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Reciprocal Impact of Molnupiravir and Favipiravir Monocomponents of the Combination Drug on Each Other's Pharmacokinetics in a Phase I Clinical Trial

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Abstract

Introduction. COVID-19 (Coronavirus disease 2019) almost 4 years after he start of the pandemic is still a significant public health problem. SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) that causes COVID-19 continues to mutate and spread throughout the world. Molnupiravir and favipiravir have been shown to be efficacious against variety of RNA viruses including the SARS-CoV-2. The Ministry of Health of the Russian Federation approved the use of these drugs as a treatment of COVID-19. The developed drug contains the combination of two antiviral agents with different mechanisms of suppressing viral RNA replication, which suggests efficacy against the vast majority of ARVI pathogens found in the human population including SARS-CoV-2 and influenza.

Aim. The aim of the pharmacokinetics study is comparison between JTBC00301 (INN: molnupiravir + favipiravir), film-coated tablets (LLC "PROMOMED RUS", Russia), Esperavir® (INN: molnupiravir), capsules (LLC "PROMOMED RUS", Russia) and Areplivir® (INN: favipiravir), film-coated tablets (LLC "PROMOMED RUS", Russia) to evaluate the impact of monocomponents on each other's pharmacokinetics.

Materials and methods. The clinical and analytical phases as well as pharmacokinetic analyses have been performed as a part of a phase I, randomized, open-label, 3-period crossover study of drug JTBC00301 (INN: molnupiravir + favipiravir), film-coated tablets, 400 + 400 mg (LLC "PROMOMED RUS", Russia). The plasma concentration of β-D-N4-hydroxycytidine (NHC), the active metabolite of molnupiravir and favipiravir were determined in 42 healthy volunteers after taking the test drug JTBC00301 (1 tablet of 400 + 400 mg), the reference drug Esperavir® (2 capsules of 200 mg) and the reference drug Areplivir® (2 tablets of 200 mg). The descriptive statistics were calculated using Microsoft Excel (Microsoft Corporation, USA). The pharmacokinetic parameters, analysis of variance (ANOVA), the intra-subject coefficient of variation (CVintra) and 90 % confidence intervals (90 % CI) were calculated by R Project 3.5.1 software (package «bear», version 2.8.3-2), originally created by Hsin-ya Lee and Yung-jin Lee, Taiwan.

Results and discussion. Pharmacokinetic parameters of NHC and favipiravir were determined, averaged pharmacokinetic profiles in linear and log-linear scales were plotted, analysis of variance was carried out. The 90% CIs for geometric mean ratios of C_{max} and $AUC_{(0-t)}$ for NHC and favipiravir were all within the acceptance range of 80–125 % which means there is no effect of monocomponents on each other's pharmacokinetics.

Conclusion. The development of the fixed-dose drug combination of molnupiravir and favipiravir has great potential as it may allow to increase the safety profile and improve the tolerability of therapy as well as increase the effectiveness of antiviral therapy. The results justified the study of the subsequent phases of clinical trials of JTBC00301 (INN: molnupiravir + favipiravir), film-coated tablets, 400 + 400 mg (LLC "PROMOMED RUS", Russia).

Keywords: molnupiravir, favipiravir, COVID-19, pharmacokinetics

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. Timofey N. Komarov, Olga A. Archakova participated in the clinical phase of the study. Natalia S. Bagaeva and Kseniia K. Karnakova carried out statistical processing of the obtained results. Maria O. Popova, Victoria S. Shcherbakova, Kira Ya. Zaslavskaya, Petr A. Bely and Igor E. Shohin carried out the organization of work in this direction. All the above authors participated in the discussion of the results in the format of scientific discussion.

