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# PRT to predict pharmacokinetic profiles as part of a bioequivalence study of the drug deferasirox

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**Abstract**

**Introduction.** Deferasirox is a complexing drug and belongs to class II according to the biopharmaceutical classification system (BCS), has acidic properties and belongs to subclass "a" (acid). This class is characterized by high permeability and low solubility, which limits the absorption of the active substance into the blood. As a result, the development of drugs with an active substance that can be assigning BCS to this class is a difficult task, and for generic drugs it is also associated with a high risk of obtaining unproven equivalence during clinical trials. To minimize the above risks, a physiologically relevant test was carried out with further data processing and construction of putative pharmacokinetic profiles.

**Aim.** The aim of the study is to conduct a physiologically relevant test (PRT) to predict *in vitro* pharmacokinetic profiles and compare them with *in vivo* data as part of a bioequivalence study of deferasirox.

**Materials and methods.** The objects of the study are "Deferasirox, film-coated tablets, 360 mg" of a domestic manufacturer and "Jadenu®, film-coated tablets, 360 mg" (WTN22 series, expiration date until 10.2023, Novartis Pharma Stein AG, Switzerland). A physiologically relevant test was performed on the device SC PRT-6, Scientific Compliance. Quantitative analysis was carried out by HPLC-UV method. Pharmacokinetic profiles were modeled using PK-Sim® (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Germany) based on data obtained from physiologically relevant test.

**Results and discussion.** A physiologically relevant drug test for deferasirox was performed and release profiles were obtained, which formed the basis of a physiologically based pharmacokinetic model together with data on the physicochemical properties of the studied compound and literature data on the pharmacokinetics of deferasirox. The pharmacokinetic profiles obtained as part of the simulation on a virtual population were compared with data obtained during clinical trials.

**Conclusion.** A physiologically relevant test for the drug deferasirox was carried out, assay was performed by HPLC with UV detection. The test resulted in data that allowed prediction of pharmacokinetic profiles that reflected the same differences observed in the profiles of the test and reference drug in the comparative pharmacokinetics and bioequivalence study of deferasirox drugs.

**Keywords:** Deferasirox, HPLC, PBPK

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

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**Contribution of the authors.** Yuri V. Medvedev took part in the development of an analytical method for the quantitative determination of deferasirox. Polina A. Losenkova was responsible for the analytical stage of the study. Alexandra V. Suvorova and Eugenia A. Malashenko carried out statistical processing of the data. Andrey M. Poluyanov was responsible for the development and scientific substantiation of the experiment. Igor E. Shokhin and Igor E. Makarenko were responsible for the organizational part of the study. All the above authors participated in discussing the results obtained in the form of a scientific discussion.

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# Применение физиологически релевантного тестера (ФРТ) для предсказания фармакокинетических профилей в рамках исследования биоэквивалентности препарата деферазирокс

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**Резюме**

**Введение.** Деферазирокс является комплексообразующим лекарственным средством и относится ко II классу по биофармацевтической классификационной системе (БКС), обладает кислотными свойствами и относится к подклассу «а» (acid). Данный класс характеризуется высокой проницаемостью и низкой растворимостью, которая лимитирует всасывание действующего вещества в кровь. Вследствие этого разработка препаратов с действующим веществом, которое можно отнести к данному классу БКС, является сложной задачей, а для воспроизведенных препаратов еще и сопряжена с высоким риском получения недоказанной эквивалентности при проведении клинических исследований. Для минимизации вышеописанных рисков был проведен физиологически релевантный тест с дальнейшей обработкой данных и построением предполагаемых фармакокинетических профилей.

**Цель.** Целью исследования является проведение физиологически релевантного теста (ФРТ) для предсказания по данным *in vitro* фармакокинетических профилей и сопоставление с данными *in vivo* в рамках исследования биоэквивалентности препарата деферазирокс.

