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Single Dose, Two-way Crossover Bioequivalence Study of Favipiravir Tablet in Healthy Male Subjects

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Abstract

Background: As WHO expresses, coronavirus disease 2019 (COVID-19) is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 is now a pandemic affecting many countries globally. Antiviral agents play fundamental role in Covid-19 treatment. Favipiravir is one of the favored agents and it still draws attention of generic drug industry which is constitutional for drug accessibility.

Objective: The aim of this study is to demonstrate the bioequivalence of a new Favipiravir tablet formulation as compared to the reference tablet formulation in healthy male subjects under fasting conditions.To prove the bioequivalence, a randomised, single oral dose, cross-over, two-period study was carried out in 30 healthy subjects under fasting conditions. Plasma Favipiravir levels were quantified by using an in-house-developed high performance Liquid Chromatography Coupled to Tandem Mass Spectrometry (LC-MS/MS) method.

Results: The 90% CIs for the test/reference geometric mean ratios of the C_{max} and $AUC_{0\text{-tlast}}$ were 92.92 – 119.89% and 94.00 – 99.77%, respectively.

Conclusions: This single-dose study has shown that the test and reference Favipiravir products met the required bioequivalence criteria. Besides, both products were well tolerated and safe.

Key Words: *Favipiravir; Bioequivalence; Covid-19*

Introduction

Favipiravir was approved in Japan for use in the event of an outbreak of novel or re-emerging influenza viral infections, where other influenza antiviral drugs are either not or insufficiently effective. [1] Favipiravir is a new antiviral drug against influenza. Chemically, it is 6-Fluoro-3-hydroxypyrazine-2-carboxamide and its molecular formula is $C_5H_4FN_3O_2$. Favipiravir is a white to light yellow powder. It is sparingly soluble in acetonitrile and in methanol, and slightly soluble in water and in ethanol.

Favipravir is metabolized into favipiravir ribosyl triphosphate (favipiravir RTP) by an intracellular enzyme, and favipiravir RTP selectively inhibits RNA polymerase (RNA-dependent RNA polymerase) of the influenza virus, preventing replication of the influenza virus. The mechanism of action of favipiravir is the selective inhibition of RNA polymerase by favipiravir ribosyl triphosphate formed by cellular enzymes in the influenza virus leading to antiviral activity. Following oral administration favipiravir reaches peak plasma concentrations in approximately 0.5 hours. After a single 200 mg dose of oral favipiravir tablet to Japanese healty volunteers C_{max} and $AUC_{0\text{-tlast}}$ were 8.39 µg/ml and 19.67 µg.h/ml respectively. The C_{max} of favipiravir was linear in the dose range from 30 to 1200 mg, while the AUC values at the dose of ≥600 mg remained higher than the value expected from the dose-proportional relationship. It is reported that the pharmacokinetics in the dose range in which the pharmacokinetic profiles were linear were compared between healthy adult subjects in Japan and the US (when the doses were normalized on the basis of a body weight of 60 kg). Favipiravir is 53.4%-54.4% bound to plasma proteins. The elimination of favipiravir largely depends via renal excretion with a mean plasma elimination half-life ($t_{½}$) of 1.5 hours. [2]

Favipiravir is efficacious in multiple types of Influenza viruses, regardless of sensitive or resistant to existing anti-influenza drugs. Of specific note is that favipiravir is active against a wide range of other RNA viruses *in vitro* and *in vivo*. In vitro studies indicate no emergence of resistance to favipiravir. [3] Although there is no specific treatment against the Covid-19 pandemic caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several drugs, including favipiravir, have been used in patients. [4] There are several clinical trials on potential antiviral therapies taking place. The therapies can be divided into two categories depending on their target. One is acting on the coronavirus directly, either by inhibiting crucial viral enzyme responsible for genome replication, or by blocking viral entry to human cells. The other is designed to modulate the human immune system, either by boosting the innate response, which has a particularly important role against viruses, or by inhibiting the inflammatory processes that cause lung injury. Most of these drugs were originally designed for other pathogens and were promptly repurposed for the current COVID-19 trials. [5] In an open-label comparative controlled study of patients with Covid-19, those treated with favipiravir apeared to have faster viral clearance and higher rates of improvement in chest imaging, and in another prospective, randomized, controlled, open-label multicenter trial favipiravir significantly improved the latency to relief for pyrexia and cough. [6,7]

The bioequivalence study is required for generic orally administered Favipiravir products by certain regulatory authorities. [8,9] Therefore, this study aims to compare the pharmacokinetic properties of a generic formulation to the reference product and to demonstrate the bioequivalence of the products with respect to the rate and extent of absorption of Favipiravir in healthy male subjects under fasting conditions.