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Оценка взаимного влияния монокомпонентов комбинированного лекарственного препарата, содержащего молнупиравир и фавипиравир, на фармакокинетику в рамках фазы I клинического исследования

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Резюме

Введение. Коронавирусная инфекция, спустя почти 4 года после начала пандемии, по-прежнему остается важной глобальной проблемой здравоохранения. Вирус SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) продолжает мутировать и распространяться по всему миру, что сохраняет потребность в препаратах для лечения коронавирусной инфекции. Молнупиравир и фавипиравир – лекарственные средства с прямым противовирусным действием в отношении РНК содержащих вирусов – рекомендованы Министерством здравоохранения Российской Федерации для включения в схемы лечения COVID-19 (Coronavirus Disease 2019). Разработанный препарат содержит комбинацию двух противовирусных средств с разными механизмами подавления репликации РНК вирусов, что позволяет предполагать эффективность в отношении преобладающего большинства возбудителей ОРВИ, встречающихся в человеческой популяции, включая SARS-CoV-2, и гриппа.

Цель. Целью исследования является изучение фармакокинетики препарата JTBC00301, таблетки, покрытые пленочной оболочкой (ООО «ПРОМОМЕД РУС», Россия) в сравнении с препаратами Эсперавир® (МНН: молнупиравир), капсулы (ООО «ПРОМОМЕД РУС», Россия) и Арепливир® (МНН: фавипиравир), таблетки, покрытые пленочной оболочкой (ООО «ПРОМОМЕД РУС», Россия) с последующей проверкой гипотезы влияния монокомпонентов препарата на фармакокинетику друг друга.

Материалы и методы. В рамках открытого рандомизированного перекрестного трехпериодного клинического исследования I фазы по изучению препарата JTBC00301, таблетки, покрытые пленочной оболочкой, 400 + 400 мг (ООО «ПРОМОМЕД РУС», Россия) проводились клинический и аналитический этапы исследования, изучение фармакокинетики и статистический анализ результатов. В исследовании определялась концентрация основного метаболита молнупиравира β-D-N4-гидроксицитидина (NHC) и фавипиравира в плазме крови 42 здоровых добровольцев после приема дозы 400 + 400 мг исследуемого препарата JTBC00301 (1 таблетка), дозы 400 мг первого препарата сравнения Эсперавир® (2 капсулы по 200 мг) и дозы 400 мг второго препарата сравнения Арепливир® (2 таблетки по 200 мг). Расчет параметров описательной статистики проводился при помощи пакета Microsoft Excel (Microsoft Corporation, США). Расчет фармакокинетических параметров, дисперсионный анализ, вычисление 90%-х доверительных интервалов и коэффициентов внутрииндивидуальной вариации проводились при помощи программного обеспечения R Project (версия 3.5.1, разработчики R Core Team, Австрия) с расширением «bear» (версия 2.8.3-2, разработчики Hsin-ya Lee и Yung-jin Lee, Тайвань).

Результаты и обсуждение. По полученным значениям концентраций NHC и фавипиравира были рассчитаны значения фармакокинетических параметров, построены усредненные фармакокинетические профили в линейных и полулогарифмических координатах, проведен дисперсионный анализ. 90%-е доверительные интервалы для отношения средних значений C_{max} и $AUC_{(0-t)}$ NHC и фавипиравира находились в пределах 80,00–125,00 %, что позволило признать гипотезу об отсутствии влияния монокомпонентов препарата на фармакокинетику друг друга.

Заключение. Разработка лекарственного препарата на основе фиксированной комбинации «молнупиравир + фавипиравир» обладает большим потенциалом, так как может повысить профиль безопасности и улучшить переносимость терапии, а также способствовать увеличению эффективности противовирусной терапии. Полученные результаты определили возможность осуществить переход к последующим фазам клинических исследований препарата JTBC00301, таблетки, покрытые пленочной оболочкой, 400 + 400 мг (ООО «ПРОМОМЕД РУС», Россия).

