pure", produced by "Component-Reaktiv" LLC, Russia); sodium chloride (NaCl) (class "extra pure", produced by "Component-Reaktiv" LLC, Russia); sodium lauryl sulphate (SDS) (class "EP/USP", produced by "Aldosa" LLC, Russia), powder for the preparation of biorelevant media (BRM) SC Powder (produced by "Scientific Compliance" LLC, Russia); acetonitrile (ACN) (class "HPLC gradient grade", produced by Biosolve, France).

Test equipment

The dissolution kinetics comparison test (DKCT) was conducted using an Agilent 708-DS dissolution tester (Agilent Technologies, USA). The physiologically relevant test (PRT) was conducted on an SC PRT-6 unit ("Scientific Compliance" LLC, Russia). The determination of concentrations in sodium lauryl sulphate medium during the DKCT was performed by the UV-Vis spectrophotometry (SPM) method using an SF-2000 UV-Vis spectrophotometer ("OKB Spectr" LLC, Russia). The chromatographic separation and quantification of Rivaroxaban during the DKCT in BRM and the PRT were carried out on a high-performance liquid chromatograph "Khromatek-Kristall HPLC 2014" (SKB "Khromatek" JSC, Russia) set at a wavelength of 250 nm. The chromatography analysis run time was 6 minutes. The chromatography column used was an HPLC Column C18, 4.6 × 100 mm, 5 μм (GL Sciences™ Inc., Japan) placed in a column thermostat maintaining temperature of 35 °C throughout the analytical cycle. The separation was performed in isocratic elution mode (A : B = 55 : 45); mobile phase A was presented by 0.2 % H_3PO_4 solution, phase B – by acetonitrile.

Test procedures

Conditions of the dissolution kinetics comparison test (DKCT) in SDS dissolution medium: The test was conducted using a paddle stirrer rotating at 50 rpm. The dissolution medium was 500 ml of 0.1 % sodium lauryl sulphate solution in phosphate buffer solution with pH 6.5, pre-heated at 37 ± 0.5 °C under thermostatic control. The sampling was performed at the following time points: 10, 15, 20, 30, 45, 60, 80, 100, 120, 180 min.

Conditions of the DKCT in biorelevant media (BRM): The test was conducted using a paddle stirrer rotating at 50 rpm. The biorelevant dissolution medium was 500 ml of FaSSIF with pH 6.5, pre-heated at 37 ± 0.5 °C under thermostatic control. The sampling was performed at time points 10, 15, 20, 30, 45, 60, 80, 100, 120, 180 min. The procedure for preparation of the dissolution medium was as follows: 1000 ml of purified water was added with 0.42 g of NaOH, 3.95 g of NaH_2PO_4, and 6.19 g of NaCl. Then the pH value was measured and brought to 6.5 ± 0.05 with either 0.1 M solution of HCl or 0.1 M solution of NaOH, as necessary. Then 500 ml of thus obtained solution was added with 2.24 g of the powder and thoroughly stirred, upon which it was added with 500 ml of the buffering solution.

Conditions of the physiologically relevant test (PRT) arranged by the sequential scheme: The first section of the test system contained a solution of 50 ml of FaSSGF biorelevant dissolution medium and 250 ml of purified water (a volume of water commonly used to wash down

a tablet); the overall initial volume of this solution was 300 ml, the pH value was 2.84. The section simulating the stomach was emptied according to the first-order kinetics equation, the half-emptying time was 18 min, and the time of complete emptying (to a residual volume of 50 ml) was 38.6 min. The procedure for preparation of the FaSSGF dissolution medium was as follows: 1000 ml of hydrochloric acid solution was added with 2.00 g of NaCl, and then the pH value was measured and brought to 2.0 ± 0.05 with 0.1 M solution of HCl, as necessary. Thus obtained solution was added with 0.060 g of the powder for preparation of biorelevant media and thoroughly stirred until completely dissolved; the prepared solution was used within 24 hours.

The second section (simulating the duodenum) was filled with FaSSIF biorelevant dissolution medium with a pH value of 6.5 at the beginning of the test; its initial volume was 75 ml and remained constant throughout the test. The third section (simulating the intestine): its volume was zero initially, but reached 390 ml by the end of the test. The sampling time points were the same for all the chambers; the sampling was performed at the 5, 10, 15, 20, 30, 35, 60, and 80th minute of the test.

Conditions of the physiologically relevant test (PRT) arranged by the hybrid scheme: At the beginning of the test, the first and third sections of the test system were empty; the second section contained 50 ml of FaSSGF biorelevant dissolution medium mixed with 250 ml of purified water (a glass of water used to wash down a tablet), the overall initial volume of this solution was 300 ml. This section, simulating the fasting stomach, was emptied into the first beaker according to the first-order kinetics equation for 40 min, after which a secretion in the form of biorelevant FaSSIF dissolution medium with a pH value of 6.5 began to flow into it. After the 45th minute of the test, the entire volume of the FaSSGF biorelevant dissolution medium was transferred into the first section, and it began to simulate the stomach; the second and third sections, after transferring the secretion into the second beaker and pumping the media from the first to the third chamber, began to mimic the duodenum and the intestine, respectively. During this process, a constant secretion of the FaSSIF medium into the second section at a rate of 1 ml/min and pumping at a rate of 2 ml/min from one section to the other were maintained. During the test, the time points of sampling from different sections varied: thus, the sample was taken from the first section at the 10, 20, 30, 40, 100, and 180th minute, and from the third section – at the 60, 100, 120, 140, 160, and 180th minute.