**Материалы и методы.** Объектами исследования являются «Деферазирокс, таблетки, покрытые пленочной оболочкой, 360 мг» отечественного производителя и «Джадену®, таблетки, покрытые пленочной оболочкой, 360 мг» (серия WTN22, срок годности до 10.2023, Novartis Pharma Stein AG, Швейцария). Физиологически релевантный тест проводили на приборе СК ФРТ-6 (ООО «Сайнтифик Комплайнс», Россия). Количественный анализ проводили методом ВЭЖХ-УФ. 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 физиологически релевантного теста.

**Результаты и обсуждение.** Был проведен физиологически релевантный тест для лекарственных препаратов деферазирокса, получены профили высвобождения, которые легли в основу физиологически обоснованной фармакокинетической модели совместно с данными о физико-химических свойствах изучаемого соединения и литературными данными о фармакокинетике деферазирокса. Полученные в рамках симуляции на виртуальной популяции фармакокинетические профили были сопоставлены с данными, полученными при проведении клинических испытаний.
**Заключение.** Проведен физиологически релевантный тест для препарата деферазирокс, количественное определение в образцах проводили методом ВЭЖХ-УФ. В результате проведения теста были получены данные, позволившие спрогнозировать фармакокинетические профили, которые отражают те же различия, что наблюдались в профилях тестового и референтного препарата при проведении исследования сравнительной фармакокинетики и биоэквивалентности препаратов деферазирокса.

**Ключевые слова:** Deferasirox, HPLC, PBPK

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

**Вклад авторов.** Ю. В. Медведев принимал участие в разработке аналитической методики количественного определения деферазирокса. П. А. Лосенкова отвечала за проведение аналитического этапа исследования. А. В. Суворова и Е. А. Малашенко проводили статистическую обработку данных. А. М. Полуянов отвечал за разработку и научное обоснование эксперимента. И. Е. Шохин и И. Е. Макаренко отвечали за организационную часть исследования. Все вышеуказанные авторы участвовали в обсуждении полученных результатов в форме научной дискуссии.

**Для цитирования:** Суворова А. В., Лосенкова П. А., Медведев Ю. В., Малашенко Е. А., Макаренко И. Е., Полуянов А. М., Шохин И. Е. Применение физиологически релевантного тестера (ФРТ) для предсказания фармакокинетических профилей в рамках исследования биоэквивалентности препарата деферазирокс. *Разработка и регистрация лекарственных средств*. 2024;13(3):166–175. https://doi.org/10.33380/2305-2066-2024-13-3-1895

## INTRODUCTION

The physiologically based pharmacokinetic (PBPK) modeling is a method of mathematical modeling that allows describing the pharmacokinetics of xenobiotics based on their physicochemical properties and physiology of humans or animals.

PBPK modeling is used in pharmaceutical research and drug development, as well as in assessment of health risks associated with the use of certain drugs.

Most often, the basic elements for building a physiologically based pharmacokinetic model are sections (vessels) simulating different organs or tissues (for example, adipose tissue, the brain, intestine, heart, kidneys, liver, lungs, muscles, skin, spleen, etc.); the transit of substances between the sections is maintained by the flow of various physiological fluids (arterial and venous blood, bile etc.) and diffusion [1, 2]. Schematic view of such a model is shown in Figure 1.

Each of such sections is described by some physiological parameters (based on literature data) that will characterize it as a particular organ. Interaction between all these sections is described by mass balance equations which, for instance, describe the blood supply to the organs, passive transit or process of diffusion through cellular membranes into the intracellular space.

PBPK models are based on a number of information blocks that are combined during the model construction and can be used for implementation of various simulations. These blocks can be divided into the following major groups:

1) properties of the organism;
2) properties of the drug;
3) mode of administration and properties of the dosage form [3].

The information blocks required for building a PBPK model are graphically represented in the block diagram, see Figure 2.