Methods

Ethical statement

This study was conducted at FARMAGEN-Good Clinical Practice Center, Gaziantep, Turkey according to the regulations run by Ministry of Health of the Republic of Turkey which are in compliance with Declaration of Helsinki and Good Clinical Principles (GCP). [10] The protocol and informed consent form were approved by an independent ethics committee (Erciyes University, Bioavailability-Bioequivalence Research Ethics Commitee, Kayseri, Turkey, Approval Date: 30.04.2020) and Turkish Medicines and Medical Devices Agency (Approval Date: 04.05.2020). All subjects voluntarily provided signed informed consent before participation in the study. The trial is registered at ClinicalTrials.gov with the identifier NCT04406194.

Study population

All subjects are adult males (aged 20-40 years) with normal weight according to the a body mass index BMI. The subjects who have atopic constitution or asthma and/or known allergy for Favipiravir and/or any of the excipients of the products and who have any history or presence of clinical relevance of cardiovascular, neurological, musculoskeletal, haematological, hepatic, gastrointestinal, renal, pulmonary, endocrinological, metabolism were excluded from the study. The inclusion and exclusion criteria were established clearly together with the reasons for withdrawal from the study. The subjects who were willing to participate in the clinical trial signed the informed consent form on their own freewill and understood that they could withdraw from the study anytime without specifying any reason.

Study design

A single centre, open-label, randomised, single oral dose, cross-over, two-sequence, two-period study was conducted in 30 healthy, Caucasian, adult, male, human subjects under fasting conditions.

This study was conducted at FARMAGEN-Good Clinical Practice Center, Gaziantep, Turkey. The clinical study Spanned a period of approximately 9 days including prestudy screening, isolation period (5 days), wash-out period (48 hours) and final examination. The standard laboratory examinations in blood and urine were done consistent with the study protocol and the volunteers were checked for presence of HBsAg, HCV-Ab and HIV-Ab in serum. Also Covid-19 PCR tests were applied to the volunteers before isolation period and hospitalization. They were requested to provide a urine sample for a drug screen which include "amphetamines, cannabinoids, benzodiazepines, cocaine, opioids and barbiturates" and an alcohol breath test on entry examinations. All laboratory tests were carried out in a certified local laboratory.

Depending on the suitability of the volunteers clinical examination and laboratory results, isolation period was provided for 4 nights in single rooms reserved and it was important that the volunteers participating in the study do not come into contact with each other during the isolation and that the rules of isolation were followed due to Covid-19 Pandemic. After isolation period volunteers were transferred to vlinical center depending on negative Covid-19 PCR tests done once more.

A total of 30 subjects have been randomised and 29 subjects completed the clinical study. 10-hour fasted subjects were not allowed to drink water from 1h before until 1h after the administration of study products, except while dosing and they remained fasted until 4 hours after administration. Immediately after pre-dose sampling, 1 tablet of the test drug or 1 tablet of the reference drug (200 mg Favipiravir each case), were taken by the subjects with 240 mL of water. After the washout period (approximately 48 hours); in Period II, the subjects were administered the other drug they did not take in the Period I. The same procedures were applied in each period.

Investigational medicinal products

The test drug used was Favicovir 200 mg Film Tablet, Atabay Kimya San. ve Tic. A.Ş.-Turkey (Batch No: FATA-P01; Expiration Date: 03.2022); the reference drug used was Avigan 200 mg Film Tablet, Toyama Chemical Industry Co.Ltd.-Japan (Batch No: FG1881; Expiration Date: 07.2028).

Blood sampling and study assessment

The samples were drawn by a short intravenous catheter at predose and at 0.17, 0.25, 0.50, 0.75, 1.00, 1.33, 1.66, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 14.00,and 24.00 hours post-dose in each clinical study period, and they were collected into polypropylene tubes using K_2 EDTA as anti-coagulating agent.

Volunteers were hospitalized at FARMAGEN-Good Clinical Practice Center after isolation period during the clinical study. An evening meal was provided at hospitalization days (total caloric value of approximately 1200 kcal during study period. On medication days, a standard lunch (total caloric value is approximately 1200 kcal) was provided 4 hours after dosing, and a standard evening meal (total caloric value is approximately 1200 kcal) was provided 10 hours after dosing in each period Also standard light breakfast was provided in the evenings during hospitalization.

