OPEN-LABEL, RANDOMISED, SINGLE ORAL DOSE, TWO-PERIOD, CROSS-OVER TRIAL TO ASSESS THE BIOEQUIVALENCE OF **FAVIR 200 MG FILM TABLET (TEST DRUG)** IN COMPARISON WITH **AVIGAN 200 MG FILM TABLET (REFERENCE DRUG)** IN HEALTHY MALE SUBJECTS UNDER FASTING CONDITIONS

CLINICAL STUDY PROTOCOL
"CONFIDENTIAL"

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Sponsor: Koçak Farma İlaç ve Kimya San. A.Ş.
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Contract Research Organisation (CRO): ALPAN Farma Ltd.Şti.
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Contracted Analytical Laboratory: Novagenix Bioanalytical Drug R&D Centre, Ankara - Turkey

STUDY SYNOPSIS

Study Title:	Open-label, randomised, single oral dose, two-period, cross-over trial to assess to bioequivalence of **Favir 200 mg Film Tablet(Test Drug)** in comparison with **Avigan 200 mg Film Tablet (Reference Drug)** in healthy male subjects under fasting conditions
Study Code:	**NOV2020/01919**
Drugs:	**Test Drug***: "**Favir 200 mg Film Tablet**" containing 200 mg favipiravir *(Koçak-Turkey).* **:* *This drug is manufactured by Koçak Farma İlaç ve Kimya San. A.Ş.- Turkey.* **Reference Drug****: "**Avigan 200 mg Film Tablet**" containing 200 mg favipiravir *(Fuji Film Toyama Chemical Industry Co.Ltd./Japan).* ***:This drug is manufactured and licenced by Fuji Film Toyama Chemical Industry Co Ltd.-Japan .*
Dosage:	Once daily 200 mg in a period.
Indication:	Bioequivalence study
Study Design:	Single oral dose, open-label, randomised, two period, cross-over study.
Variables:	**Pharmacokinetics:** Primary variables: $AUC_{0-tlast}$ and C_{max} Secondary variables: $AUC_{0-\infty}$, t_{max}, $t_{1/2}$ Safety and Tolerability: Adverse events, clinical laboratory, medical examinations
Sample Size:	30 volunteers will be included. Drop-outs will not be replaced.
Subjects:	20 - 40 aged healthy male volunteers, normal weight according to the BMI
Sponsor:	Koçak Farma İlaç ve Kimya San. A.Ş.- Turkey.
Phase:	I (Bioequivalence study)
Planned Initiation:	2Q 2020 (inclusion of first subject)
Planned Duration:	9 days (approximately) including the wash-out period of **48 hours** and the time between last blood sampling in the last period to the final examination tests.

Primary Endpoint:	$AUC_{0\text{-}tlast}$ and C_{max} of **favipiravir**
Secondary Endpoint:	$AUC_{0\text{-}\infty}$, $t_{1/2}$, t_{max} of **favipiravir**
Safety Endpoints:	Adverse events, clinical and laboratory examinations.
Principal Investigator:	Prof. Dr. Muradiye Nacak
Co-investigators:	İsmail Taner Ezgi, MD Erol Durucu, MD Gaziantep Üniversitesi, FARMAGEN-GCP Center, Gaziantep- Turkey
Analytics:	Plasma concentrations of **favipiravir** will be analysed in LC system with appropriate detection system.
GCP Statement:	This study will be conducted to compliance with Good Clinical Practice (ICH-GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.
Blood Sampling:	**The samples will be drawn in <u>the clinical study period</u>:** at pre-dose* 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, 24.00** hours post-dose *(1 x 8 mL each; totally 19 blood sample points)* *** Note:** **1. Only in Period I; at t_0 the blood sample amount will be 20 mL.** **2. Not to have difficulty to draw blood through catheter; the cannula will be kept patent by injecting approximately 0.5 mL of 5 IU/mL of heparin in normal saline solution at determined blood sampling points. In such cases, before collecting the blood samples at the first blood sampling points after heparin administration, first 0.5 mL blood will be discarded. The aim of this procedure is to eliminate the possible effect of heparin on <u>favipiravir</u> analysis** *[for details see section 13.7 (Blood Sampling for Drug Analysis)]*
Wash-out duration:	At least 48 hours.
Acceptance Range:	80% - 125% for C_{max} and $AUC_{0\text{-}tlast}$ of **favipiravir.**

1. THE PARTIES of PROJECT

Study Code: NOV2020/01919

Study Title: Open-label, randomised, single oral dose, two-period, cross-over trial to assess bioequivalence of **Favir 200 mg Film Tablet (Test Drug)** in comparison with **Avigan 200 mg Film Tablet (Reference Drug)** in healthy male subjects under fasting conditions

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Monitor*: **Halime Bekdik**

***:** for the absence of principal monitor, the monitoring will be done by AlpanFarma's authorized personnel.

2. TABLE OF CONTENTS

3. RESPONSIBILITIES, SIGNATURES AND ADDRESSES

We, herewith, confirm that the study protocol, CRFs and appendices contains all the information and rules necessary to conduct the study according to GCP regulations and that the study will be carried out and documented in complete compliance with this study protocol. The legal regulations and described agreements will be observed. The study medication will be used only for the purpose of the clinical trial. The clinical investigator will be informed about the pharmacological/toxicological tests and all new knowledge about the drug as well as about any newly occurring, hitherto unknown adverse events of test and reference drug.

Principal Investigator:

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4. LIST OF ABBREVIATIONS AND TERMS

AE / ADR	Adverse Event / Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT / AST	Alanin- / Aspartate Aminotransferase
AUC	Area under the curve
AUC_{0-24}	**Area under the plasma concentration-time curve from zero up to 24 hours**
$AUC_{0-tlast}$	Area under the plasma concentration-time curve from zero up to the last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase
BMI	Body Mass Index (body weight in relation to height and age): $BMI = \frac{weight\ (kg)}{height(m)^2}$
BP	Blood Pressure
C_{max}	Maximum plasma concentration
CBC	Complete Blood Count
CDER	Center for Drug Evaluation and Research
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
EGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl transferase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HB_sAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCV-Ab	Antibodies against Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-Ab	Antibodies against Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
ITF	Investigator's Trial File
LC	Liquid Chromatography
log	Logarithmic
MAOI	Monoamine oxidase inhibitor
MoH	Ministry of Health
MRT	Mean Residence Time
n	Number (observations; volunteers; sampling points; etc.)
NA	Not Applicable
PR	Pulse rate
PTH	Parathyroid hormone
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach maximum concentration
UADR	Unexpected Adverse Drug Reaction
λ_z	Terminal rate constant

5. SUMMARY AND SCHEDULE FOR THE CLINICAL TRIAL

5.1. Summary

Title:	Open-label, randomised, single oral dose, two-period, cross-over trial to assess to bioequivalence of **Favir 200 mg Film Tablet (Test Drug)** in comparison with **Avigan 200 mg Film Tablet (Reference Drug)** in healthy male subjects under fasting conditions
Study objective:	The aim of this study is to evaluate the pharmacokinetic profiles and the relative bioavailability of **favipiravir** from the test product (**Favir 200 mg Film Tablet, *Koçak-Turkey***) in comparison with the reference product **(Avigan 200 mg Film Tablet, *Fuji Film Toyama Chemical Industry Co Ltd.-Japan*)** under fasting conditions. The primary objective is to demonstrate the bioequivalence of test and reference products.
Test Drug*:	"**Favir 200 mg Film Tablet**" containing 200 mg favipiravir *(Koçak-Turkey).* **: This drug is manufactured by Koçak Farma İlaç ve Kimya San. A.Ş.-Turkey.*
Reference Drug:**	"**Avigan 200 mg Film Tablet**" containing 200 mg favipiravir *(Toyama Chemical Industry Co Ltd.-Japan).* ***: This drug is manufactured and licenced by Fuji Film Toyama Chemical Industry Co Ltd.-Japan.*
Dosage:	Once daily **200 mg favipiravir** in a period
Indication:	Bioequivalence study
Study design:	Single oral dose, open-label, randomised, two period, cross-over trial.
Variables:	**Pharmacokinetics:** Primary variables: $AUC_{0-tlast}$ and C_{max} of **favipiravir** Secondary variables: $AUC_{0-\infty}$, t_{max}, $t_{1/2}$ of **favipiravir** Safety and Tolerability: Adverse events, clinical laboratory, medical examinations
Sample size:	30 volunteers will be included. Drop-outs will not be replaced.
Subject selection criterion:	20 - 40 aged healthy male volunteers. Normal weight according to the BMI.
Blood sampling:	**The samples will be drawn in the clinical study period: at pre-dose* 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, 24.00 hours post-dose *(1 x 8 mL each; totally 19 blood sample points)***

*** Note:**

1. **Only in Period I; at t_0 the blood sample amount will be 20 mL.**
2. **Not to have difficulty to draw blood through catheter; the cannula will be kept patent by injecting approximately 0.5 mL of 5 IU/mL of heparin in normal saline solution at determined blood sampling points. In such cases, before collecting the blood samples at the first blood sampling points after heparin administration, first 0.5 mL blood will be discarded. The aim of this procedure is to eliminate the possible effect of heparin on favipiravir analysis** *[for details see section 13.7 (Blood Sampling for Drug Analysis)]*

Route of Administration: Oral

Duration of Treatment: **9 days** (approximately) including the wash out period of **48 hours** and the time between last blood sampling in the last period to the final examination tests.