In both tests, the paddle stirrer rotated at 25 rpm, with periodical (once every 5 minutes for 15 seconds) rotation acceleration up to 180 rpm in order to simulate the actual gastrointestinal motility.

RESULTS AND DISCUSSION

Rivaroxaban belongs to BCS Class II substances with low water solubility and high permeability [10]. At the same time, the substance is classified as Subclass "c" (non-ionizable substances), which indicates that the solubility of the substance is not affected by the pH throughout the gastrointestinal tract (GIT) [11]. Given these particular properties, the substance requires careful attention in pharmaceutical development and quality assessment of the drug product.

The design of the experiment was drawn up in a reverse order, different from the sequential process of pharmaceutical development (see Figure 1): following unsatisfactory results in the clinical phase, a set of in vitro tests were conducted for the batches that were used in the clinical trial, aiming to identify the discriminate validity of the existing instruments and to assess correlation with the results of the clinical part of the study.

In the course of preclinical trials of the drug, a DKCT test in compendial dissolution media was conducted according to the requirements of regulatory documentation, where comparable results were obtained for the drugs under study. Therefore, as a pilot experiment, a test in 0.1 % sodium lauryl sulfate solution in phosphate buffer solution with pH 6.5 was conducted, as this medium is tentatively more discriminative due to the presence of surface active agents (surfactants). The resulting release profiles are shown in Figure 2.

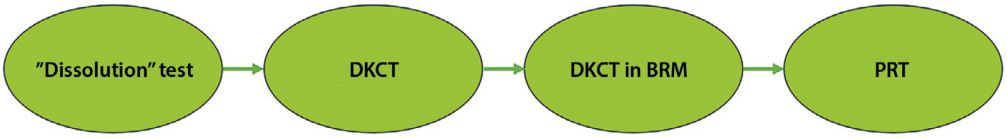

Figure 1. The stages of tests in pharmaceutical development

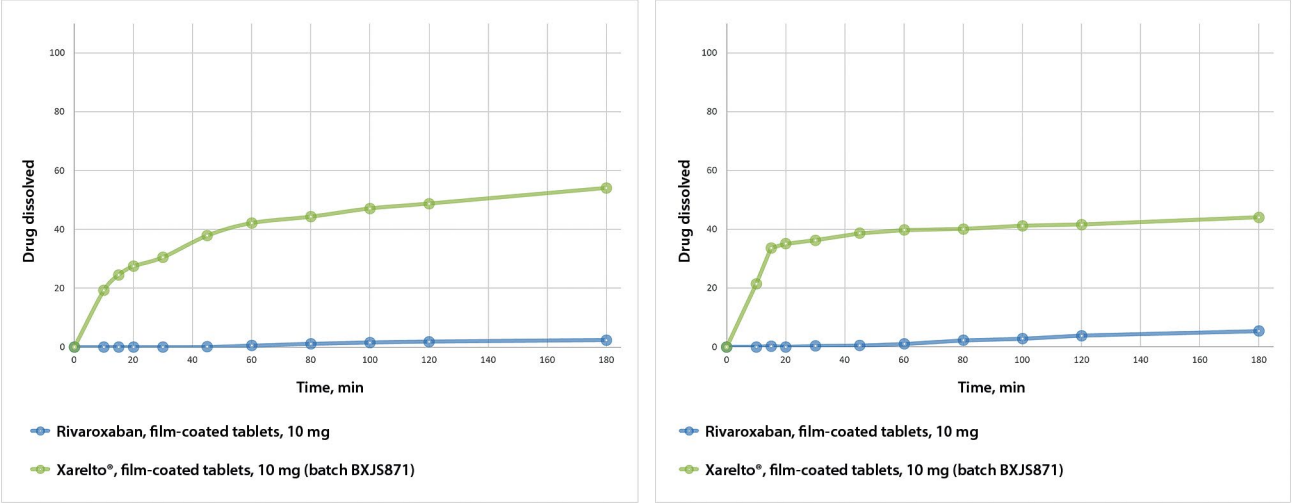

Figure 2. Results of DKCT in a 0.1 % sodium lauryl sulfate solution in a phosphate buffer solution pH 6.5

The analysis of the obtained data showed qualitative and quantitative differences in release of the two drugs. But, taking into account the specificity of media containing anionic surfactants caused by their poor physiological adequacy, it was decided to use biorelevant dissolution media that provide properties close to the conditions of the human gastrointestinal tract.