The blood samples were taken by a short intravenous catheter and they were collected into polypropylene tubes using K_2 EDTA as anti-coagulating agent. After sampling, the samples were immediately refrigerated at approximately 2-8°C and will remain there for not more than 30 minutes. Following the centrifugation (3.000 rpm, 4-6°C, 10 min), the separated plasma from each sample were transferred into two 3 mL transparent, polypropylene tubes. All the aliquoted plasma samples will be flash freezing immediately. The flash frozen samples (aliquoted plasma samples) were transferred to a deep-freezer and stored at -70°C until they were transported to the bioanalytical center.

Determination of favipiravir plasma concentrations

The bioanalytical phase of the study has been run at Novagenix Bioanalytical R&D Center, Ankara, Turkey. In order to avoid bias, the analytical studies were operated as analytically blinded.

Materıals and Methods

Chemicals

Reference; Favipiravir, was supplied from Kohn&Shawn Pharmatech Co., Ltd.,China., (Batch No: KSY34-22-20200415) and Internal Standard; [13C15N] Favipiravir (IS), was supplied from AlsaChim, (MJ-ALS-20-026-P2), France.

Solvents: Methanol and acetonitrile were supplied from Merck, Germany. Ultrapure (Type 1) Water was supplied from Milipore MilliQ Water Purification System; K2Edta Blank Human Plasma was supplied from Bioivt Laboratories International Ltd, UK.

Instrument and conditions

Shimadzu 8040 Tandem Mass Spectrometer (Shimadzu, Japan) was used equipped with electrospray ionization in the negative ion mode. Optimum seperation conditions were obtained with Shiseido Capcell PAK C18, 250 x 4.6 mm, 5 µm with mobile phase consisting of water and acetonitrile (15/85, v/v) with column oven temperature maintained at 30°C. Flow rate was 1.2 mL/min. The multiple reaction monitoring (MRM) transitions were performed at m/z 156.1>113.1 and 158.1>113 for favipiravir and [13C15N] Favipiravir, simultaneously. Total run time for the method was 3.5 min. The nebulizing gas and drying gas flow rates and the ESI voltage were 2.5 L/min, 15 L/min and 5500 V, respectively. The gas used for nebulizing and drying was high pure nitrogen generated by Peak Scientific NL-60. Shimadzu LabSolutions Software version 5.93 was used for data acquisition and evaluation of chromatographic data.

Preparation of standard and quality control (QC) samples

Stock standard solutions of Favipiravir were prepared in methanol at a concentration of 5 mg/mL. Working solutions in the concentration range of 1.6-600 µg/mL were prepared by diluting with methanol. The working IS was prepared in methanol at a concentration of 10 µg/mL. Stock solutions of Favipiravir and IS were stored at -20°C.

Calibration standards were prepared by spiking the appropriate amounts of standard solutions into blank plasma to obtain final concentration levels of 80, 160, 1000, 5000, 10000, 20000, 27000, 30000 ng/mL. The quality control samples were prepared similarly, at concentrations of 80, 240, 1500, 12000 and 24000 ng/mL. The lower limit of quantification (LLOQ), using 100 µL human plasma, was 80 ng/mL. Calibration standards and QC samples were stored at -70°C freezer until analysis.

Sample preparation

The protein precipitation was the preferred choice of seperation because of the minimized steps in extraction of drug from matrix. Aliquots of 100 µL plasma samples and 50 µL of IS (10 µg/mL) was added into 10 mL centrifuge tube and vortexed for 5s. The mixture was precipitated with 500 µL acetonitrile. After vortexing for 30s, the samples were centrifuged at 5500 rpm for 10 min. An aliquot of 5 µL of the supernatant was injected into the LC–MS/MS system for analysis.

Method validation

The method validation was performed with K_2EDTA human plasma according to European Medicines Agency Guideline on Bioanalytical Method Validation. [11] The method was validated for selectivity, specificity, carry-over, linearity, precision and accuracy, recovery, dilution integrity, influence of haemolysed and hyperlipidaemic plasma, drug-drug interaction, matrix effect and stabilities.