Duration of Wash-out: At least 48 hours.

Procedure: In the **1st period**, each volunteer will receive after an overnight fasting in random order one single oral dose of **200 mg favipiravir** product (either 1 tablet of the test drug or 1 tablet of the reference drug). Blood samples will be drawn immediately before the dosing 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, 24.00** hours after the dosing. In the **2nd period** there will be the same procedure.

Analysis of favipiravir : Plasma concentrations of **favipiravir** will be analysed in LC system.

Statistical analysis: Statistical analysis will be performed using **Phoenix WinNonlin (Version 8.1, Certara L.P.)** or above. Analysis of Variance (ANOVA), two one-sided tests and 90% confidence intervals for the geometric mean ratios (test/reference) of C_{max} and $AUC_{0\text{-}tlast}$ will be calculated.

Acceptance range: C_{max} : 80-125 % (ln-transformed)
$AUC_{0\text{-}tlast}$: 80-125 % (ln-transformed)

Evaluation of bioequivalence: In order to investigate the bioequivalence of all products, the 90% confidence intervals will be calculated for the geometric mean ratios of test and reference for C_{max} and $AUC_{0\text{-}tlast}$ of **favipiravir.** These confidence intervals will then be compared with the corresponding acceptance ranges.

In order to achieve a better approximation to a normal distribution, C_{max} and $AUC_{0\text{-}tlast}$ data for **favipiravir** will be logarithmically transformed (base e) before analysis. The sources of variation will be treatments, periods, sequences and subjects within the sequence. Evaluation of treatment, period, sequence and subject (nested within sequence) effects at 5% level of significance will be performed. From the result, the two one-sided hypothesis at the 5% level of significance

	will be tested by constructing the 90% confidence interval for the geometric mean ratios of test/reference products. The confidence interval is calculated by retransformation of the shortest confidence interval for the difference of the ln-transformed mean values. Differences in t_{max} will be evaluated non-parametrically.
Sponsor:	Koçak Farma İlaç ve Kimya San. A.Ş. Representative: Cem Koçak
Protocol code:	NOV2020/01919
Phase:	I (Bioequivalence study)
Planned initiation:	2Q 2020 (inclusion of first subject)
Planned duration:	**9 days** (approximately) including the wash out period of **48 hours** and the time between last blood sampling in the last period to the final examination tests.
Primary Endpoint:	$AUC_{0\text{-}tlast}$ and C_{max} of **favipiravir**
Secondary Endpoint:	$AUC_{0\text{-}\infty}$, $t_{1/2}$, t_{max} of **favipiravir**
Safety Endpoints:	Adverse events, clinical and laboratory examinations.
Principal Investigator:	Prof. Dr. Muradiye Nacak
Co-investigators:	İsmail Taner Ezgi, MD Erol Durucu, MD Gaziantep Üniversitesi, FARMAGEN-GCP Center, Gaziantep- Turkey
Project Manager	Prof. Dr. Aydın Erenmemişoğlu Alpan Farma Ltd.Şti. Kayseri - Turkey
Analytical laboratory:	Novagenix Bioanalytical Drug R&D Centre Esenboğa Yolu 25. km. Akyurt 06970 Ankara, Turkey
GCP statement:	This study will be performed in compliance with Good Clinical Practice (ICH-GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.

5.2. Schedule

Estimated time frame for each step is given below:

X -Contract signed

Y -Ethics Committee and the Ministry of Health (MoH) approvals

W -End of clinical part of trial

Q -End of Analytical Analysis

Z -End of Statistical Analysis

- Approvals: X + 1-1½ month
- Enrollment of volunteers: Y + ½ month
- Clinical trial, monitoring: Y + 9 days
- Evaluation of plasma samples: W + 2-3 months
- Data input, statistical evaluation Q + ¼ month
- Final Report (Draft) Z + ½ month

6. STUDY FLOW CHART

	SCREENING AND ISOLATION				PERIOD I			PERIOD II		*Final examination
Study Day:	1st DAY screening	2nd DAY (isolation)	3rd DAY (isolation)	4th DAY (isolation)	5th DAY Hospitalization day (Day 0)	6th DAY 1st dosing day and blood sampling (Day 1)	7th DAY blood sampling ($t_{24.00}$) Wash-out day/ (Day 2)	8th DAY 2nd dosing day and blood sampling (Day 3)	9th DAY blood sampling ($t_{24.00}$) (Day 4)	9th DAY Final examination
Informed consent	●									
Covid-19 PCR Test#	●				●					●
Inclusion criteria	●									
Demography (Birth date, ethnic group, gender, height, weight, BMI)	●									
"Medical/Surgical history	●									
HBsAg, anti-HCV, HIV	●									
ECG	●									●
Clinical examination (Physical examination)	●									●
Clinical chemistry, haematology, urinalysis	●									●
Blood pressure, pulse rate	●	●	●	●	●		●			●
Body temperature°	●	●	●	●	●	●	●	●	●	●
Drug abuse screening**	●									
Alcohol breath test	●									
Check of restrictions, diet					●	●	●	●		
Exclusion criteria and Withdrawal of volunteers	●	●	●	●	●	●	●	●	●	
Hospitalization day					●					
Randomisation	●									
Drug administration						●		●		
Blood sampling*** (0-24.00 h)						●	●	●	●	
Adverse event questioning****	●	●	●	●	●	●	●	●	●	

* The final examination will be carried out on the day of last blood sampling **.**

Two Covid-19 PCR tests will be applied on screening day.

° Body temperature monitoring will be performed at the following times: at "screening/isolation days", "hospitalisation day (Day 0)", "during study period" and "final examination".

** For **amphetamines, cannabinoids, benzodiazepines, cocaine, opioids, and barbiturates**.

***Blood sampling points (for each period): **at pre-dose (20 mL only in Period I)** 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, 24.00 hours post-dose (*1 x 8 mL each; totally 19 blood sample points*)

Note:

1. Only in Period I; at t_0 the blood sample amount will be 20 mL.
2. Not to have difficulty to draw blood through catheter; the cannula will be kept patent by injecting approximately 0.5 mL of 5 IU/mL of heparin in normal saline solution at determined blood sampling points. In such cases, before collecting the blood samples at the first blood sampling points after heparin administration, first 0.5 mL blood will be discarded. The aim of this procedure is to eliminate the possible effect of heparin on **favipiravir** analysis. *[for details see section 13.7 (Blood Sampling for Drug Analysis)]*

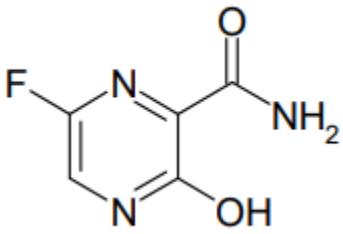
******Adverse event questioning**: at "screening/isolation days", hospitalisation day (Day 0) and pre-dose, 1.00, 4.00, 8.00, 14.00, 24.00 hours post-dose in each period.

7. INTRODUCTION

7.1. Chemical and Pharmaceutical Properties

Favipiravir is an antiviral compound with a wide range of antiviral activity against various influenza virus strains. Chemically, it is 6-Fluoro-3-hydroxypyrazine-2-carboxamide and its molecular formula is $C_5H_4FN_3O_2$. Its molecular weight is 157.10.

Figure 1. Chemical Structure of Favipiravir



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.

7.2. Pharmacological Properties

Favipiravir is a drug with a mechanism of action different from that of the existing influenza antiviral drugs and effective against all types and sub-types of human influenza A, B and C viruses *in vitro*, showing anti-viral activity against various influenza virus strains including avian and swine viruses. Favipiravir also has shown anti-viral activity even against amantadine, oseltamivir and zanamivir-resistant influenza viruses *in vitro*. 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.