Taking into account the BCS Class and Subclass of the substance, the FaSSIF dissolution medium (a medium simulating the intestinal secretion in fasting state) containing surfactants in the amount of 2.24 g per 1 liter of solution was selected. The quantification was performed by the HPLC-UV method, since the substances included in the powder for preparation of biorelevant dissolution media absorb radiation in the ultraviolet region and may have a maximum similar to that of the target analyte. The results obtained in DKCT in BRM for the 20 mg dosage are presented in Figure 3.

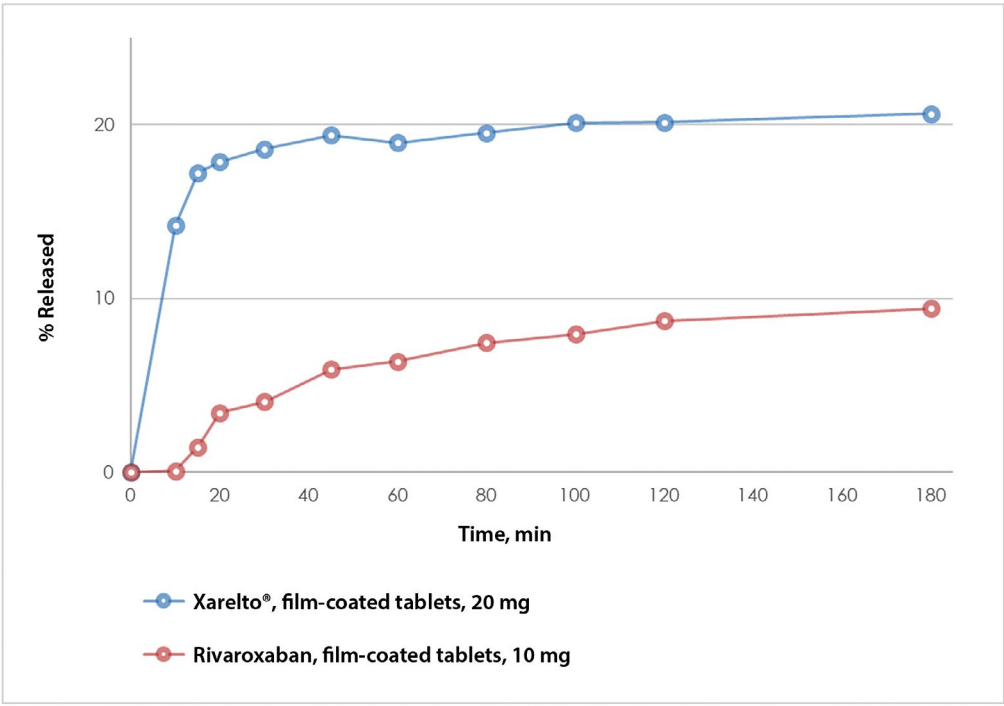

Figure 3. Results of the release of rivaroxaban at a dosage of 20 mg during DKCT in the BRM

It may be noted that the results obtained in FaSSIF and SDS media differ from each other; the release rate of the reference drug decreased by half, but at the same time the test drug was released better. Taking these specifics into account, it was decided to apply PRT in order to maximally recreate the conditions of the human gastrointestinal tract *in vitro* and, still more important, to add the factor of physiological transit between the test system sections.

In the two drugs trial, in addition to the classical sequential test design (see Figure 4 A), a hybrid design was used for the first time (Figure 4 B).

The use of a hybrid scheme is justified primarily for drugs belonging to the BCS Subclass IIa, which is related to their poor solubility in acidic medium (the first section of the PRT apparatus) and a decrease in the degree of the active substance transfer to subsequent sections during the test. Furthermore, this scheme is acceptable for drugs with a low rate of disintegration of the dosage form, which leads to slower or no transit, although transit of substances to subsequent sections is not by any means limited in the human GIT. The use of a hybrid scheme in the study of Rivaroxaban is justified due to its low solubility regardless of pH.

The resulting release profiles of Rivaroxaban for the reference and test drugs in 10 mg dosage obtained in DKCT arranged by the hybrid scheme are presented in Figures 5 and 6, respectively; the release profiles for 20 mg dosage are presented in Figures 7 and 8, respectively.

It may be noted that in the test arranged by the sequential scheme there is no transit of the tested drug to the subsequent sections, apparently due to the low degradability of the tablet in the first section of the apparatus, simulating the stomach. The results of the PRT arranged by the hybrid scheme provided more representative data allowing to predict the pharmacokinetic profiles, which made possible to draw a conclusion on comparability of the test results with the clinical studies that were conducted for the studied drug batches.

The prediction was based on the data on Rivaroxaban molecule summarized in Table 1.