Relying upon a priori knowledge of partially independent physiological processes and information about properties of the studied compound integrated into the mechanistic structure, PBPK models make it possib-

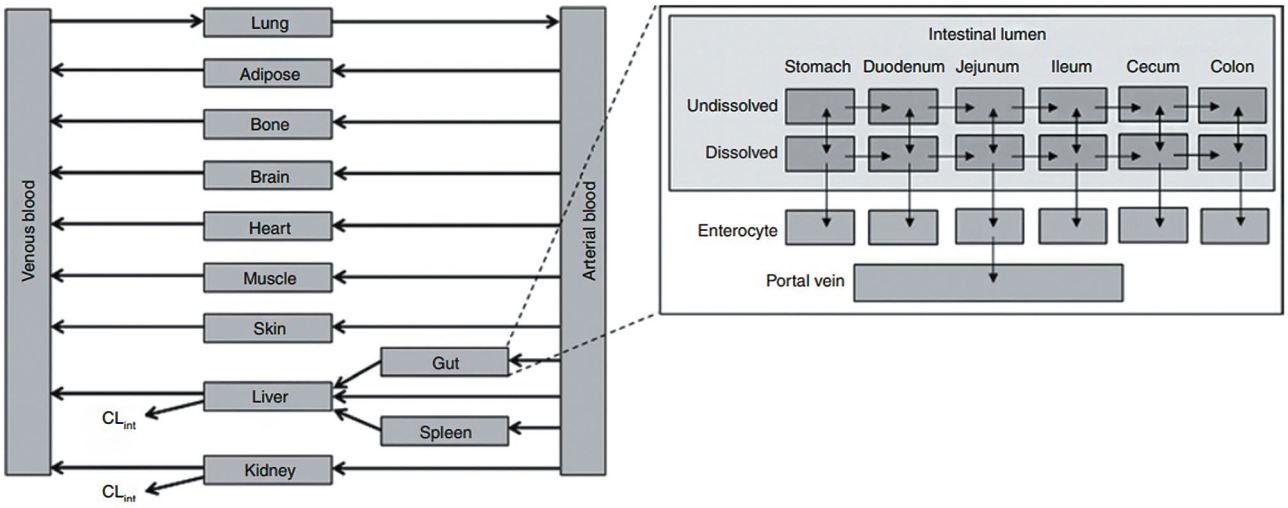


**Figure 1.** **Scheme of a PBPK model**

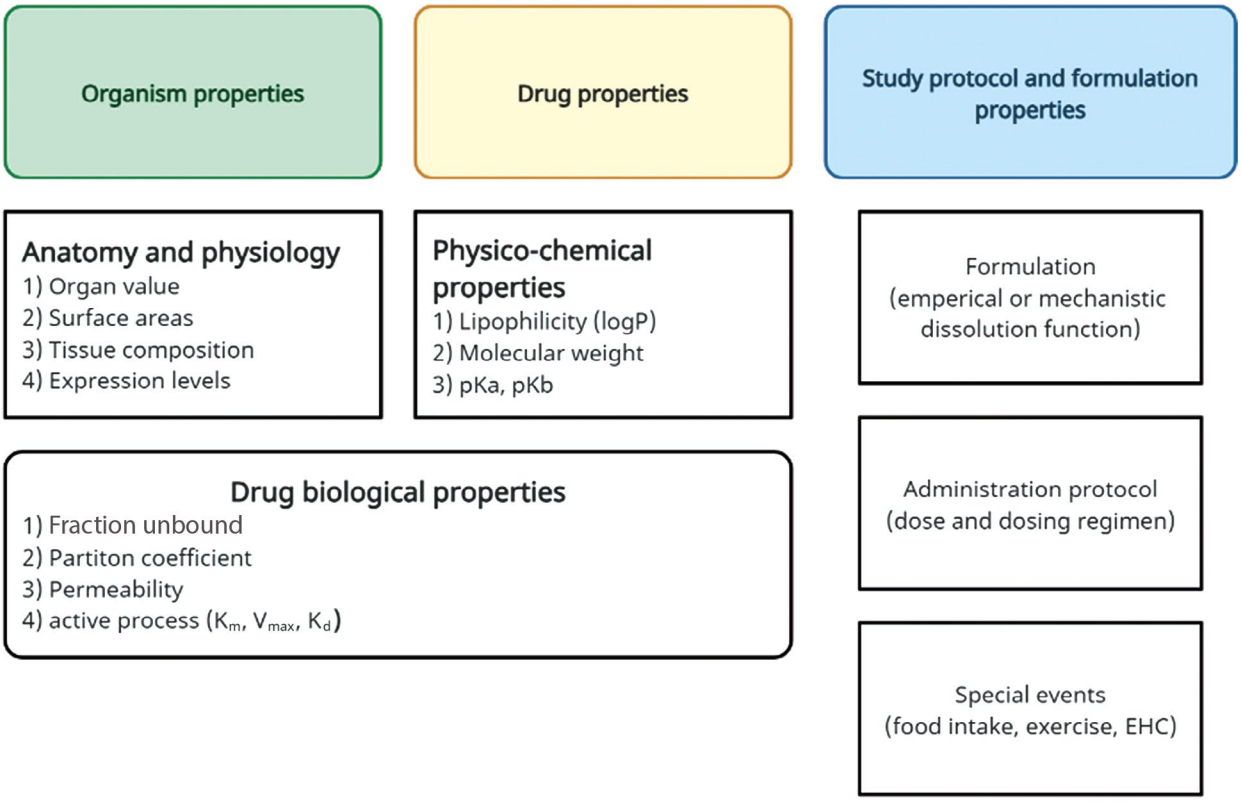


**Figure 2.** **Blocks of a PBPK model**

le to predict and describe the absorption, distribution, metabolism and excretion (ADME) properties of a drug and to describe its pharmacokinetic profile [4].

The model's high flexibility and complexity allows it to be used for various studies: study of drugs behavior in children [5], study of pharmacokinetic parameters for different dosages, study of drugs behavior in populations with specific diseases [6, 7] or of a particular nationality [8], animal studies [9], simulation of a drug behavior in pregnant women [10], multi-drug interaction research and modeling [11], and many other experiments. PBPK models are also useful in the development of generic

drugs at the stage of screening candidates for clinical trials [12]. Such an approach reduces the risk of getting unexpected research results, especially for drugs requiring a particularly careful approach in developing a finished dosage form, including the BCS Class II or IV drug substances.