7.3. Pharmacokinetics

Absorption and Distribution

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-t} were 8.39 µg/ml and 19.67 µg.h/ml respectively. The Cmax 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 thah 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).

When oral tablet of favipiravir was given with a high-fat meal a decrease in Cmax and AUC was observed.

Favipiravir is 53.4%-54.4% bound to plasma proteins.

Metabolism and Excretion
Favipiravir M1 and glucuronide conjugate of favipiravir (M2) were found in the human plasma and urine obtained after single-dose administration.
The elimination of favipiravir largely depends via renal excretion with a mean plasma elimination half-life ($t_{½}$) of 1.5 hours.

Some pharmacokinetics parameters of oral Favipiravir tablet are shown in the following table:

t_{max} (h)	Cmax (µg/mL)	Protein binding (%)	$t_{½}$ (h)	Excretion
0.5	8.39 (*200 mg single dose)*	53.4-54.4	1.5	via renal excretion

7.4. Indications

Favipiravir is indicated for the treatment of highly pathogenic influenza virus infections (limited to patients in whom other influenza antiviral drugs are ineffective or not sufficiently effective)

7.5. Contraindications

Favipiravir is contraindicated in the patients with a history of hypersensitivity to favipiravir or any ingredient of the drug. Also it is contraindicated in women who are known or suspected as being pregnant.

7.6. Adverse Reactions

The main adverse events of favipiravir seen during the development of the product for influenza include mild to moderate diarrhoea, abdominal pain, headache and asymptomatic elevations of blood uric acid, decrease of neutrophil count, increase of AST (GOT), increase of ALT (GPT).

Adverse reactions observed in Japanese clinical studies and the global phase III clinical study (studies conducted with dose levels lower than the approval dosage) are shown in the table below with frequency.

	≥ 1%	%0.5 - < 1	< 0.5%
Hypersensitivity		rash	eczama, pruritus
Hepatic	AST (GOT) increased,ALT (GPT) increased, γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea (4.79%)	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic	Neutrophil count decreased, white blood cell count decreased		White blood cell count increased, reticulocyte count decreased, monocyte increased
Metabolic disorders	Blood uric acid increased (4.79%), blood triglycerides increased	Glucose urine present	Blood potassium decreased
Respiratory			Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others			Blood CK (CPK) increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo, supraventricular extrasystoles

Clinically significant adverse reactions such as, shock, anaphylaxis, pneumonia, hepatitis fulminant, hepatic dysfunction, jaundice, toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute kidney injury decrease of white blood cell, neutrophil count and platelet count, neurological and psychiatric symptoms (consciousness disturbed, abnormal behavior, deliria, hallucination, delusion, convulsion, etc.) haemorrhagic colitis have been reported with other anti-influenza virus agents.

7.7. Cautions and Precautions

Administration of favipiravir should be started promptly after the onset of influenza-like symptoms.

Favipiravir use is limited with cases in which other influenza antiviral drugs are ineffective or not sufficiently effective.

Favipiravir should be administered with care in patients with gout or a history of gout, and patients with hyperuricaemia.

Increase of plasma level of favipiravir has been reported in patients with liver function impairment in pharmacokinetic study. Necessity of the dose adjustment of favipiravir in those patients should be considered.

Although the causal relationship is unknown, psychoneurotic symptoms such as abnormal behavior after administration of anti-influenza virus agents including favipiravir have been reported.

In case of bacterial infection or suspected to be bacterial infection, appropriate measures should be taken, due to favipiravir is not effective in bacterial infections.

7.8. Interaction with other medicinal products and other forms of interaction

In vitro **drug-drug interaction**

(a)Inhibitory effect against human cytochrome P-450 (CYP)

In the *in vitro* CYP inhibition study, the inhibitory effects of favipiravir against major human hepatic CYP isoforms (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) activity were investigated in human liver microsome. As a result, favipiravir inhibited the CYP2C8 activity in a concentration-dependent manner. The metabolic activities of the other CYP isoforms in the presence of favipiravir at the maximum concentration were all ≥60% of the control. M1, the major metabolite of favipiravir, decreased the CYP2E1 activity to 72.6% of the control at the maximum concentration, but hardly inhibited activities of other CYP isoforms for any isoforms.

In the case of concomitant use of favipiravir with repaglinide, CYP2C8 substrate drugs, it cannot be ruled out that the risk of hypoglycemia, a serious adverse drug reaction, is increased. In the case of concomitant use of favipiravir with paclitaxel, it cannot be ruled out that the risk of white blood cell decreased and peripheral neuropathy, serious adverse drug reactions, is increased.

(b) Induction action on CYPs
In the *in vitro* CYP induction study, the effects of favipiravir on human hepatic CYP isoforms (CYP1A2, 2C9, 2C19, 3A4) were investigated in fresh human primary hepatocytes. As a result, favipiravir increased the expression of the CYP isoforms up to 1.7 times (mean) in the concentration range examined, and this induction rate of favipiravir was ≤6.6% of those of the positive controls (omeprazole, rifampicin).

(c) Inhibitory effect against Aldehyde Oxidase (AO)
In the *in vitro* inhibition study, the inhibitory effects of favipiravir against the AO activity were investigated in human hepatic cytosol. As a result, the residual metabolic activity (phthalazone formation activity) of phthalazine, a substrate of AO, decreased favipiravir concentration (20-6000 μmol/L) and preincubation time (0-60 minutes)-dependently. the risk of concomitant use of favipiravir with AO inhibitors may not be high. Currently, a drug interaction study of favipiravir with raloxifene hydrochloride, an AO inhibitor, is under preparation, and if the risk of concomitant use is suggested by this study, precautions will be provided in the package insert.

Based on the currently available pharmacokinetic data, drugs that act as AO substrates and would require special attention are hydralazine hydrochloride, which shows a high relative contribution of AO, and famciclovir and sulindac, whose effect may be decreased by concomitant favipiravir.
A drug interaction study with hydralazine hydrochloride is under preparation, and if the risk of concomitant use is suggested by this study, precautions will be provided in the package insert.

(d) Inhibitory effect against Xanthine Oxidase (XO)
In the *in vitro* inhibition study, the inhibitory effects of favipiravir against the XO activity were investigated in human hepatic cytosol. As a result, favipiravir did not inhibit the metabolism of 1-methylxanthine, a metabolite of theophylline (substrate of XO), concentration or preincubation time-dependently.

(e) Interaction with acetaminophen
In the *in vitro* inhibition study, the inhibitory effects of favipiravir and M1 against acetaminophen metabolism were investigated in human liver S9. As a result, favipiravir did not inhibit the glucuronide conjugation metabolism of acetaminophen in the concentration range examined, but inhibited the sulfate conjugation metabolism. M1 did not inhibit glucuronide or sulfate conjugation metabolism of acetaminophen in the concentration range examined. Favipiravir is expected to be concomitantly used with acetaminophen in the treatment of influenza infection in many patients. The results from this study can serve as important information for clinical use of favipiravir and therefore should be included in the package insert for information provision. When the results are obtained from other interaction studies ongoing or to be conducted, relevant information should be provided to healthcare providers in clinical practice appropriately.

(f) Interaction with oseltamivir

In the *in vitro* inhibition study, the inhibitory effects of favipiravir and M1 against oseltamivir metabolism were investigated in human liver S9. As a result, favipiravir inhibited deesterification of oseltamivir in the concentration range examined, but IC50 values were high. M1 did not inhibit deesterification of oseltamivir in the concentration range examined.

(g) P-gp transportation

A membrane fraction from the human MDR1 expressing cells was used to investigate P-gp's substrate recognition. As a result, favipiravir and M1 did not increase the adenosinetriphosphatase (ATPase) activity concentration-dependently, suggesting that neither of them will act as a substrate of P-gp.

***In vivo* drug-drug interaction**

(a) Theophylline

Favipiravir and/or theophylline were administered to 10 healthy adult Japanese male subjects. For combination therapy with theophylline, subjects received a certain regimen. Both favipiravir and theophylline were administered between the meals. It is found that the combination therapy with theophylline affected the pharmacokinetics of favipiravir and M1. On the other hand, both parameter ratios of theophylline fell within the above range.

(b) Oseltamivir

Favipiravir and/or oseltamivir phosphate were administered to 10 healthy adult Japanese male subjects in a certain regimen. Both favipiravir and oseltamivir phosphate were administered between the meals. There were no significant differences in the cumulative urinary excretion rate or CLr of M1 and oseltamivir carboxylate up to 12 hours after dosing between the monotherapy and combination therapy. When any new relevant finding becomes available after marketing of favipiravir; however, it is necessary to provide the information to healthcare providers in clinical practice appropriately.