The analytical curves were constructed from a blank sample (plasma sample processed without IS), a zero sample (plasma processed with IS) and eight concentrations of Favipiravir, including the LLOQ, ranging from 80 to 30000 ng/mL. The concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using least squares regression analysis employing a weighted (1/x) linear (y=mx+b) for Favipiravir. The acceptance criteria for each calculated standard concentration was not more than 15% deviation from the nominal value, except for the LLOQ which was set at 20%. The within-batch precision and accuracy was evaluated by analyzing QC samples at five different concentration levels (80 ng/mL (LLOQ), 240 ng/mL (QC Low), 1500 ng/mL (QC Medium), 12000 ng/mL(QC High) and 24000 ng/mL (ULOQ)) with six replicates in a batch.The between-batch precision and accuracy were determined by analyzing three different batches. The within-batch and between-batch values did not exceed 15% for QC samples, expected for LLOQ which did not exceed 20%.

The selectivity was studied by checking the chromatograms obtained from eight different sources of human plasma including one haemolytic and one lipemic plasma. By comparing the chromatograms of those plasma samples spiked with Favipiravir and IS with the chromatograms of the blank plasma samples, no peak was found at the retention time of Favipiravir and IS in ten of the blank plasma samples.The recoveries were estimated by comparing the peak areas of Favipiravir in three replicates of QC samples with those of post-extraction blank matrix extracts at the corresponding concentrations. The matrix effects of Favipiravir were evaluated by comparing the peak areas of post-extraction blank plasma that were spiked at certain concentrations of QC samples with the areas obtained by the direct injection of the corresponding standard solutions. The stability of Favipiravir in the plasma samples was determined from three QC levels with six replicates each under the following conditions: Long-term stability at -70°C for 60 days, short-term stability at RT for 5h, using processed samples in

autosampler vials for 24h, and after four freeze/thaw cycles (-70 to RT).

An in-house high performance liquid chromatography with tandem mass spectrometry method (LC-MS/MS) was developed and validated to quantify Favipiravir in plasma.

The plasma samples were maintained at -70°C during the assay. 0.1 mL of thawed samples to room temperature were transferred in a polypropylene tube and were prepared for analysis using protein precipitation according to SOP of bioanalytical center.

Pharmacokinetic and statistical analyses

According to only one literature [2], the intra-subject coefficient of variation (ISCV) for maximum plasma concentration (C_{max}) was 17.0%. Since there was insufficient information for ISCV, sample size was chosen as 30 subjects in order to demonstrate bioequivalence for a 2x2 crossover design.

Cmax and area under the curve from time 0 to the last measurable concentration ($AUC_{0\text{-}tlast}$) were considered as the primary target variables; area under the curve from time 0 to the infinite time ($AUC_{0\text{-}\infty}$), time to reach the peak concentration (t_{max}), terminal half life ($t_{½}$), terminal disposition rate constant (λ_z) and mean residence time (MRT) were declared as the secondary target variables in this bioequivalence study.

C_{max} and t_{max} for Favipiravir were obtained directly by plasma concentration-time curves. $AUC_{0\text{-}tlast}$ was calculated using the linear-log trapezoidal rule. $AUC_{0\text{-}\infty}$ was calculated by summing $AUC_{0\text{-}tlast}$ and extrapolated area. The latter was determined by dividing the last measuredconcentration by λz which was estimated byregression of the terminal log-linear plasma concentration time points.

C_{max} and $AUC_{0\text{-}tlast}$ were tested for statistically significant differences by means of the Analysis of Variance (ANOVA) test procedure after logarithmic transformation (ln). The effects of ANOVA were treatment, period, sequence and subject within the sequence and tested at 5% level of significance.

In the assessment of bioequivalence, confidence intervals approach was used. The two one-sided hypotheses at the 5% level of significance were tested by constructing the 90% confidence intervals (90% CIs) for the geometric mean ratios of test/reference products. The two formulations were considered as bioequivalent if the 90% CIs were within 80.00-125.00% for C_{max} and $AUC_{0\text{-}tlast}$. Difference in tmax was evaluated non-parametrically using Mann–Whitney U test.

All statistical analysis were done using Phoenix WinNonlin (Version 8.1, Certara L.P.).

Also, ANOVA and determination of 90% CIs were applied to non-logaritmic transformed data of t_{max}, t1/2, λ_z and MRT and to ln transformed data of $AUC_{0\text{-}\infty}$.