Table 1. Summary of parameters used in PBPK model

Parameter	Value
MW	435.881 g/mol
Log P	1.74
Fraction unbound	5 %
pKa	13.6
Dissolution at pH = 7,0	10.0 ug/ml
Metabolizing enzymes	CYP3A4, CYP2J2
Transport protein	P-gp, BCRP

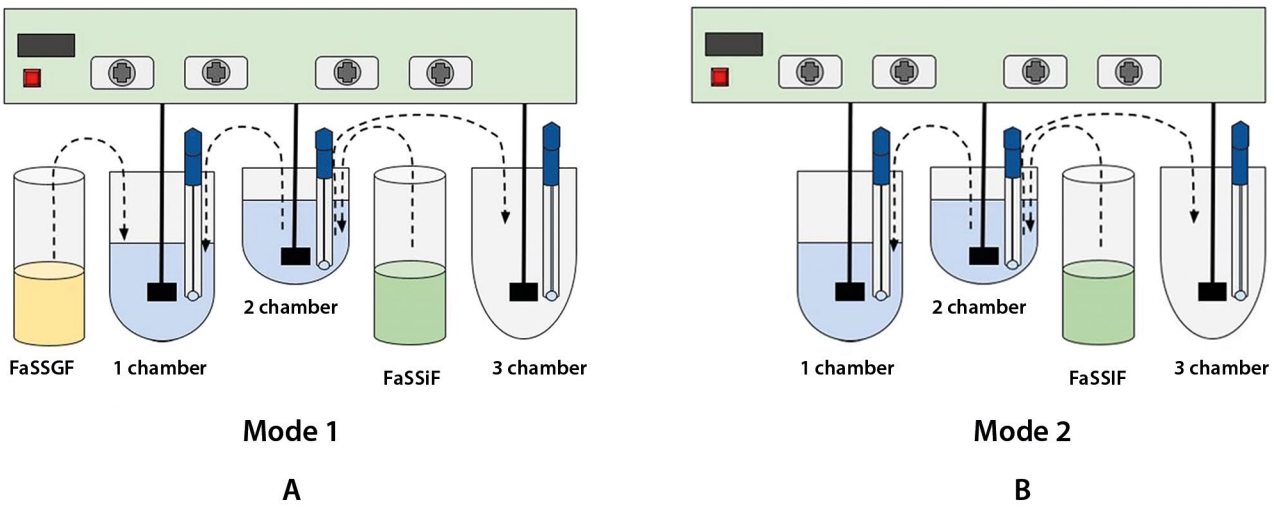

Figure 4. Operation modes:
A – sequential scheme; B – hybrid scheme

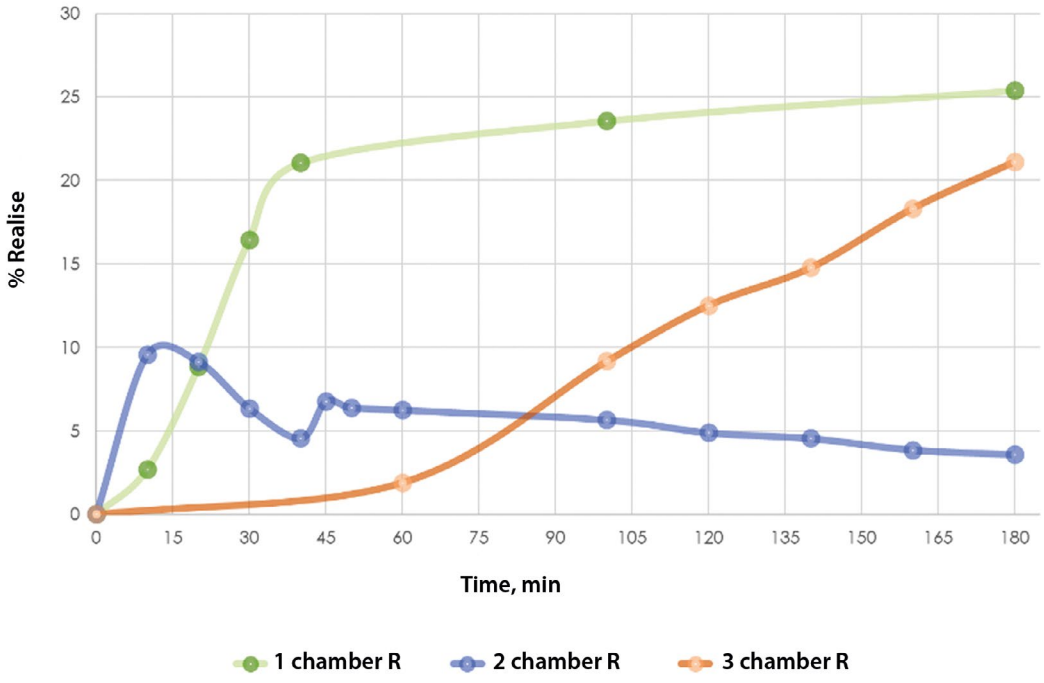

Figure 5. **Average dissolution profiles of rivaroxaban in "Xarelto® film-coated tablets, 10 mg" in three chambers of the apparatus**