One of the drugs belonging to the BCS Class II is Deferasirox (Figure 3) – a specific, highly selective iron chelator that does not cause zinc or copper excretion [13, 14]. It should be noted that this substance has weakly acidic properties and falls into the Subclass "a" (acid) which, in turn, implies poor solubility in compendial media with pH value of 1.2.

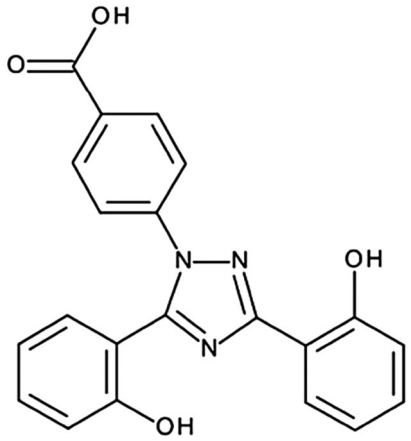


**Figure 3. Chemical structure of deferasirox**

## MATERIALS AND METHODS

### *Objects of study*

The objects of study were as follows: "Deferasirox, film-coated tablets, 360 mg" (domestic production) and "Jadenu®, film-coated tablets, 360 mg" (serial WTN22, expiration date: 10.2023, Novartis Pharma Stein AG, Switzerland).

### *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", Scharlau, Spain); sodium hydroxide (NaOH) (class "p.a.", "Component-Reaktiv" LLC, Russia); dehydrated sodium dihydrogen phosphate ($NaH_2PO_4 \cdot 2H_2O$) (class "extra pure", "Component-Reaktiv" LLC, Russia); sodium chloride (NaCl) (class "extra pure", "Component-Reaktiv" LLC, Russia); 3F Powder (Biorelevant, United Kingdom); acetonitrile (ACN) (class "HPLC gradient grade", Biosolve, France).