Ключевые слова: молнупиравир, фавипиравир, COVID-19, фармакокинетика

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

Вклад авторов. Т. Н. Комаров, О. А. Арчакова участвовали в проведении аналитического этапа исследования. Н. С. Багаева, К. К. Карнакова проводили статистическую обработку данных и расчет фармакокинетических параметров. М. О. Попова, В. С. Щербакова, К. Я. Заславская, П. А. Белый, И. Е. Шохин отвечали за организационную часть исследования. Все вышеуказанные авторы участвовали в обсуждении полученных результатов в форме научной дискуссии.

Финансирование. Клиническое исследование спонсировалось ООО «ПРОМОМЕД РУС». В. С. Щербакова, К. Я. Заславская и П. А. Белый являются представителями данной компании.

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INTRODUCTION

The SARS-CoV-2 infection (severe acute respiratory syndrome coronavirus 2), virus from the *Coronaviridae* family was recorded in December 2019 in China. A new infectious disease, called Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO)[1], has spread rapidly around the world and caused a pandemic [1–6].

In May 2023, the WHO Director-General[2] declared the end of the COVID-19 public health emergency. Despite this, the coronavirus infection, almost 4 years after the start of the pandemic, is still an important global health problem. The SARS-CoV-2 virus continues to mutate and spread in all countries, which continues the need for drugs to treat the coronavirus infection [7–9].

Recently, due to the increased availability of diagnostic and treatment tools, as well as the formation of population immunity against COVID-19 as a result of vaccination or past infection, there has been a significant decrease in the impact of coronavirus infection[3]. Despite a clear trend of decreasing mortality and hospitalization rates, deaths from the coronavirus infection are still recorded around the world. Moreover, the significant number of people with the past coronavirus infection have sequalae after the disease, experiencing health problems for many months [10]. It is important to continue studies of approved drugs for the treatment of COVID-19, as well as to develop new drugs that promote reducing the intensity of the virus spread and may be widely used[4] [9, 11].

Molnupiravir and favipiravir are drugs with a direct antiviral action against SARS-CoV-2 and other RNA-containing viruses [12–17]. Molnupiravir and favipiravir are recommended by the Ministry of Health of the Russian Federation for inclusion in COVID-19 treatment regimens[5]. Both molnupiravir and favipiravir have high oral bioavailability [18–21].

The developed drug contains a combination of two antiviral drugs with different mechanisms for suppressing viral RNA replication, which suggests efficacy against the vast majority of ARVI pathogens found in the human population, including SARS-CoV-2, and influenza.

MATERIALS AND METHODS

The clinical, analytical stages of the study, the study of pharmacokinetic parameters were carried out within the phase I clinical trial "Open randomized crossover comparative study of the pharmacokinetics, safety and tolerability of drug JTBC00301 (LLC "PROMOMED RUS", Russia) involving healthy volunteers" to investigate the combined drug JTBC00301 containing molnupiravir and favipiravir, film-coated tablets, 400 + 400 mg (LLC "PROMOMED RUS", Russia) (hereinafter referred to as JTBC00301). This study was approved by the Ministry of Health of the Russian Federation RKI № 309 dated 25.04.2022, protocol № MLF-022022[6].

The study determined the plasma concentrations of the major metabolite molnupiravir β-D-N4-hydroxycytidine (hereinafter NHC) and favipiravir after receiving in a fasted condition a dose of 400 + 400 mg (1 tablet) of the study drug JTBC00301, a dose of 400 mg (2 capsules of 200 mg) of the comparator Esperavir® (INN: molnupiravir), a capsule of 400 mg (LLC "PROMOMED RUS", Russia) (hereinafter referred to as Esperavir®), or a dose of 400 mg (2 tablets of 200 mg) of the comparator drug Areplivir® (INN: Favipiravir), film-coated tablets, 400 mg (LLC "PROMOMED RUS", Russia) (hereinafter referred to as Areplivir®).

[1] Timeline of WHO actions to combat COVID-19. Available at: Available at: https://www.who.int/ru/news-room/detail/29-06-2020-covidtimeline. Accessed: 16.10.2023.