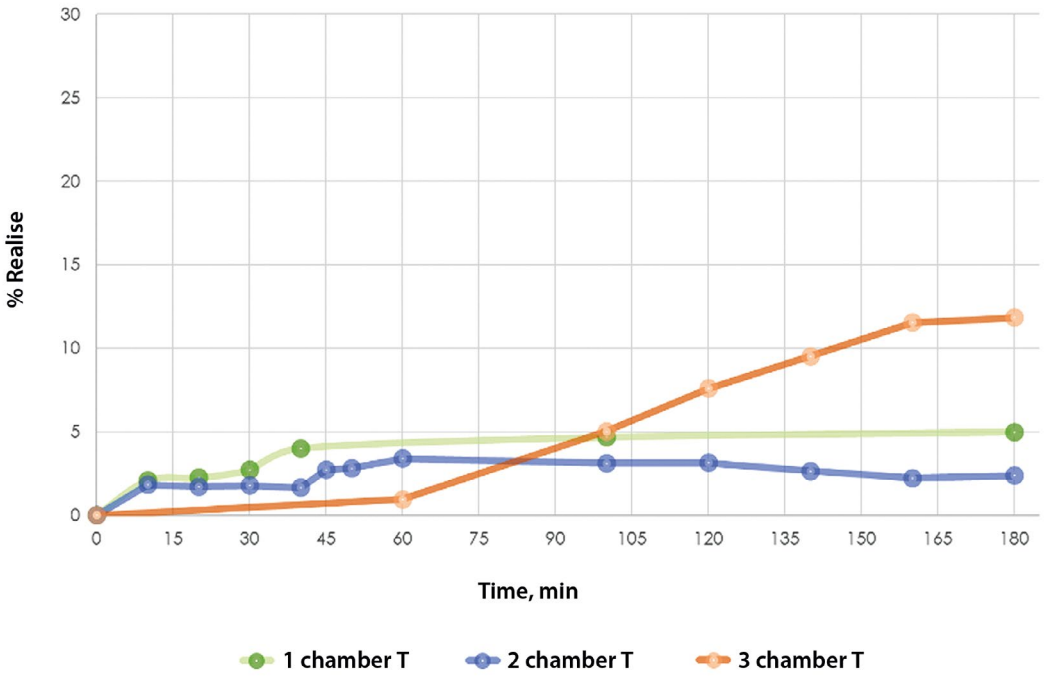

Figure 6. **Average dissolution profiles of rivaroxaban in "Rivaroxaban, film-coated tablets, 10 mg" in three chambers of the apparatus**

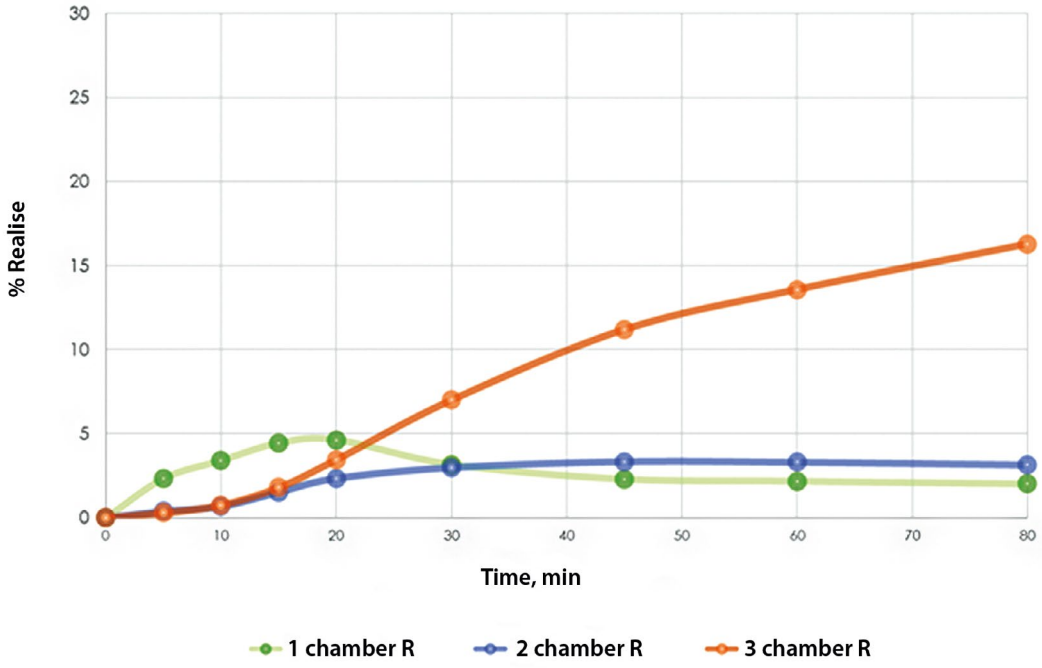

Figure 7. **Average dissolution profiles of rivaroxaban in "Xarelto® film-coated tablets, 20 mg" in three chambers of the apparatus**