### *Equipment and software*

The physiologically relevant test was conducted using an SC PRT-6 unit ("Scientific Compliance" LLC, Russia). Chromatographic separation was carried out on a high-efficient liquid chromatograph "Khromatek-Kristall HPLC 2014" (SKB "Khromatek" JSC, Russia) equipped with a column thermostat, degasser, automatic sampler, and a UV detector. Modeling of the pharmacokinetic profiles was carried out with the "PK-Sim®" software (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Germany).

## RESULTS AND DISCUSSION

### *Elaboration of the physiologically relevant test procedure*

An important feature of substances having acidic properties (BCS Subclass "a") is their poor solubility in acidic media, which in the case of Deferasirox has been confirmed by literature and *in vitro* tests. Therefore, the serial scheme for conducting the PRT is not relevant because due to poor solubility the active substance would not get into the subsequent sections of the apparatus, and a distortion of results would occur. That is why more physiologically relevant for the BCS Class II, Subclasses "a", "ac" and "c" substances is the test scheme presented in Figure 4.

The first section of the apparatus simulates the stomach. At the beginning of the test its content volume was 0 ml. Further on, it was filled by way of the gastric juice transit from the second section according to the equation of first order kinetics, and by the 40th minute its content volume reached 250 ml. This volume remained constant till the end of the test.

The second section simulates the drug transit from the stomach into the duodenum. The transit mechanism was implemented as follows: first, a mixture of 50 ml of FaSSGF (Fasted State Simulated Gastric Fluid) with 250 ml of water (a glass of water used to wash down a tablet) was placed into the section; pH value of this mixture was about 2.84 (these starting conditions simulated the stomach in fasted state after ta-

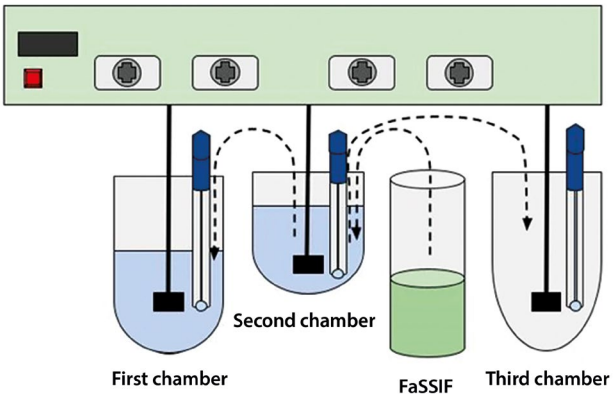


**Figure 4.** **Scheme of the PRT**

king the drug). Then this section was emptied according to the equation of first order kinetics; the emptying time (down to residual volume of 50 ml) was 40 minutes [15].

From the 40th to 55th minute, FaSSIF (Fasted State Simulated Intestinal Fluid) was being secreted into this section until its volume reached 75 ml, which simulated the transit from the stomach into the duodenum. This volume remained constant throughout the test because such a volume is known as physiologically relevant, which has been depicted in publications [16].

The third section of the apparatus simulates the intestine and serves for collecting the secretion from the second section. Its volume was increasing from the 40th minute to the end of the test. The initial volume of this section was 0 ml.

Figure 5 shows the volumes of the sections at different time points.

The quantification of Deferasirox content in samples obtained during the PRT was carried out by HPLC-UV method. Based on the data obtained, averaged diagrams "drug release percentage – time" were plotted (Figures 6 and 7).

### *Plotting the pharmacokinetic profiles on the basis of in vitro testing results*

There are many programs designed for PBPK modeling; in our work the PK-Sim® software was used (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Germany).

The software is based on a structure comprising 18 organs and tissues, which allows to simulate the ADME processes for different administration routes [17].

In the PK-Sim® software, oral administration is implemented by means of a model that incorporates the small intestine as a single continuous section with spatially varying properties. The transit of the administered dose of a drug substance is described by the function of emptying the stomach dependent on food intake and the transit function describing the transfer of the drug through the intestine. At each time point, the amount of substance sucked into the portal vein is calculated. For solid dosage forms, the substance release into the solution is either assumed to be instantaneous (for immediate release dosage forms) or can be described according to the dissolution models pre-set in the program, or can be specified by the user-defined release functions [18].