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[3] Right there.

[4] Right there.

[5] Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 18 (26.10.2023)". Available at: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/064/610/original/BMP_COVID-19_V18.pdf. Accessed: 27.10.2023.

[6] GRLS – Ministry of Health of the Russian Federation: Register of permits for clinical trials 309. Available at: https://grls.rosminzdrav.ru/CIPermissionMini.aspx?CIStatementGUID=a480039d-7d34-4f8d-83fe-bf0c7bfc5d68&CIPermGUID=8b99d5fb-a60a-46b8-b5db-150478b658cc. Accessed: 27.10.2023.

Clinical stage of the study

The sample of volunteers consisted of 42 healthy men aged 18 to 45 years who met the inclusion criteria of the clinical study. Subjects were randomized into three groups of 14 persons.

Volunteers had a cubital heparinized catheter inserted for 13 hours. After removal of the catheter, blood sampling was carried out by venipuncture. After the catheter insertion, a zero blood sample was taken (5–10 minutes before dosing). Further sampling was carried out after 0.5 hours; 0.75 h; 1 hour; 1.25 hours; 1.5 hours; 1.75 hours; 2 hours; 2.25 hours; 2.5 hours; 3 hours; 3.5 hours; 4 hours; 6 hours; 8 hours; 10 hours; 12 hours; 24 hours after taking the drug. The washout period between doses of the studied drugs was 7 days.

Blood samples were taken into tubes containing the anticoagulant K_2EDTA and centrifuged at 3000 rpm for 10 minutes at a temperature of +4 °C. The obtained plasma was divided for each substance to be detected into an aliquot for analysis and an aliquot for repeated analyses in pre-labeled cryotubes, which were frozen and stored at a temperature not exceeding –35 °C, not higher than –35 °C.

Analytical stage of the study

A detailed description of the method of quantitative determination of the studied active substances in human blood plasma by the HPLC-MS/MS method and its validation are given in the article [11].

Statistical data processing and pharmacokinetic analysis

The values of NHC and favipiravir concentrations in human blood plasma over time, obtained during the analytical stage of the study, were characterized by the following pharmacokinetic parameters:

- ✓ C_{max} – the maximum concentration of the drug substance;
- ✓ t_{max} – the time to reach the maximum concentration of the drug substance;
- ✓ $AUC_{(0-t)}$ – the area under the concentration-time curve from the dosing to the last detectable concentration at time point *t*;
- ✓ $AUC_{(0-\infty)}$ – the area under the concentration-time curve from the dosing to infinity;
- ✓ k_{el} – the constant of the rate of terminal elimination of a drug substance;
- ✓ $t_{1/2}$ – is the half-life of the drug;
- ✓ $AUC_{(0-t)}/AUC_{(0-\infty)}$ – the ratio of the area under the concentration-time curve from the dosing to the last detectable concentration at time point *t* to the value of the area under the concentration-time curve from the dosing to infinity;
- ✓ $AUC_{(t-\infty)}$ – the extrapolated area under the concentration-time curve.

After logarithming the values of pharmacokinetic parameters, an analysis of variance (hereinafter referred to as ANOVA) was carried out at a given level of significance $\alpha = 0{,}05$. A general linear model procedure was used with fixed factors contributing to the observed data variation: drug, dosing sequence, volunteer pre-set to the "dosing sequence" factor (hereinafter referred to as volunteer * dosing sequence), period.

Based on the results of the analysis of variance, 90% confidence intervals were calculated, which were inversely transformed, and the hypothesis of the effect of the monocomponents of the studied drug on the pharmacokinetics of each other was tested.