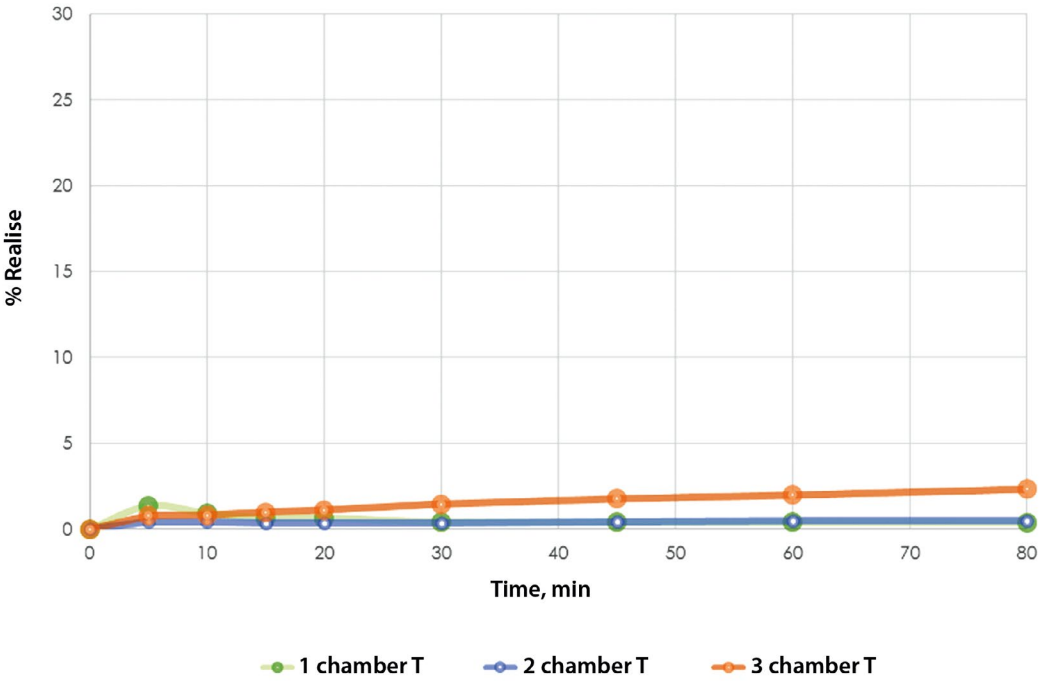

Figure 8. **Average dissolution profiles of rivaroxaban in "Rivaroxaban, film-coated tablets, 20 mg" in three chambers of the apparatus**

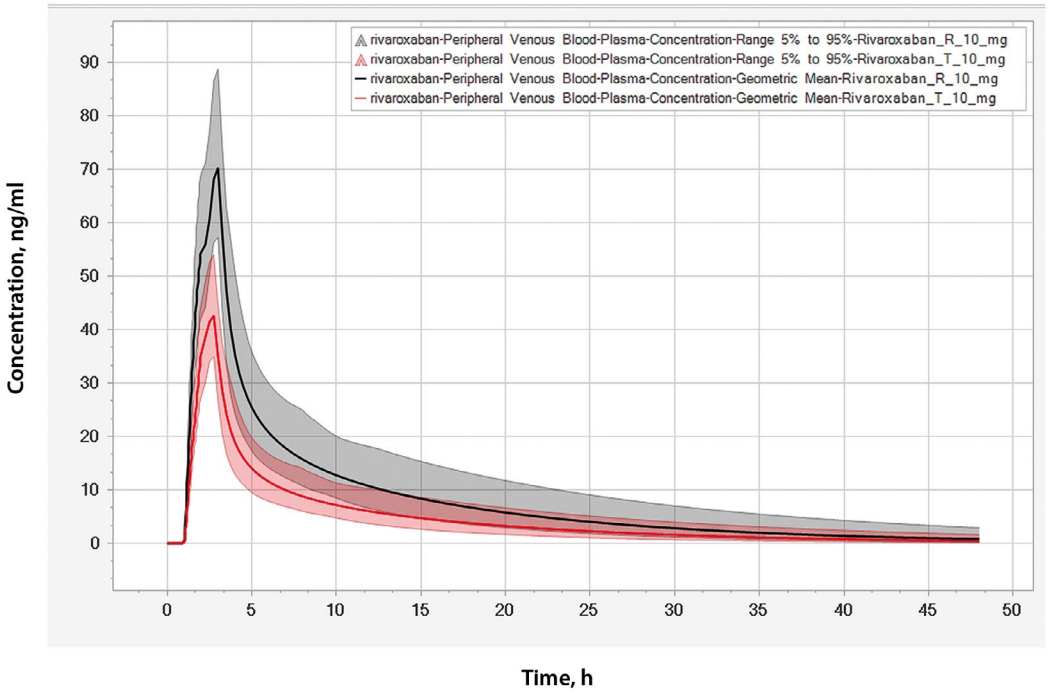

Figure 9. Pharmacokinetic profiles test and reference drugs predicted by PBPK for dose 10 mg

For the simulation of the pharmacokinetic profiles, a virtual population was used, consisting of 30 male volunteers, white, at the age of 18 to 45, with body mass index 18.5–29.9 kg/m^2; the drug was taken once on an empty stomach; blood sampling was performed within 48 hours. The parameters of the virtual population were based on the volunteers data from the clinical trials conducted.