Results

57 subjects were screened. 30 subjects were randomised and included into the study. The subjects were divided into two groups according to the randomisation table. There was one drop-out (Subject 05 didn't want to continue trial by his freewill at isolation days). As a result, 29 subjects completed the clinical phase of the study. All of the subjects were Caucasian. The mean ± SD age of subjects is 25.45 ± 3.86 years and the mean ± SD body mass index (BMI) was 26.12 ± 2.10. The demographic data of subjects are presented in Table 1. There was no protocol deviation through the clinical period.

n = 29	Age (year)	Weight (kg)	Height (cm)	Body mass index
Mean	25.45	79.52	174.45	26.12
SD	3.86	7.96	6.41	2.10
Minimum	20	68	161	23
Maximum	35	95	183	30
Range	15	27	22	7.3

Table 1: *Demographic data of the subjects.*

Actual time of sampling was used in the estimation of the pharmacokinetic parameters.

In period II, there was observed no pre-dose drug concentrations, which indicates that the washout period of 48 hours was sufficient.

The pharmacokinetic parameters for test and reference products are summarised in Table 2, the geometric least square means, ratios and 90% CIs are summarised in Table 3. Average plasma concentration-time curves and average ln plasma concentration-time curves of test and reference products for single dose of Favipiravir are displayed in Figure 1 and 2, respectively.

For Test and Reference products, the mean ± sd of C_{max} were found 5411.624 ± 2025.680 ng/mL and 5002.171 ± 1231.177 ng/mL, and the mean ± sd of $AUC_{0\text{-tlast}}$ were found 9641.989 ± 2545.142 hr.ng/mL and 9907.170 ± 2423.528 hr.ng/mL, respectively (Table 2).

The primary target variables data demonstrate the bioequivalence of test and reference products with regard to 90% CI for C_{max} of 92.92–119.89 and for $AUC_{0\text{-tlast}}$ of 94.00-99.77, which are within acceptance limits (80.00-125.00%). [4] The geometric mean ratios were found as 105.55% and 96.84% for C_{max} and $AUC_{0\text{-tlast}}$, respectively (Table 3).

For the secondary endpoint data, the median of t_{max} for Test and Reference product were found 0.50 hr and 0.75 hr, respectively and ranged from 0.17 hr to 1.66 hr for test product and 0.17 hr to 2.5 hr for reference product. Besides, the mean ± sd of $t_{1/2}$ for Test and Reference product were found 1.266 ± 0.251 hr (ranged from 0.867 hr to 1.998 hr) and 1.319 ± 0.245 hr (ranged from 0.907 hr to 2.072 hr), respectively. The mean ± sd of λ_z for Test and Reference product were 0.566 ± 0.099 1/hr (ranged from 0.347 1/hr to 0.799 1/hr) and 0.542 ± 0.094 1/hr (ranged from 0.334 1/hr to 0.764 1/hr), respectively (Table 2).

Test (n=29)						
Parameter (Units)	**Arithmetic Mean ± SD**	**Geometric Mean**	**Median**	**Minimum**	**Maximum**	**Range**
C_{max} (ng/mL)	5411.624 ± 2025.680	5110.196	4809.194	2844.214	11927.807	9083.593
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	9641.989 ± 2545.142	9352.910	9596.654	5174.504	18239.044	13064.540
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	9910.494 ± 2618.916	9615.660	9786.539	5309.145	18975.563	13666.418
t_{max} (hr)	0.50 (0.17-1.66)	0.526	0.500	0.170	1.660	1.490
$t_{1/2}$ (hr)	1.266 ± 0.251	1.244	1.185	0.867	1.998	1.131
λz (1/hr)	0.566 ± 0.099	0.557	0.585	0.347	0.799	0.452
MRT (hr)	2.105 ± 0.429	2.067	2.040	1.488	3.435	1.947
Reference (n=29)						
Parameter	Arithmetic Mean ± SD	Geometric Mean	Median	Minimum	Maximum	Range
C_{max} (ng/mL)	5002.171 ± 1231.177	4854.560	4975.216	2870.521	7632.102	4761.581
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	9907.170 ± 2423.528	9645.615	9736.880	6392.444	16822.614	10430.171
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	10152.115 ± 2507.694	9881.328	9910.111	6519.140	17585.898	11066.758
t_{max} (hr)	0.75 (0.17-2.5)	0.605	0.750	0.170	2.500	2.330
$t_{1/2}$ (hr)	1.319 ± 0.245	1.298	1.334	0.907	2.072	1.165
λz (1/hr)	0.542 ± 0.094	0.534	0.520	0.334	0.764	0.430
MRT (hr)	2.161 ± 0.428	2.125	2.087	1.514	3.601	2.087