The null hypothesis was that the true ratio of the geometric mean of the study drug JTBC00301 to the geometric mean of comparator Esperavir®/Areplivir® for $AUC_{(0-t)}$ and C_{max} of less than 80.00 % or greater than 125.00 %, i.e., the monocomponents of the drug affect each other's pharmacokinetics. An alternative hypothesis was that the true ratio of the geometric mean of the study drug JTBC00301 to the geometric mean of comparator Esperavir®/Areplivir® was in the range of 80.00–125.00 % for the pharmacokinetic parameters $AUC_{(0-t)}$ and C_{max}, i. e. the mono-components of the drug do not affect each other's pharmacokinetics.

The parameters of descriptive statistics were calculated using the Microsoft Excel package (Microsoft Corporation, USA). Pharmacokinetic parameters, ANOVA and 90 % confidence intervals were calculated using R Project software (version 3.5.1, developed by R Core Team) with the "bear" extension (version 2.8.3-2, developed by Hsin-ya Lee and Yung-jin Lee, Taiwan). Statistical analysis of the differences in the t_{max} parameter was carried out using the nonparametric Mann-Whitney U-test for independent samples (unconverted data, two-way test) using the R Project software (version 3.5.1, R Core Team developers) with

the "stats" extension (version 3.5.1, R Core Team developers), wilcox.test function, specified significance level α = 0,05).

RESULTS AND DISCUSSION

The pharmacokinetic analysis included data from 42 volunteers who took the study drug JTBC00301 (T), the comparators Esperavir® (R1) and Areplivir® (R2) and completed the study according to the Clinical Trial Protocol.

β-D-N4-hydroxycytidine (NHC)

The average values of the pharmacokinetic parameters of NHC after administration of JTBC00301 and Esperavir® are shown in Table 1. Averaged pharmacokinetic profiles in linear and semi-logarithmic coordinates with standard deviations at each time point for NHC are shown in Figures 1–2.

Table 1. Summary data of pharmacokinetic parameters

Pharmacokinetic parameter	β-D-N4-hydroxycytidine (NHC)	
	JTBC00301	Esperavir®
C_{max}, ng/mL	1830,99 (595,36) [42]	1677,30 (529,53) [42]
$AUC_{(0-t)}$, ng · h/mL	4531,77 (1288,30) [42]	4398,15 (1179,13) [42]
$AUC_{(0-\infty)}$, ng · h/mL	4708,33 (1284,50) [42]	4666,39 (1100,30) [40]
t_{max}, h	1,75 (0,75–3) [42]	1,5 (0,75–4) [42]
k_{el}, h^{-1}	0,607 (0,149) [42]	0,624 (0,153) [40]
$t_{1/2}$, h	1,26 (0,55) [42]	1,18 (0,33) [40]
$AUC_{(0-t)}/AUC_{(0-\infty)}$, %	95,96 (2,87) [42]	96,09 (2,09) [40]
$AUC_{(t-\infty)}$, %	4,04 (2,87) [42]	3,91 (2,08) [40]

Note. Parameters are expressed as Mean (SD) except for t_{max}, which is expressed as Median (Min – Max).

Mean – arithmetic mean, SD – standard deviation, Median – median, Min – minimum value, Max – maximum value, *n* – number of subjects for pharmacokinetic parameter calculation.

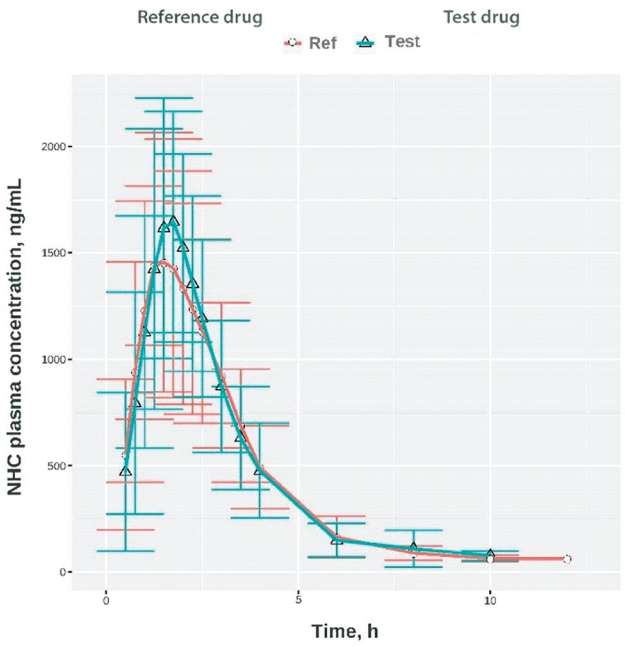

Figure 1. Average pharmacokinetic profiles of NHC (linear scale with standard deviations)