(c) Oral Contraseptive

In studies conducted according to the proposed dosage regimen, only 1 subject concomitantly used favipiravir and oral contraceptives and reported rhinitis and dysgeusia as adverse events, which were not considered specific to favipiravir or ethinyl estradiol.

(d) Pyrazinamide

Blood uric acid levels increased in all the subjects treated with favipiravir with pyrazinamide, although the effect on the blood drug concentration was not significant. As a serious adverse event, hepatic function abnormal was reported as well. Hence, it is necessary to collect post-marketing information about patients to whom favipiravir is administered in combination with pyrazinamide.

8. OBJECTIVE OF THE TRIAL

The aim of this study is to evaluate the pharmacokinetic profiles and the relative bioavailability of **favipiravir** of the Test Drug **(Favir 200 mg Film Tablet, Koçak-Turkey)** in comparison with Reference Drug **(Avigan 200 mg Film Tablet, *Fuji Film Toyama Chemical Industry Co Ltd.-Japan***) under **fasting** conditions. The primary objective is to demonstrate the bioequivalence of all products.

9. BENEFIT-RISK EVALUATION

For the approval of any product, its efficacy and safety has to be proved. There are two possibilities to do this for a new generic product: either by proving therapeutic equivalence or by proving bioequivalence with a marketed reference on the basis of comparison of relative bioavailability. The first option requires huge numbers of patients and a long period of administration of either the test or the reference product. A bioequivalence trial on the basis of bioavailability is therefore generally accepted as the better alternative. This trial is conducted with the aim to investigate whether any differences concerning the rate and extent of absorption exist between the test and the reference products.

10. DESIGN

In this open-label, randomised, single-dose, two period, cross-over study, **30 healthy** male subjects (intention to treat population) will receive one single oral dose of **200 mg favipiravir (one tablet of the test drug or one tablet of the reference drug)** after an overnight fasting in each period according to a sequence determined by randomisation *[In each study period, subjects will take different products (either one dose of Test Drug or one dose of Reference Drug)]*.

Data of **the subjects** who have completed the study according to the Clinical Study Protocol (per protocol population for pharmacokinetic evaluation) will be used for analytical, pharmacokinetic and statistical evaluation.

Test Drug: "Favir 200 mg Film Tablet" is manufactured by Koçak Farma İlaç ve Kimya San. A.Ş., Turkey and is will be licensed by Koçak Farma İlaç ve Kimya San. A.Ş., Turkey.

Reference Drug: "Avigan 200 mg Film Tablet" is manufactured and licenced by Fuji Film Toyama Chemical Industry Co Ltd.-Japan.

In study period, the subjects will be admitted to the FARMAGEN Clinical Unit in the evening (18:00) prior to morning of the administration of medication after screening and isolation period as described in Appendix VII.

Volunteers will be confined to the clinical unit and dosing will occur under conditions of hospitalization. Medications will be orally administered at approximately at 8:00 (t=0) after an overnight fasting (at least 10 hours in fasting). The lunch will be 4 hours post dosing and the dinner will be 10 hours post dosing. Blood sampling for the determination of favipiravir plasma concentrations will be drawn at specified time points. In study period including wash-out period, volunteers will be hospitalized in FARMAGEN Clinic Unit. After taking the last blood sample in 2nd period and carried out the post-study and final examination, the subjects will be allowed to leave the clinic.

An overview of the study procedures is given in the Study Flow Chart provided in section 6.

11. SELECTION OF VOLUNTEERS

11.1. Inclusion Criteria

Only volunteers fulfilling all of the following criteria should be enrolled in the present trial:

1. Healthy Caucasian male subjects aged between **20 and 40** years,
2. Non smokers or smoking maximum 5 cigarettes a day, those who won't smoke or drink coffee during the study period,
3. **Two Negative Covid-19 PCR test results.**
4. Negative alcohol breath test results,
5. Normal physical examination at screening visit,
6. Having the Body Mass Index ranged between **18.5-30 kg/m^2** (see Appendix I) which is in the desirable range according to the age,
7. Ability to communicate adequately with the investigator himself or his representatives,
8. Ability and agreement to comply with the study requirements,
9. Normal blood pressure and heart rate measured under stabilised conditions at the screening visit after at least 5 minutes of rest under supine position: SBP within 100 to 140 mmHg, DBP within 60 to 90 mmHg and HR within 50 to 90 bpm,
10. Normal/ acceptable 12-lead electrocardiographic results at least after 5 minutes of rest,
11. Laboratory results within normal range or clinically non-significant (CBC, glucose, urea, uric acid, creatinine, *estimated GFR (eGFR)*, total bilirubin, sodium, potassium, calcium, chloride, SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase, total protein and urinalysis), drug addiction scanning in urine results in negative (amphetamine, barbiturate, benzodiazepine, cannabinoid, cocaine, opiate),
12. Understanding of the study and agreement to give a written informed consent according to section 20.3.
13. **Understanding of that he and his partner will use a practice adequate contraception during the study and at least 7 days after the study.**

11.2. Exclusion Criteria

Volunteers presenting any of the following exclusion criteria will not be included in the trial:

1. **Who have atopic constitution or asthma or known allergy for favipiravir and/or any other ingredients of the products.**
2. **Who have positive Covid-19 PCR test result.**
3. Any history or presence of clinical relevance of cardiovascular, neurological, musculoskeletal, haematological, hepatic, gastrointestinal, renal, pulmonary, endocrinological, metabolism or psychiatric disease, any type of porphyria**.**
4. Symptomatic or asymptomatic orthostatic hypotension at screening or before the first drug administration defined by a decrease of SBP more than 20 mmHg or DBD more than 10 mmHg occurs between sitting/supine to standing position subject will be excluded ***(if it deemed necessary by the investigator)***,
5. Presence or history of malabsorption or any gastrointestinal surgery except appendectomy or except herniotomy.
6. Subjects who have given more than 400 mL blood within the last two months before the first drug administration and subjects who have participated to any drug research within the last two months before the first drug administration.
7. Subjects suspected to have a high probability of non-compliance to the study procedure and/or completion of the study according to the investigator's judgement.
8. Subjects who used any of prescribed systemic or topical medication (including OTC medication) within 2 weeks (or six elimination half lives of this medication, whichever is longer) before the initiation of the study (except single doses of analgesics which have no drug interaction with study product).
9. Use of any vitamins or herbal products within 7 days prior to the initial dose of the study medication.
10. History of allergic response to heparin.
11. Subjects who have any chronic disease which might interfere with absorption, distribution, metabolism or excretion of the drug.
12. Subjects who regular consumed of beverages or food containing methylxanthines (e.g. coffee, tea, cola, caffeine, chocolate, sodas,) equivalent to more than 500 mg methylxanthines per day.
13. Subjects who has taken any grapefruit or grapefruit juice during 7 days prior to drug administration, during the study.
14. History of drug abuse.
15. History of alcohol abuse and/or regular use of more than 2 units of alcohol per day or 10 units per week and/or positive alcohol breath test results (Note: one unit of alcohol equals 250 mL beer, 125 mL wine or 25 mL spirits).

16. Positive blood test for HBV, HCV and HIV.
17. Who have relationship to the investigator.
18. Who are not suitable to any of inclusion criteria.
19. History of difficulty of swallowing.
20. Intake of depot injectable solutions (including study medications) within 6 months before start of the study.
21. Intake of enzyme-inducing, organotoxic or long half-life drugs within 4 weeks before start of the study.
22. Special diet due to any reason, e.g. vegetarian.

11.3. Other Conditions

Diseases present at entry into the study are regarded as concomitant illnesses and generally as an exclusion criteria. Illnesses occurring during the study period (intercurrent illnesses) are to be regarded as adverse events and will be documented on a separate page ("adverse event form" and "drop-out sheet") in the Case Report Forms (CRF) (see **Appendix II**).

11.4. Coding Subjects

The subject screening number will be also assigned as the subject code throughout the study. A volunteer code will be assigned to each subject.

12. MEDICATION

12.1. Study Medication

The study medications will be supplied together with certificates of analysis by the company responsible for manufacturing the product, **Koçak Farma İlaç ve Kimya San. A.Ş., Turkey.** The packaging and labelling will be done according to the GMP and GCP requirements.