The profiles for Rivaroxaban drugs at 10 mg dosage obtained by physiologically based pharmacokinetic modeling and the clinical study are shown in Figures 9 and 10, respectively. For the 20 mg dosage, the modeled profiles and the profiles obtained from the clinical trial are presented in Figures 11 and 12.

In the figures presented above, the disposition of the profiles of the test and reference drugs relative to each other is consistent between the modeled data and the data obtained in the clinical study. The similar relative disposition of the profiles is maintained within the PBPK modeling for different dosages of Rivaroxaban (10 and 20 mg), despite the different schemes of conducting the physiologically relevant tests. However, the differences between the test and reference drugs are not reliable in the tests performed according to the classical sequential scheme, as the predicted pharmacokinetic profile of the test drug goes well below the profile obtained in the clinical trial of the same drug.

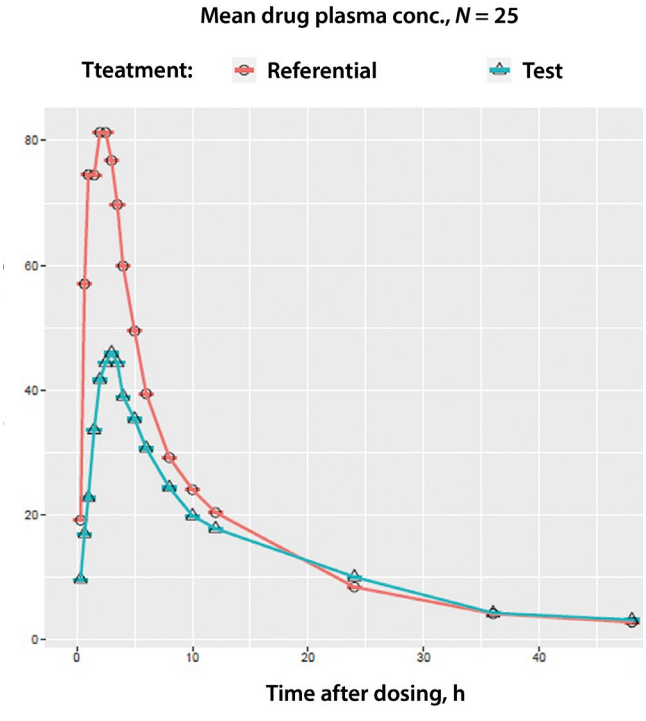

Figure 10. Pharmacokinetic profiles test and reference drugs obtained during the clinical trial for dose 10 mg

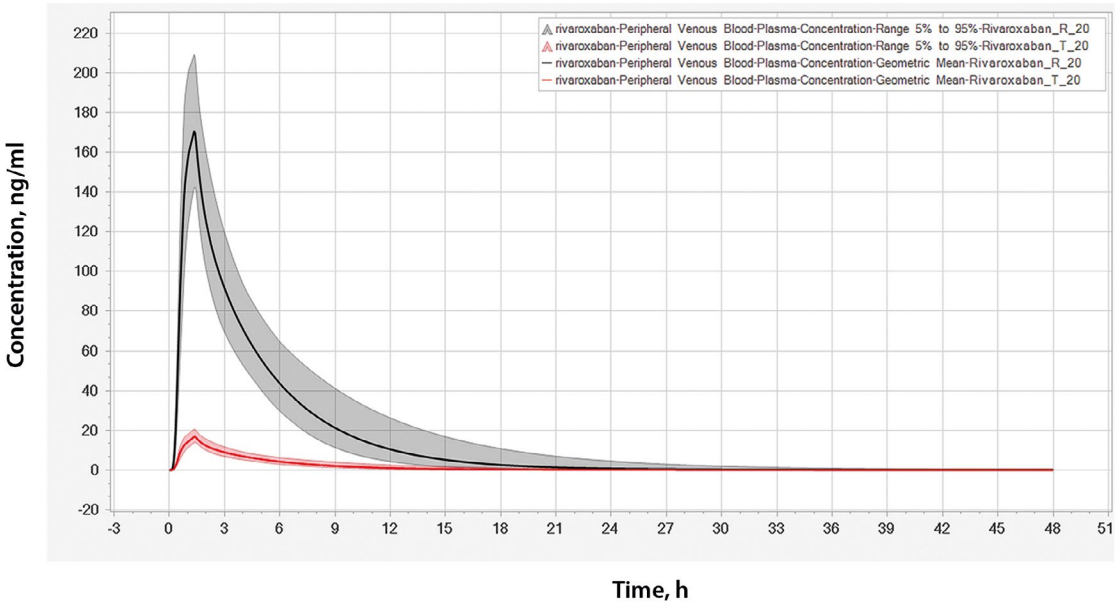

Figure 11. **Pharmacokinetic profiles test and reference drugs predicted by PBPK for dose 20 mg**