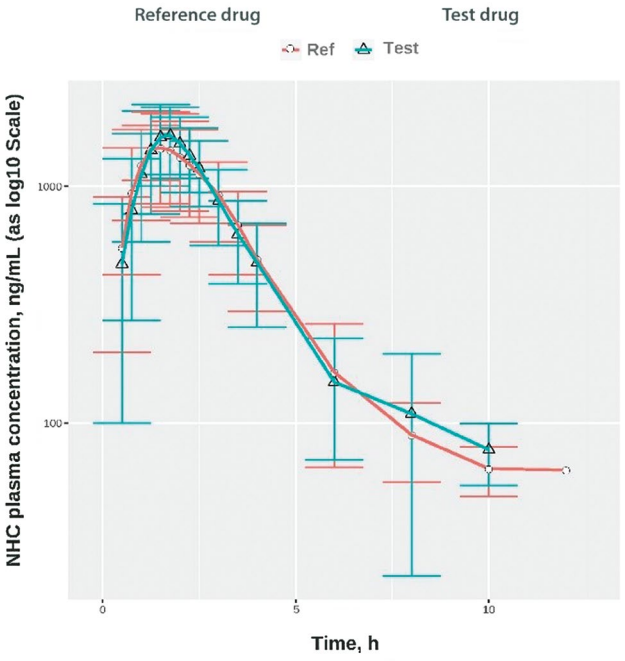

Figure 2. Average pharmacokinetic profiles of NHC (log-linear scale with standard deviations)

Differences in the pharmacokinetic parameter t_{max} between the study drug JTBC00301 and the comparator Esperavir® are not statistically significant ($p = 0.37$, Mann – Whitney U-test).

The results of the analysis of the pharmacokinetic parameters of NHC are given in Table 2. The results ha-

Table 2. **Analysis of variance results of NHC pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ [DF – Degrees of Freedom; SS – Sum of Squares; MS – Mean Squares]**

Parameter	Source of variation	DF	SS	MS	F-value	p-value	Significance
ln C_{max}	Sequence	1	0.045	0.045	0.343	0.56	Non-significant
	Period	1	0.123	0.123	1.940	0.17	Non-significant
	Drug	1	0.254	0.254	3.991	0.05	Non-significant
	Subject * Sequence	40	7.954	0.199	3.125	<0.05	Significant
	Residual	40	2.545	0.064			
ln $AUC_{(0-t)}$	Sequence	1	0.012	0.012	0.147	0.70	Non-significant
	Period	1	0.053	0.053	1.235	0.27	Non-significant
	Drug	1	0.046	0.046	1.084	0.30	Non-significant
	Subject * Sequence	40	4.965	0.124	2.916	<0.05	Significant
	Residual	40	1.703	0.043			

Note. For the factor "Sequence" Mean Square (MS) of "Subject * Sequence" factor is used as an error term.

ve allowed to accept the null hypothesis for the pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ that the differences in the mean values of the main pharmacokinetic parameters are not caused by differences between the compared drugs (except for the "volunteer * dosing sequence" factor).

The coefficients of intra-individual variation (CV_{intra}) of NHC obtained from the analysis of variance for the pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ were 25.63 and 20.85 %, respectively. The obtained confidence intervals lie in the range of 80.00–125.00 %, which has concluded that the monocomponents of the drug do not affect the pharmacokinetics of NHC (Table 5).