The reference drug is manufactured and licenced by Fuji Film Toyama Chemical Industry Co Ltd.-Japan. All study drugs, together with relative documentation, will be supplied to **FARMAGEN- Good Clinical Practice and Research Center** by **SPONSOR** after approval of the study protocol by MoH. **After arriving study drugs to clinical center, the clinic schedule will be determined.** The delivery address for study medication is:

Prof. Dr. Muradiye Nacak

Gaziantep Üniversitesi FARMAGEN GCP Center
Gaziantep Üniversitesi Teknoloji Geliştirme Bölgesi (Teknopark),
Burç Yolu, Şahinbey 27260, Gaziantep-TURKEY

12.1.1. Test Drug:

Active substance:	Favipiravir
Formulation:	Film Tablet for oral administration
Strength:	200 mg
Manufacturer:	Koçak Farma İlaç ve Kimya San. A.Ş.- Turkey
Marketing Authorisation Holder:	Koçak Farma İlaç ve Kimya San. A.Ş.- Turkey
Batch Number:	3388001
Expiry Date:	04.2022
Trade name:	**Favir 200 mg Film Tablet**
Storage requirements:	Store below 25°C at room temperature.
Certificate of analysis:	To be provided by the Sponsor together with medication

12.1.2. Reference Drug:

Active substance:	Favipiravir
Formulation:	Film Tablet for oral administration
Strength:	200 mg
Manufacturer:	Fuji Film Toyama Chemical Industry Co.Ltd./Japan
Marketing Authorisation Holder:	Fuji Film Toyama Chemical Industry Co.Ltd./Japan
Batch Number:	FG1881
Expiry Date:	07.2028
Trade name:	**Avigan 200 mg Film Tablet**
Storage requirements:	Store below 25°C at room temperature.
Certificate of analysis:	To be provided by the Sponsor together with medication

12.2. Blinding

12.2.1. For Clinical Phase

This trial is planned as open-labelled in clinical phase. Investigator will have the information of which subject will take which **product** [Test or Reference] in study. Also, the subjects will have the information about the **products** which will be administered in the study period.

12.2.2. For Analytical Phase

This trial is planned as fully blinded in analytical phase. The exact list will be in a sealed envelope and this envelope will be opened at Novagenix in a "Project Evaluation Meeting" when all laboratory analyses are over. Once the sealed envelope is opened, no more reanalyse or data change/exclusion will be allowed.

12.3. Dosage, Duration of Treatment

All volunteers will receive once daily either **200 mg favipiravir** of the **test drug** (in one period) or **200 mg favipiravir** of the **reference drug** (in one period) according to the randomisation table. The instructions for intake of the study medication are given

in section 13.5 and separately on a sheet to be kept in the room where administration takes place.

12.4. Compliance

On each day of administration and/or sampling the identity of the volunteer will be confirmed by checking the Identity Card. Administration of the study medication will be performed by the investigator(s) and nurse(s) and supervised by a second medical professional to ensure the correctness of drug administration. Also, a personnel (monitor) from **Sposor** will attend during this procedure. The administration of the study medication is to be followed by a mouth check, to be documented in the CRF and certified by the Investigator.

12.5. Handling and Drug Accountability

The study medication will be packed and labelled according to GMP requirements. The study medication will be provided by the Sponsor together with certificates of analysis in a sufficient quantity for the needs of the whole trial. The Sponsor is responsible for keeping an appropriate amount of each study medication at the facility or at **ALPAN Farma** in order to allow repeated pharmaceutical analysis.

The investigator will confirm receipt of study medication in writing, including all follow-up supplies. The investigator will administer the study medication only to volunteers included in the study by following the procedures set out in the study protocol, as given in chapter 13.2. All drug supplies (test and reference medication, unused medication, empty blisters) which have not been used have to be returned to **ALPAN Farma or Koçak Farma İlaç ve Kimya San. A.Ş.** after completion of the study. It is not allowed to use the study medication for any other purpose.

12.6. Concomitant Medication

Concomitant medication is generally not allowed for the duration of the trial. If this is considered necessary for the volunteer's welfare, it may be given at the decision of the investigator. The volunteers have to inform the investigator about any intake of other drugs in the course of the trial. *If necessary, for the treatment of ordinary pain (e.g. headache), some analgesics which have no drug interaction with study products, may be given by investigator.* Any intake of concomitant medication has to be documented in the Case Report Form (“concominant medication form”, “adverse event form” and “drop-out sheet”) specifying the substance, dose, time and reason for use of concomitant medication and may be regarded as an exclusion criterion.

12.7. Rescue Medication

No specific rescue medication is planned for the present trial since it is not a therapeutic trial and the safety / tolerability profiles of the administered drug substance are well known.

12.8. Storage of Study Medication

The investigator will be responsible for proper storage of the investigational products. All drug supplies must be stored in a dry place at room temperature and separately from normal hospital/practice stocks, locked and only accessible for authorized personnel, in accordance with the manufacturer's instructions. All supplies must be accounted for at the end of the study. A drug inventory form is to be filled in for this purpose.

13. STUDY PROCEDURE

13.1. General Procedure

Volunteers eligible for inclusion within the age limits as defined in section 11.1 will be asked for informed consent as described in **Appendix VII due to the Covid-19 outbreak precautions** and as described in section 20.3 and will be thereafter screened with respect to inclusion and exclusion criteria.

The initial examination will be carried out on the day of the beginning of the isolation as described in **Appendix VII**. The standard clinical screening includes demographic data, brief anamnestic data (medical history with information about relevant previous diseases of all body systems), physical examination, determination of body temperature, weight and height, standard ECG (12 lead), measurements of blood pressure (BP) and pulse rate (PR) after 5 minutes supine rest.

The standard laboratory screening includes serum levels of "CBC, glucose, urea, uric acid, creatinine, *estimated GFR (eGFR)*, total bilirubin, sodium, potassium, calcium,chloride, **SGOT (AST), SGPT (ALT), GGT**, alkaline phosphatase, total protein and urinalysis". The blood specimen (**20 mL**[#] for entry and 12 mL for final) for the safety laboratory will be taken under fasting conditions. Total blood sampling for both laboratory examinations (entry and final) will be 32 mL. The volunteers will also be checked for presence of HBsAg, HCV-Ab and HIV-Ab in serum and **Covid-19 PCR test**.

Clinical laboratory tests will be performed using the auto analyser at a contracted and certified laboratory **(GAMA Tıp Laboratuvarı-Gaziantep)**. ***Covid-19 PCR test*** will be performed at "FARMAGEN-GCP Center, Gaziantep- Turkey".

 # At entry examination the blood sample amount will be 20 mL and 8 mL sample of 20 mL sample will be divided into tubes and one of this tube will be used for the anti-coagulant validation purpose during the analytical validation process. This plasma sample will send to Novagenix with master and back-up samples.

The following parameters are determined in urine (30 mL): pH, protein, glucose (semi quantitatively by means of strip test), ketones, blood, leukocytes, bilirubin, nitrites. If the strip test for any urine parameter is positive, a microscopic examination of the sediment has to be done.

At screening volunteers will be requested to provide a urine sample for a drug screen which will include "*amphetamines, cannabinoids, benzodiazepines, cocaine, opioids and barbiturates*" and for an alcohol breath test. All laboratory tests will be carried out in a certified local laboratory. A list of the normal ranges and units of measurement of the laboratory parameters to be determined during the study and the certificate of the laboratory will be provided by the investigator before the start of the study. The reference ranges and the results of the individual laboratory examination will be documented in each CRF. The investigator will be provided with a print-out or authorized copy of the original laboratory values.

If in the course of initial screening any clearly pathological value (laboratory value outside reference range, clinically relevant or significant) is observed, this finding will be regarded as an exclusion criterion.

Laboratory values outside the normal range will be judged by the investigator in a written form in the CRF. Single laboratory values outside the normal range will generally not be regarded as an exclusion criterion provided that:

a) they are not accompanied by clinical symptoms,

b) the context of related laboratory values gives no indication of a pathological process and

c) the investigator regards them as clinically irrelevant in written form in the CRF.

If any positive result in Covid-19 PCR test is observed, the volunteer will be transfer to Gaziantep University Şahinbey Research Hospital, Emergency Department* under appropriate conditions immediately. This finding will be regarded as an exclusion criterion.

***Contact Physician: Prof. Dr. Şevki Hakan EREN**

Gaziantep University Şahinbey Research Hospital,
Emergency Department
GSM: 0506 2379579

The test and reference product will be administered **under fasting conditions each in a randomised manner in two-period with at least 48 hours wash-out period.**Volunteers will be treated under hospitalization conditions in study period and will be hospitalised at the Clinical Facility (FARMAGEN-Good Clinical Practice and Research Center) from the evening of Day 0 (hospitalization day) normally until taking the last blood sample in 2nd period and carried out the post-study and final examination to ensure subjects' safety as well as standardised trial conditions during profiling days (e.g. in view of food and fluid intake, diet, **fasting** conditions, drug administration, clinical and other procedures). Adverse events will be monitored throughout the study. The medical care of the volunteers will be guaranteed by the presence or stand-by of the investigator or one of the co-investigators throughout the clinical phase of this trial.