Table 2: *The arithmetic mean ± sd, geometric mean, median, minimum, maximum and range of pharmacokinetic parameters of single oral dose of 200 mg Favipiravir in test drug (Favicovir 200 mg Film Tablet, Atabay Kimya San. ve Tic. A.Ş.-Turkey) and reference drug (Avigan 200 mg Film Tablet, Toyama Chemical Industry Co.Ltd.-Japan) in healthy adult male subjects under fasting conditions.*[a]

Parameter	Difference	DiffSE	TESTLSM	REFLSM	Ratio%	90% CI	ISCV%
$\ln(C_{max})$	0.0540	0.0748	8.5400	8.4860	1.0555	0.9292 - 1.1989	29.053
$\ln(AUC_{0\text{-tlast}})$	-0.0321	0.0175	9.1435	9.1756	0.9684	0.9400 - 0.9977	6.668
$\ln(AUC_{0\text{-}\infty})$	-0.0285	0.0171	9.1713	9.1998	0.9719	0.9440 - 1.0006	6.511
t_{max} (hr)	-0.1330	0.1090	0.6053	0.7383	0.8199	0.5685 - 1.0714	
t½ (hr)	-0.0541	0.0198	1.2654	1.3195	0.9590	0.9334 - 0.9846	
λ_z (1/hr)	0.0247	0.0081	0.5662	0.5415	1.0456	1.0202 - 1.0711	
MRT (hr)	-0.0636	0.0636	2.1018	2.1654	0.9706	0.9206 - 1.0207	

Table 3: *Geometric Least Square Means, Ratio and 90% Confidence Intervals of test drug (Favicovir 200 mg Film Tablet, Atabay Kimya San. ve Tic. A.Ş.-Turkey) and reference drug (Avigan 200 mg Film Tablet, Toyama Chemical Industry Co.Ltd.-Japan) in healthy adult male subjects under fasting conditions*

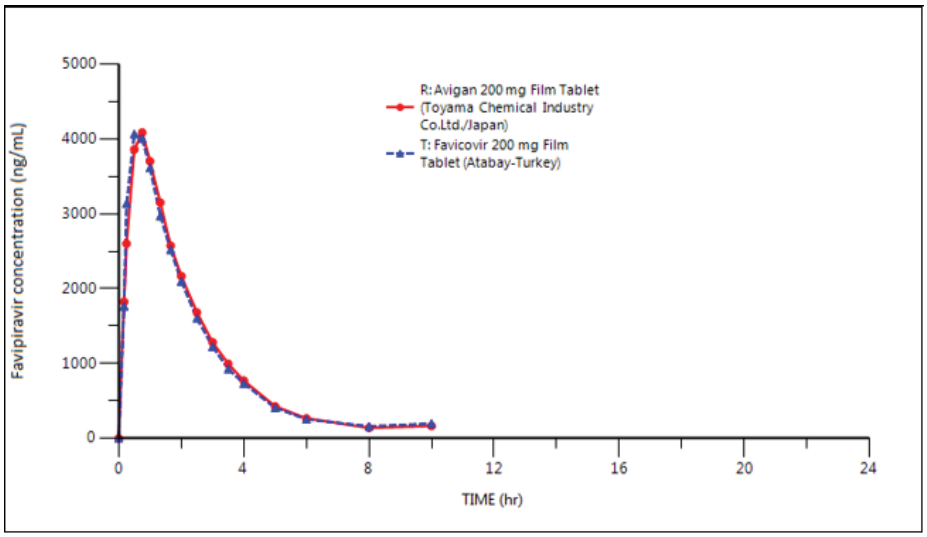

Figure 1: *Mean plasma concentration-time curves after a single dose of a test drug (Favicovir 200 mg Film Tablet, Atabay Kimya San. ve Tic. A.Ş.-Turkey) and a reference drug (Avigan 200 mg Film Tablet, Toyama Chemical Industry Co.Ltd.-Japan) of oral Favipiravir in healthy adult male subjects (n = 29) under fasting conditions.*