Favipiravir

The average values of the pharmacokinetic parameters of favipiravir after administration of JTBC00301 and Areplivir® are given in Table 3. Average pharmacokinetic profiles in linear and semi-logarithmic coordinates with standard deviations for favipiravir are shown in Figures 3–4.

The differences in the pharmacokinetic parameter t_{max} between the study drug JTBC00301 and the comparator Areplivir® are statistically significant ($p = 0{,}001$, Man – Whitney U-test).

Table 3. **Summary data of pharmacokinetic parameters**

Pharmacokinetic parameter	Favipiravir	
	JTBC00301	Areplivir®
C_{max}, ng/mL	9293,34 (2780,23) [42]	9938,70 (3013,34) [42]
$AUC_{(0-t)}$, ng · h/mL	31607,57 (20374,99) [42]	29812,25 (15162,05) [42]
$AUC_{(0-\infty)}$, ng · h/mL	34324,82 (23244,08) [42]	31386,51 (16222,25) [42]
t_{max}, h	1,13 (0,5 – 3,5) [42]	0,75 (0,5 – 2) [42]
k_{el}, h^{-1}	0,396 (0,150) [42]	0,398 (0,127) [42]
$t_{1/2}$, h	2,18 (1,33) [42]	1,93 (0,63) [42]
$AUC_{(0-t)}/AUC_{(0-\infty)}$, %	93,75 (6,13) [42]	95,09 (1,82) [42]
$AUC_{(t-\infty)}$, %	6,25 (6,13) [42]	4,92 (1,82) [42]

Note. Parameters are expressed as Mean (SD) except for t_{max}, which is expressed as Median (Min – Max).

Mean – arithmetic mean, SD – standard deviation, Median – median, Min – minimum value, Max – maximum value, *n* – number of subjects for pharmacokinetic parameter calculation.

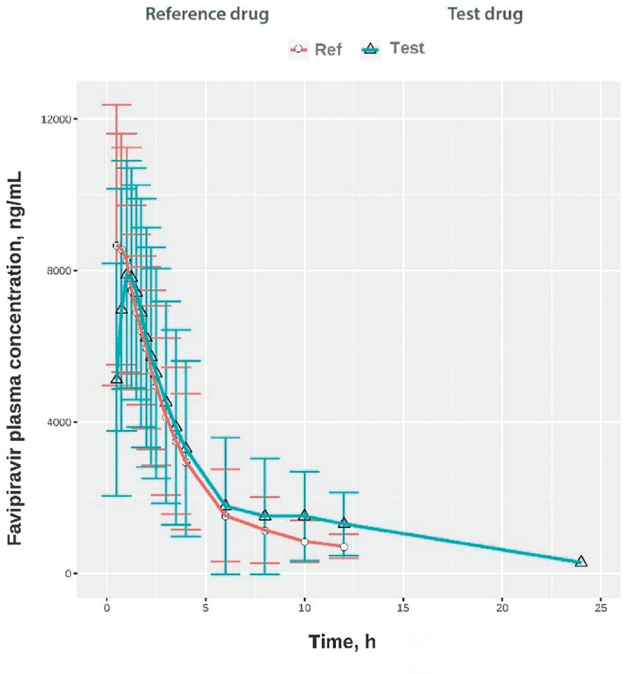

Figure 3. Average pharmacokinetic profiles of favipiravir (linear scale with standard deviations)