The volunteers will come to the clinic from isolation, described at Appendix VII, at approximately **18:00** on the day before the treatment (Day 0) and will remain there for **90 hours**. A measurement of body temperature will be performed once a day in the mornings during the study period.They will not be allowed to drink water between 1 h before to 1 h after administration, except while dosing (the total intake of water on the days of dosing will be maximum 1.5 L). The investigator will check on each volunteer's wellbeing prior to their discharge from the clinic. If necessary, some volunteers will remain at the clinic until any adverse events have resolved. All volunteers will be subjected to a post-study and final examination and laboratory tests on the day of last sampling in **second period.**

For each volunteer being withdrawn from the study prior to regular termination of the individual study period, due to whatever reason, a complete final examination has to be performed at the time of withdrawal as far as possible with regard to the volunteer's health conditions and as far as necessary with regard to safety aspects. **All taken plasma samples will be analysed. But will not be included to statistical calculations.**

13.2. Special Procedures

Special procedures due to the Covid-19 outbreak will be done as described in Appendix VII.

Study drugs will be administered on the Day 1 and Day 3 (as given in the Study Flow Chart provided in section 6). The subjects will be fasted overnight (minimum of 10 hours) and administrations will take place in the morning approximately at 08:00 a.m. and the exact time will be recorded on CRFs.

The subjects will remain fasting until 4 hours after administration. Subjects are not allowed to drink water from **1 h before** until **1 h after** administration, except that while dosing. Subjects will be dosed in sitting position and they will be instructed to remain in **sitting position in bed** for **4 hours** after drug administration without lying in bed for each period . ***In this interval ($t_{0.17}$-$t_{4.00}$); the blood samples will be performed in bed and lunch will be provided on bed***.

During this study all clinical unit personal will be checked daily by Covid-19 PCR test for safety

13.3. Daily Activities during the Trial

Entry examination:

The entry examination will be carried out on the day of screening of the trial as described in Appendix VII. The following parameters will be documented:

- Written Informed consent
- Inclusion criteria (according to protocol)
- Exclusion criteria (according to protocol)
- Demographic data (date of birth, height, weight, gender, BMI)
- Anamnestic data (medical history, relevant previous diseases)
- Clinical screening and examination (clinical state: body temperature, BP, PR, ECG, registration of pathological findings, if any, **clinical chemistry**, **Covid-19 PCR test**, haematology, HB_sAg, HIV-Ab, HCV-Ab, drug screening, alcohol breath test, urinalysis).

Period 1:

- Interview (possible presence of exclusion criteria and/or adverse events)
- Standardised dinner will be served before dosing on day 0 *(between 18:00 p.m. to 21:00 p.m.)*
- Blood samples will be collected before dosing on day 1 with separation of plasma.
- Treatments will be given according to randomised administration [single oral dose of 1 tablet of the test drug or 1 tablet of the reference drug] with compliance check *(approximately 08:00 a.m.)*
- Blood sampling (0.17-24.00 hours) will be done after drug administration with separation of plasma
- Standardised lunch will be served at 4 hours after the dosing *(between 12:00 p.m. to 13:00 p.m.)*

- Standardised dinner will be served at 10 hours after the dosing *(between 18:00 p.m. to 19:00 p.m.)*
- Standardised light breakfast will be served at approximately 21.30 pm.
- Questioning for and registration of adverse events **at hospitalisation day (Day 0), pre dose and 1.00, 4.00, 8.00, 14.00, 24.00 hours** post-dose*.
- Standardised breakfast, lunch, dinner and light breakfast will be served on Day 2 (including wash-out period)

Note: Covid-19 PCR test will be done at Day 0.

Period 2:

- Interview (possible presence of exclusion criteria and/or adverse events)
- Standardised dinner and light breakfast will be served before dosing day *(at 18:00 p.m. and 21:30 p.m.respectively)*
- Blood samples will be collected before dosing with separation of plasma.
- Treatments will be given according to randomised administration [single oral dose of 1 tablet of the test drug or 1 tablet of the reference drug] with compliance check *(approximately 08:00 a.m.)*
- Blood sampling (0.17-24.00 hours) will be done after drug administration with separation of plasma
- Standardised lunch will be served at 4 hours after the dosing *(between 12:00 p.m. to 13:00 p.m.)*
- Standardised dinner will be served at 10 hours after the dosing *(between 18:00 p.m. to 19:00 p.m.)*
- Standardised light breakfast will be served at approximately 21.30 pm.
- **Questioning for and registration of adverse events** at hospitalisation day (Day 0), pre dose and 1.00, 4.00, 8.00, 14.00, 24.00 hours **post-dose*.**
- Standardised breakfast and lunch will be served on day 4.
- Discharge from the clinic **(after final examinations)**

Final examination:

- The final examination will be carried out on the day of last blood sampling of the **2nd period**. The following parameters will be documented: Interview (occurrence of adverse events)
- Clinical screening and examination (clinical state: body temperature, BP, PR, ECG, registration of pathological findings, if any, clinical chemistry, **Covid-19 PCR test**, haematology, urinalysis)
- Laboratory screening. The sampling for laboratory screening can be performed together with the last sampling for the kinetic profile in **24 hours** post-dose. Abnormal laboratory findings which are judged by the investigator as adverse event at the final examination should be followed up until it will be resolved or is assessed as stable condition or a causality other than trial medication was found and **whole data that collected during the entry examination, study period and final examination will be documented in the CRF.**

13.4. Restrictions

The volunteers will be requested not to undertake vigorous exercise during the 2 days before the initial screening laboratory tests until after the final laboratory safety tests.

When confined to the clinical centre, the volunteers have to avoid from alcohol starting one week before hospitalization day until the last blood sampling of period. Smoking will not be permitted during the study of blood sampling during hospitalization of study. Chewing gum is not allowed. No foods and beverages containing caffeine or other methylxanthines (coffee, tea, coke, chocolate) and fruit-juice from 2 days prior to dosing until the last blood sampling of study will be allowed. No grapefruit containing products from 7 days prior to the dosing until the last sampling will be allowed. The volunteers will abstain from food and beverages from 21:00 on the hospitalization evening until final examination.*(Subjects will not be allowed to drink water between 1 h before to 1 h after administration, except while dosing)*.The total intake of water on the days of dosing during hospitalization will be maximum 1.5 L, beginning **1 hour** post-dosing.

For the ambulatory phases of the study, volunteers will be requested to abstain from alcohol containing foods and beverages for the study starting 24 hours before the initiation of the study until confinement to the clinic. Upon admission to the clinic for study, all volunteers will undergo an alcohol breath test and drug screening in the urine (see 13.1). Volunteers with a positive result of the test will be discontinued from the study.

13.5. Drug Administration

The following treatments will be administered:

Test Drug; Favir 200 mg Film Tablet *(Koçak-Turkey)*

Reference Drug; Avigan 200 mg Film Tablet *(Fuji Film Toyama Chemical Industry Co.Ltd./Japan)*

The precise instructions for drug administration are given in Ethical Committee (EC) and Ministry of Health (MoH) submission file.

Immediately after pre-dose sampling, the volunteers will swallow 1 tablet of the test drug or 1 tablet of the reference drug (favipiravir each case) with 240 mL water. **After the washout period; in Period II, the subjects will be administered by the other drug that they will not administered in the Period I.**

This will be followed by a mouth check. The investigator or the co-investigator will administer the study medication and this will be supervised by a second medical professional to ensure the correct drug administration.

The subjects will be dosed in ascending numerical order according to the randomisation list whilst sitting position and they will be instructed to remain in **sitting position** in bed for **4 hours** after drug administration without lying in bed for each period. In this interval ($t_{0.17}$-$t_{4.00}$); the blood samples will be performed in bed and lunch will be provided on bed.

13.6. Dietary Regimen

An evening meal (total caloric value of approximately 1200 kcal) will be served no later than 21:00 in the 1st hospitalization day (Day 0) in study.

Period I and **Period II:** In treatment day (Day 1 and Day 3);

A standard lunch *(total caloric value is approximately 1200 kcal)* will be provided 4 hours after dosing in study.

A standard evening meal *(total caloric value is approximately 1200 kcal)* will be provided 10 hours after dosing in study.