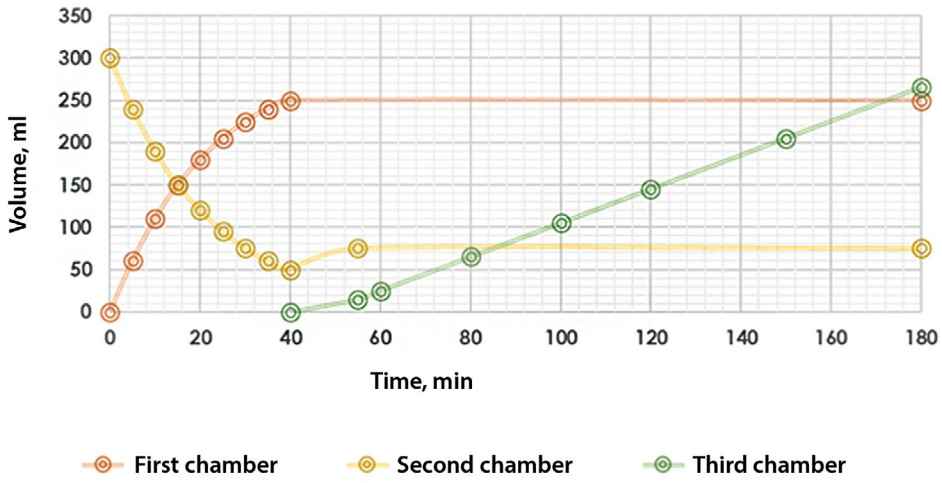


**Figure 5.** **Diagram of the volume in different time point**

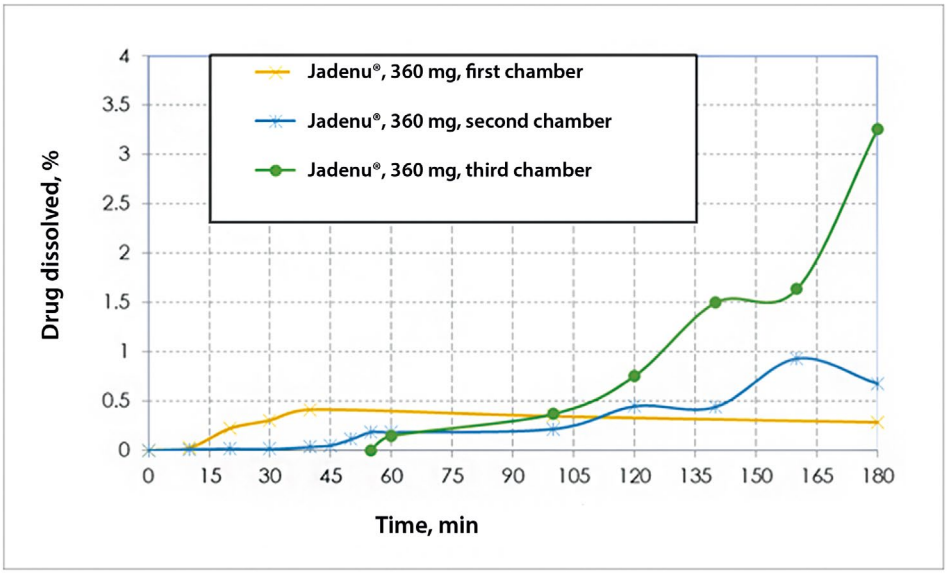


**Figure 6. Average dissolution profiles of deferasirox in "Jadenu®, film-coated tablets, 360 mg" (batch WTN22) in three chambers**