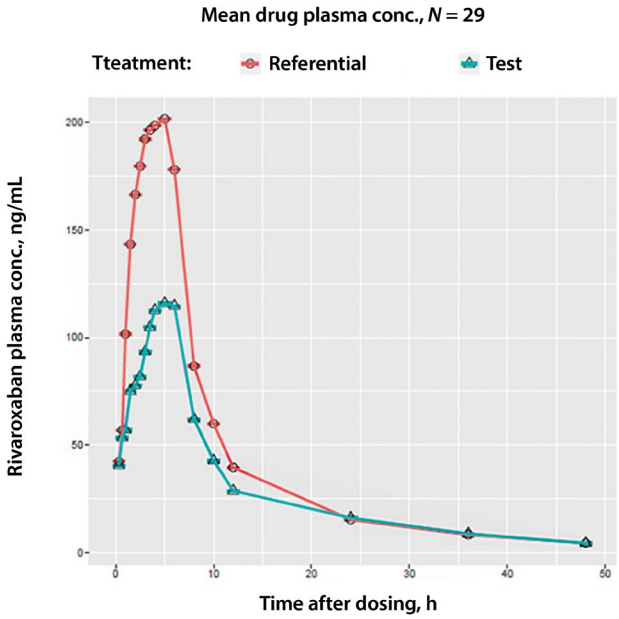

Figure 12. **Pharmacokinetic profiles test and reference drugs obtained during the clinical trial for dose 20 mg**

In order to assess the degree of difference between the modeled data and the data from the clinical study, the ratios of geometric mean values of pharmacokinetic parameters of the tested drug in relation to the reference drug were calculated. Based on the values obtained, the prediction error was calculated; the obtained results are summarized in Table 2.

Table 2. **Values of the ratio of the geometric mean values of the pharmacokinetic parameters of the studied drug to the reference drug**

Parametr	Data from clinical trials	Data from the simulation	Prediction error (PE) for geometric mean ratio T/R, %
Data for dose 10 mg			
AUC_{0-t}	77.95	56.63	–37.64
C_{max}	51.68	59.21	12.71
Data for dose 20 mg			
AUC_{0-t}	69.43	9.71	–614.83
C_{max}	64.12	9.84	–551.72

Because of the prediction data obtained for the test drug at the 20 mg dosage, the prediction error (PE), i.e. the discrepancy between the predicted data and the clinical trial data, is so high (PE for AUC_{0-t} = –14,83 % and PE for C_{max} = –551,72 %) that we can conclude that the classical sequential scheme of PRT is not optimal for the drug under test.

The prediction error for the C_{max} parameter for 10 mg dosage is close to 10 %, which appears to be a more correct result (according to the regulatory requirements for IVIVC, the mean absolute percent prediction error for Cmax and AUC should not exceed 10 %). For the AUC_{0-t} parameter, lower prediction accuracy is observed, which in turn can be connected with several factors:

1. In modeling, the time interval between the points of plotting in all sections of the profile is the same, while the profiles obtained in clinical trials are constructed by points at different time intervals, which affects the shape of the profile in the elimination phase;
2. In the analysis of pharmacokinetic profiles obtained from volunteers, cases of atypical form were noted, but no such cases were observed within the predicted profiles obtained in the *in vitro* test.

The experimental results open up new ways to improve *in vitro* testing and PBPK modeling with the aim of predicting the results of pharmacokinetic studies with a high degree of confidence in prediction assessment. It is also worth noting the importance of an individualized scientific approach to the methodology of testing.

CONCLUSION

A set of *in vitro* PRT studies of the drug products "Xarelto®" and "Rivaroxaban" was carried out. Quantification was performed by validated SFM and HPLC-UV methods.

In the process of studies of the domestically produced drugs "Rivaroxaban, film-coated tablets, 10 mg and 20 mg", a DKCT test in medium containing SDS solution was conducted, which showed extremely low release and non-equivalence to the reference drug "Xarelto®, film-coated tablets, 10 mg and 20 mg". In order to further predict the behavior of the drugs "Rivaroxaban, film-coated tablets, 10 mg and 20 mg" and "Xarelto®, film-coated tablets, 10 mg and 20 mg", a PRT study was conducted, the results of which formed the basis for a PBPK modeling study. The modeling results were compared with the results of pharmacokinetics of the studied drugs and the prediction error was calculated for the ratio of geometric mean values of pharmacokinetic parameters. For the 20 mg dosage, it was 614.83 % for AUC_{0-t} and –551.72 % for C_{max}; for the 10 mg dosage, it was 37.64 % for AUC_{0-t} and 12.71 % for C_{max}.

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