A standardised light breakfast will be served approximately 21:30 p.m.

Also standard breakfast, standard lunch, standard evening meal and a standardised light breakfast will be served in Day 2. In 4th day of the study standard breakfast and lunch will be served.

The same meal composition has to be served in all study of the trial. This will be documented in the CRF.

13.7. Blood Sampling for Drug Analysis

Venous blood will be drawn at the following times:

Period	Day	Time (hour)*	Tube No
1-2	1	$t_{0.00}$	P01
		$t_{0.17}$	P02
		$t_{0.25}$	P03
		$t_{0.50}$	P04
		$t_{0.75}$	P05
		$t_{1.00}$	P06
		$t_{1.33}$	P07
		$t_{1.66}$	P08
		$t_{2.00}$	P09
		$t_{2.50}$	P10
		$t_{3.00}$	P11
		$t_{3.50}$	P12
		$t_{4.00}$	P13
		$t_{5.00}$	P14
		$t_{6.00}$	P15
		$t_{8.00}$	P16
		$t_{10.00}$	P17
		$t_{14.00}$	P18
	2	$t_{24.00}$	P19

** In the statistical analysis, if the deviation in the planned sampling time is 1 minute and within the range of ± 5% deviation, the values will be used without any correction.*

8 mL blood samples will be drawn at predetermined sampling times during the clinical study to determine plasma **favipiravir** concentrations.

Note: Only in Period I; at t_0 the blood sample amount will be 20 mL and this sample will be divided into tubes and one of this tube will be used for the anti-coagulant validation purpose during the analytical validation process. This plasma sample will send to Novagenix with master and back-up samples.

The blood samples will be taken by a short intravenous catheter. The blood samples will be collected into polypropylene tubes using **K_2 EDTA** as anti-coagulating agent. The total amount of blood taken from each subject will be approximately **358 mL**.

*[Including "The Heparinised Discarded Blood (approximately 10 mL during the study)","Blood for Entry/Final examinations Tests (*approximately 32 mL)"and "Other Repeat Clinical Laboratory Tests that may be deemed necessary during the study"].*

******At entry examination* *the blood sample amount will be 20 mL and 8 mL sample of 20 mL sample will be divided into tubes and one of this tube will be used for the anti-coagulant validation purpose during the analytical validation process. This plasma sample will send to Novagenix with master and back-up samples.* ***At final examination*** *the blood sample amount will be 12 mL and only will be used for clinical laboratory tests.*

After sampling the blood samples for pharmacokinetic analysis, the tubes will be immediately refrigerated at 2 - 8°C and will remain there for not more than 30 minutes. After centrifugation (3.000 rpm, 4 - 6°C, 10 min), the separated **plasma** from each sample will be transferred into two 3 mL transparent, polypropylene tubes per sample (at least 1.5 mL per tube). **All the aliquoted plasma samples will be flash freezing immediately. The flash frozen samples (aliquoted plasma samples) will be transferred to a deep-freezer and stored at -70°C**.

At the end of the study one aliquot will be shipped on dry ice (solid CO_2) according to the sample transport SOP of FARMAGEN-Good Clinical Practice and Research Center by courier for the determination of plasma drug concentrations to the analytical laboratory:

Novagenix Bioanalytical Drug R&D Centre

Esenboğa Yolu 25. Km.

Ankara-Turkey

As precautionary measure, the other aliquot will at first be retained at the clinical unit in case that any adverse conditions, for example due to transport damage of the first shipment.Once the bioanalytical laboratory confirms receipt of the first shipment, the second set of aliquots will be sent.

The samples will be packed on dry ice for transport, no interruption of the freeze chain is allowed and also data loggers will be included for temperature recording.

All labels for blood and plasma samples will be provided by NOVAGENIX and will contain the following information: active ingredient name, study code, subject number, period, tube number and time (e.g. 2 h post-dosing). An example is given below:

Favipiravir	
Study # : **NOV01919**	
Subj # **1**	Period : **1**
Time: 0 h P # : P1	

13.8. Endpoint(s) For The Study

Primary Endpoint: $AUC_{0\text{-}tlast}$ and C_{max} of **favipiravir**

Secondary Endpoint: $AUC_{0\text{-}\infty}$, $t_{1/2}$, t_{max} of **favipiravir**

Safety Endpoints: Adverse events, clinical and laboratory examinations.

14. PREMATURE DISCONTINUATION

The conditions for premature discontinuation of the trial in some particular volunteers or in general are summarized in this chapter.

14.1. Withdrawal of Volunteers

Volunteers may be withdrawn for the following reasons:

- at their own request with or without giving reasons,
- at the discretion of the investigator for reasons of medical prudence.

In either event, the Sponsor will be immediately notified and the date and reasons for the withdrawal will be clearly stated in the volunteer's CRF.

Volunteers must be withdrawn under the following circumstances:

- if personal circumstances suggest that the visits required by the protocol cannot be guaranteed any longer,

- **if Covid-19 PCR test result is positive, the volunteer(s) will be dropped out from study.**

- if adverse events (including intercurrent illnesses) develop, which rule out continuation of the study medication, or, due to impaired validity of the results, make it appear inadvisable to further participate in the study,

- if subjects who have intaked or administrated of any prescribed systemic or topical medication (including OTC medication) within **2 weeks** of the start of the study *(except singles doses of analgesics which have no drug interaction with study products)* given in case of an adverse event (e.g. headache) during the study,

- if circumstances defined as exclusion criteria are registered,

- if administration of any drug is necessary, which is not permitted according to the exclusion criteria (see section 11.2), independently of its necessity due to the occurrence of adverse events (including intercurrent illnesses) or of its use due to other reasons,

- if vomiting occurs at or before 2 times median t_{max}.

- if diarrhea exists during screening and /or medication day.

14.2. Replacement of Drop-outs

A total of **30** volunteers will be enrolled in the trial. If drop-out exists in isolation or in study period, then these dropouts **WILL NOT BE replaced**.

For each volunteer being withdrawn from the study prior to regular termination of the individual study period, due to any reason, a complete final examination has to be performed on the day of drop-out, as far as possible with regard to the volunteer's health conditions and as far as necessary with regard to safety aspects and the validity

of study results. The reason for withdrawal has to be documented in the case report form and in the volunteer's medical records**.**

14.3. Early Termination of the Study

The Sponsor may discontinue the study at any time.

If, in the opinion of the investigator, the clinical observations in the study suggest that it might not be justifiable for medical reasons to continue, she/he may terminate the study after consultation with the Sponsor or the Sponsor may terminate the trial for safety, administrative or other reasons.

Reasons for discontinuation have to be documented appropriately and to be provided to the Sponsor and the Ethics Committee and MoH. In case of premature discontinuation of the study a complete final examination has to be performed for each volunteer as far as possible with regard to the volunteer's health conditions and as far as necessary with regard to safety aspects and the validity of study results.

14.4. Drop-out Samples

All drop-out samples which will be sent by the clinic will be analysed and results will be given in the Final Study Report.

15. ADVERSE EVENTS

15.1. Definition of Adverse Event / Serious Adverse Event / Adverse Drug Reaction / Unexpected Adverse Drug Reaction

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medical product.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- results in persistent or significant disabling/ incapacity
- requires inpatient hospitalization
- prolongs inpatient hospitalization
- is a congenital anomaly/birth defect

An adverse event is defined as an **Adverse Drug Reaction (ADR)** if further analyses prove that the adverse event was caused or partially caused by the study medication:

In the pre-approval clinical experience with a new medicinal product or its new usage all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reaction. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction (UADR) is an adverse reaction, the nature or severity of which is not consistent with applicable product information (e.g., Investigator's Brochure for an unapproved experimental medicinal product, summary of product characteristics for an approved product) or events previously unobserved or undocumented which are not on the basis of what might be anticipated from the pharmacological properties of a medicinal product.

In the course of the study, the investigator will determine whether any adverse events have occurred and will grade their intensity as follows:

- Mild: Awareness of symptoms but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or to carry out usual activity.

15.2. Relationship to the Study Medication

The investigator will make judgement considering whether or not, in his opinion, the adverse event was related to the drug according to the following classification. However, even if the investigator feels that there is no relationship to the drug, the adverse event should be reported.

The likelihood of the relationship of adverse event to the study drug is to be recorded as follows.

Causality assessment of suspected adverse reactions (criteria defined by members of WHO Drug Monitoring Programme):

Certain: A clinical event, including laboratory test abnormality, which occurs in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitely pharmacological or phenomenological, using a satisfactory re-challenge procedure if necessary.