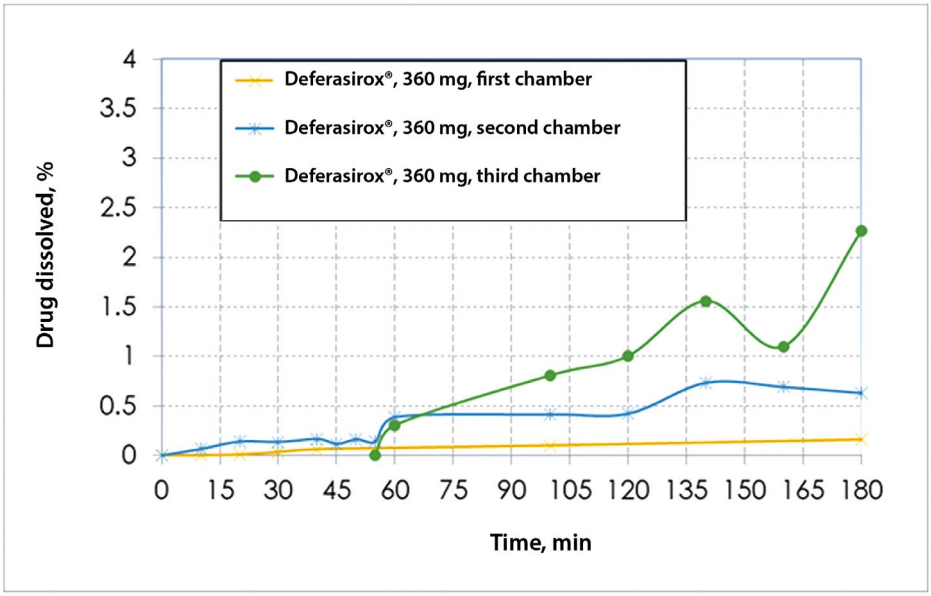


**Figure 7. Average dissolution profiles of deferasirox in "Deferasirox, film-coated tablets, 360 mg" in three chambers**

Developing the PBPK model of Deferasirox, we used data on the drug release rate obtained in the conducted PRT, literature data on physicochemical and biological properties of the compound under study (Table 1), and data on the pharmacokinetics of Deferasirox in the human organism.

As the aim of our work was to carry out an *in vitro* comparative pharmacokinetic and bioequivalence study of Deferasirox, the pharmacokinetics curves were not built for one virtual subject, but for a whole virtual population, which maximizes the model's relevance to real clinical trials. The virtual population consisted of white individuals aged 18 to 50, with height of 168 to 190 cm and weight from 55 to 85 kg; half of the population were women. The virtual mode of administration of the drug was as follows: a single administration of one 360 mg tablet of Deferasirox in the fasted state.

**Table 1.** **Summary of parameters used in PBPK model**

| Parametr | Value |
|---|---|
| MW | 373.362 g/mol |
| Log P | 3,52 |
| Fraction unbound | 1 % |
| pKa | 4,57 |
| Dissolution at pH = 6.8 | 0.04 mg/ml |
| Metabolizing enzyme | UGT1A1 |
| Transport protein | BCRP, cMOAT |

After entering all the necessary data into the program, we obtained the pharmacokinetic profiles as shown in Figure 8. The black line in the figure shows the geometric mean concentration values for the drug "Jadenu®, film-coated tablets, 360 mg» (Novartis Pharma Stein AG, Switzerland), and the red line represents the corresponding values for the drug "Deferasirox, film-coated tablets, 360 mg" of domestic origin. The pharmacokinetic profiles obtained in clinical trials are shown in Figure 9.

Table 2 shows the ratios of the geometric mean values of pharmacokinetic parameters for the drug under study to the corresponding values for the reference drug, and the calculated prediction error.