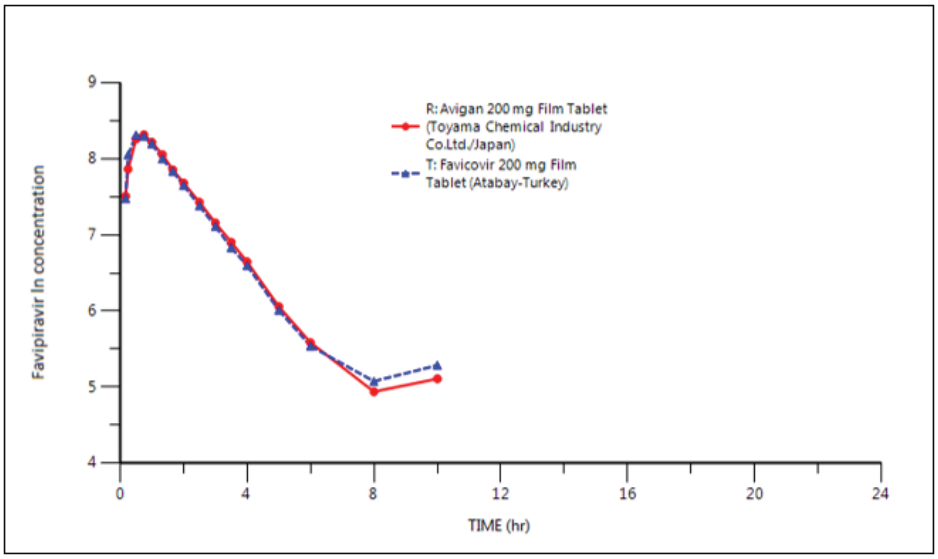

Figure 2: *Average ln plasma concentration curves of Favipiravir after a single dose of a test drug (Favicovir 200 mg Film Tablet, Atabay Kimya San. ve Tic. A.Ş.-Turkey) and a reference drug (Avigan 200 mg Film Tablet, Toyama Chemical Industry Co.Ltd.-Japan) of oral Favipiravir in healthy adult male subjects (n = 29) under fasting conditions.*

Safety and tolerability

No adverse event occurred in all two periods. The overall tolerability of the products found to be good. There were no serious adverse events or adverse reactions reported throughout the study.

Discussion

Although a fully effective and easily accessible treatment option has not been found yet, the researches and fight continues against the COVID-19 outbreak. Favipiravir is one of the main drugs in Covid-19 treatment protocols. A novel generic formulation of favipiravir, which is an antiviral compound with a wide range of antiviral activity against various influenza virus strains and is being used for Covid-19 treatment was developed and the pharmacokinetic properties were assessed in a bioequivalence study. This study, which is necessary to obtain the favipiravir generic product license approval, which is needed during the pandemic, was carried out on healthy volunteers during the pandemic. In addition, with this study, the pharmacokinetic properties of favipiravir, which is not commonly used outside of the Far East countries, were evaluated on Caucasian race.

The ANOVA results showed that treatment, sequence, period and subject within sequence had no statistically significant effects on C_{max} and $AUC_{0\text{-}tlast}$ (except subject within sequence effect for only $AUC_{0\text{-}tlast}$). Since the sequence or carry-over effect was not significant, ANOVA was valid.

Besides, ISCVs were found as 29.053% and 6.668% and the geometric mean ratios were found as 105.55% and 96.84% for C_{max} and $AUC_{0\text{-}tlast}$, respectively.

Although there were five sampling points within the first hour and these samples collected 10 and 15 minutes post-dose, only three subjects have first point C_{max} for Test and Reference products. However, all extrapolated areas were found below 20% which could be interpreted as the study had the adequate sample collection times.

t_{max} was analyzed using Mann–Whitney U test and there were not significant difference between two formulations with a significance level of 5% in regard to t_{max} (p=0.321).

In conclusion, since the 90% CIs for the test/reference geometric mean ratios for Cmax and $AUC_{0\text{-}tlast}$ of Favipiravir are contained within the acceptance limits preset in the Clinical Study Protocol, 80.00-125.00%, according to the applied bioequivalence study, it is concluded that test and reference Favipiravir products are bioequivalent under fasting conditions and test product can be licensed under the requirements of regulatory authorities. Moreover, both study drugs were well-tolerated and considered to be safe.

Acknowledgements

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Competıng Interests

There are no competing interests to declare.

Data Avaılabılıty

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Conflıct Of Interest

Authors declare no conflict of interest.

Funding Information: Atabay Pharmaceutıcals and Fıne Chemıcals Inc., Istanbul, Turkey

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