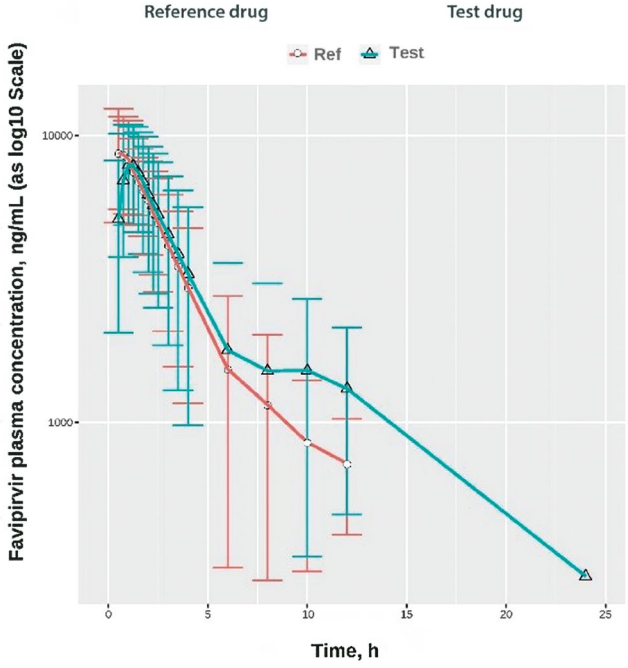

Figure 4. Average pharmacokinetic profiles of favipiravir (log-linear scale with standard deviations)

The results of the analysis of pharmacokinetic parameters of favipiravir are given in Table 4. The results obtained have allowed to accept the null hypothesis for the pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ that the differences in the mean values of the main pharmacokinetic parameters are not caused by differences between the compared drugs only for the "Period" factor for the pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$, as well as for the "Drug" factor for the pharmacokinetic parameter $AUC_{(0-t)}$.

Table 4. Analysis of variance results of favipiravir pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ [DF – degrees of freedom; SS – Sum of Squares; MS – Mean Squares]

Parameter	Source of variation	DF	SS	MS	F-value	p-value	Significance
ln C_{max}	Sequence	1	1,875	1,875	28,390	<0,05	Significant
	Period	1	0,064	0,064	1,563	0,22	Non-significant
	Drug	1	0,187	0,186	4,575	<0,05	Significant
	Subject * Sequence	40	3,536	0,088	2,169	<0,05	Significant
	Residual	40	1,630	0,041			
ln $AUC_{(0-t)}$	Sequence	1	4,297	4,297	22,630	<0,05	Significant
	Period	1	0,178	0,178	3,115	0,09	Non-significant
	Drug	1	0,005	0,005	0,082	0,78	Non-significant
	Subject * Sequence	40	13,104	0,328	5,734	<0,05	Significant
	Residual	40	2,285	0,057			

Note. For the factor "Sequence" Mean Square (MS) of "Subject * Sequence" factor is used as an error term.

The coefficients of intra-individual variation (CV_{intra}) of favipiravir for the pharmacokinetic parameters C_{max} and AUC_{0-t} were 20.40 and 24.35%, respectively. The obtained confidence intervals lie in the range of 80.00–125.00%, which has concluded that the mono-components of the drug do not affect the pharmacokinetics of favipiravir (Table 5).

Table 5. Point estimate, 90 % confidence intervals of NHC and favipiravir pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$

Pharmacokinetic parameter	Point estimate, %	L-90, %	U-90, %
β-D-N4-hydroxycytidine (NHC)			
C_{max}	112.37	101.85	123.98
$AUC_{(0-t)}$	105.10	96.98	113.90
Favipiravir			
C_{max}	90.49	83.64	97.90
$AUC_{(0-t)}$	98.43	89.67	108.04

CONCLUSION

Based on the obtained values of pharmacokinetic parameters, average pharmacokinetic profiles were constructed, and an analysis of variance was carried out. The obtained confidence intervals for NHC and favipiravir allow us to recognize the hypothesis that the mono-components of the drug have no effect on each other's pharmacokinetics.

The development of a drug based on a fixed combination of molnupiravir + favipiravir has a great potential, as it can increase the safety profile and improve the tolerability of therapy, as well as contribute to increasing the efficacy of antiviral therapy.

The study results have determined the possibility of moving to the next phases of clinical trials of the drug JTBC00301, film-coated tablets, 400 + 400 mg (LLC "PROMOMED RUS", Russia).

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