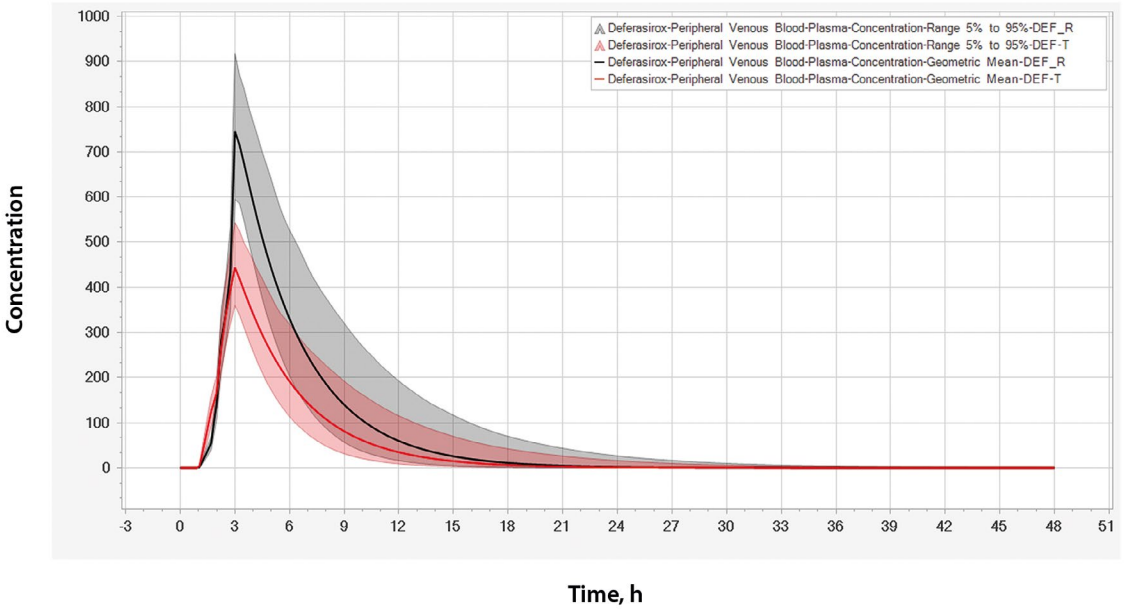


**Figure 8.** **Modeled pharmacokinetic profiles for study drugs**

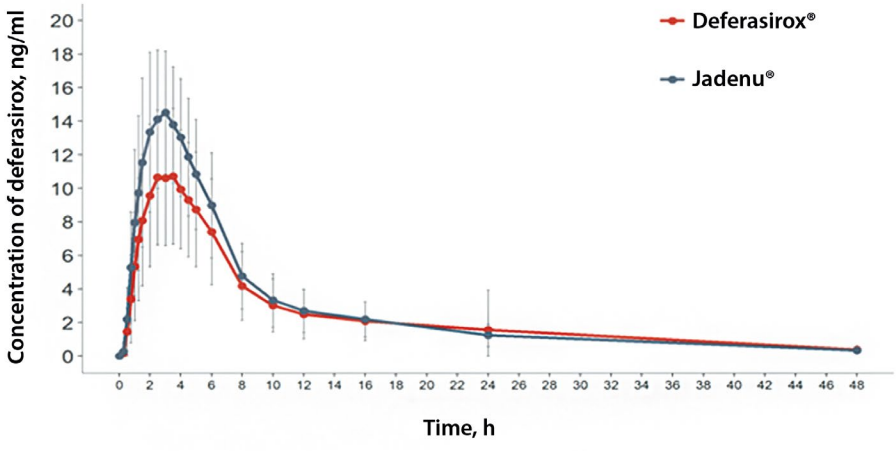


**Figure 9.** **Pharmacokinetic profiles for the study drugs obtained in the context of clinical trials**

The pattern of pharmacokinetic profiles of the drugs Jadenu and Deferasirox is the same in both the graphs obtained during clinical trials and the graphs obtained in the modeling.

Of further interest is the refinement of the PRT study methodology to reduce the prediction error in pharmacokinetic profiles modeling.

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

| Parametr | Data from clinical trials | Data from the simulation | Prediction error (PE) for geometric mean ratio T/R, % |
|---|---|---|---|
| $AUC_{0-t}$ | 0,85 | 0,63 | –34,9 |
| $C_{max}$ | 0,74 | 0,60 | –23,3 |

## CONCLUSION

A procedure for a physiologically relevant test of a drug with an active substance of BCS Class II was developed. The quantification of Deferasirox content in the samples was carried out by HPLC-UV method. The profiles of dissolution of Deferasirox were obtained which, in combination with data on the physicochemical properties of the compound under investigation and literature data on the pharmacokinetics of Deferasirox, provided the basis for a physiologically based pharmacokinetic model. The pharmacokinetic profiles obtained in simulation tests on a virtual population are similar to the data obtained in clinical studies.

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