Probable/likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and on which a clinically reasonable response on withdrawal (de-challenge) follows. Re-challenge information is not required to fulfil this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanation.

Conditional/unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessable/unclassified: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

15.3. Reporting and Documentation of Adverse Event(s)

AEs/ADR will be assessed by spontaneous, unsolicited reports of the volunteers, by observation and by routine open questionings of the volunteers. Questionings will be done by experienced staff of FARMAGEN-Good Clinical Practice and Research Center during admission to the clinical facility and at least at the following times of the study period: at **Day 0, pre dose and $t_{1.00}$, $t_{4.00}$, $t_{8.00}$, $t_{14.00}$, $t_{24.00}$** hours after the drug administration. If any adverse event occurs, it will be recorded on the Adverse Event Report page of the CRF. All findings will be recorded in English. The documentation includes type of AE/ADR, date and time of onset, treatment initiated (if applicable), outcome, intensity/severity code (mild, moderate, severe) and whether the event is serious. It is important that the investigator immediately reports any adverse event which by the definitions given above would be considered serious, even if the investigator does not consider the adverse event to be clinically significant or drug-related.

Occurrence of any serious adverse event has to be reported by the investigator immediately (within 24 hours), the latest on the next working day, by phone and e-mail and/or by fax to **Koçak Farma İlaç ve Kimya San. A.Ş. or to ALPAN FARMA** as an initial report.

As soon as new information about the SAE becomes known, the investigator has to forward it without any delay to **Koçak Farma İlaç ve Kimya San. A.Ş. or to ALPAN FARMA**. This applies to the follow-up and/or final SAE report and all medical records associated with it.

A copy of the updated CRF-page for AE and SAE documentation will be forwarded to **ALPAN FARMA or Koçak Farma İlaç ve Kimya San. A.Ş.** as soon as possible.

The responsible sites for the upper procedure are:

Koçak Farma İlaç ve Kimya San. A.Ş. **Contact Person**	**Alpan Farma Ltd.Şti.** **Contact Person**
Cem Koçak Phone: (+90) 212 410 39 50 Fax: +90 212 447 61 63 E-mail: ckocak@kocakfarma.com	**Prof. Dr. Aydın Erenmemişoğlu** Phone: +90 536 216 27 21 GSM: +90 532 551 00 82 E-mail: erenmemis@gmail.com

Serious adverse events will be reported to sponsor and/or CRO by investigator immediately. After that, sponsor and/or CRO will report to the EC, MoH and to the regulatory authorities of the study site according to the local legal requirements in 7 days.

Serious Adverse Events which occurred within two weeks after termination of the clinical trial and which are considered to be related to the trial must also be reported.

Any Adverse Event which is not resolved at the final visit should be followed-up until it will be resolved or assessed as a stable condition or causality other than the trial medication has been found.

16. STUDY DOCUMENTATION

16.1. Investigator's File

The investigator Trial File of the study will be included at least the following documents:

1. Investigator and co-investigator's curriculum vitae
2. Correspondence including relevant notes from telephone contacts
3. List of monitoring visits/audit visits/inspections
4. Signature sheet of clinical team
5. Final volunteer information and informed consent form and volunteer identification
   5.1 Signed informed consent forms
   5.2 Sample Volunteer information and informed consent with any translation
   5.3 Volunteer identification (screening log, identification list)
6. Test and Reference Products
   6.1 Drug accountability sheets (receipt, dispense, return)
   6.2 Shipment, receipt, return, etc.
   6.3 Sample of labels attached to investigational product(s) containers
7. Investigational products accountability at the site
8. Trial Material (orders, deliveries, shipments, return and disposal if applicable)
9. Study Protocol
10. Special instructions concerning the conduct of the study, if available
11. Sample CRF book
12. Analytical Study Plan
13. Hematology, Biochemistry and Serology tests' normal ranges and certification/accreditation of Test's Laboratory
14. Safety Documentation
    14.1 Documentation of SAE reports
    14.2 Safety overviews: periodic reports sent to EC and MoH (country specific/whole study)
    14.3 Erroneous SAE reports
15. EC and MoH approval
16. Insurance statement and conditions
17. Subject screening and enrolment log
18. Subject identification code list
19. Regulatory Authority Approval/Notification (if applicable for the centre)
20. GCP statement of investigator, personnel responsibilities signatures and CVs
21. Financial arrangements and contracts with sponsor/investigator/CRO
22. Product information (Investigator' Brochure or Summary of Product Characteristics)
23. ICH-GCP Guidelines and local law (if applicable)
24. CRFs of volunteers screened but not randomised (copies)
25. CRFs of volunteers enrolled in the study in ascending order (copies), source Documents
26. According to ICG GCP a copy of site initiation report should be added in Investigator's site File

16.2. Case Report Form (CRF)

NOVAGENIX will design the Case Report Form in close co-operation with the Sponsor. Standardized CRFs will be used as **source document regarding** volunteers' raw data during the course of the study. The investigator will assure that all data are entered promptly, legibly, completely, accurately and in accordance with other source documents **(e.g. ECGs, laboratory results, diet and fluid intake records)**. This procedure will be applied to the data of both volunteers who met the inclusion criterion and will be included into the study and the volunteers that will not be included into the study because of a valid reason.

To ensure legibility, the CRFs should be filled out only with a blue ball-point.

Any corrections to the CRFs must be carried out by the investigator or his designate. A single stroke must be drawn through the original entry. The reason for the correction has to be given and it has to be dated and initialled. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way.

Even if there are no changes from a previous examination, in the interests of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full text. A reasonable explanation must be given by the investigator for all missing data.

The CRFs will be completed immediately after termination of the individual treatment and observation periods and the final examination. After being signed by the investigator, they will be sent to NOVAGENIX for data validation. Thereafter, CRFs will be returned to NOVAGENIX and eventually forwarded to the Investigator for final corrections, if applicable. CRFs can not be sent by post but only be personally submitted to the NOVAGENIX monitor during a visit or sent by courier. Any other way of transport is to be previously discussed with the NOVAGENIX. NOVAGENIX will send the original CRFs to Sponsor with the final report of the study. NOVAGENIX will store the copy of all CRFs.

All medical records upon which the CRFs are based must be kept for **at least 14 years** after completion of the study. At this time **ALPAN Farma** will discuss with the Sponsor whether or not storage is required for a longer period. Image carriers or other data carriers can be used for the purpose of storage.

17. ANALYTICAL EVALUATION

Plasma concentrations of **favipiravir** will be determined by means of a validated **LC** method, according to Novagenix's SOP NOV-ENG-08-TEC1.

Detailed characteristics of the analytical method applied will be described in the "Analytical Study Plan" (see **Appendix III: Analytical Study Plan**). *All assay validations will be performed in consideration of the Guideline on Bioanalytical Method Validation,EMA,21 July 2011 and US FDA Guidance for Industry, Bionalytical Method Validation May 2018 or current guidance on method validation date.*

Volunteer's all samples will be measured in a single analytical run in order to eliminate the influence of the inter-assay variance on the assessment. The analyst has to provide a final analytical report with tables for all samples that were analysed.

Already measured samples will be stored at <-20°C for at least 6 months (storage period can be prolonged in exceptional cases, e.g. upon special request of authorities) after termination of bio-analysis. At that point a further decision by the Sponsor will be taken.

20% of the chromatograms are to be included in printed Final Study Report. But 100 % of chromatograms will be given also as electronically.

17.1. Reanalysis of study samples

The reasons for reanalysis of study samples are presented in **Appendix III: Analytical Study Plan.**

17.2. Incurred Sample Reanalysis

Incurred Sample Reanalysis (ISR) will be performed at any time after starting subject analysis by choosing two sampling points near or at C_{max} and two sampling points in the elimination phase per period (total 8 sampling points per subject). These ISR points will be selected according to the literatures and/or in the very first batches of subject analysis. The subjects will be randomly selected and the number of subjects that defined as ISR points will be equal or more than 10% of samples for the first 1000 study samples and an additional 5% of samples for study samples in excess of 1000. The difference between the study samples' and incurred samples' values obtained should be within 20% of the mean for at least 67% of the repeats according to EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2. Guideline on Bioanalytical Method Validation. London, 21 July 2011, p.13-14; Novagenix's SOP-NOV-ENG-08-CQU4 and documented in the Final Study Report.

18. PHARMACOKINETIC EVALUATION

Pharmacokinetic parameters of **favipiravir** will be determined using non-compartmental methods from measured plasma concentrations.

For each treatment (**Test Drug** or **Reference Drug**) and each volunteer participating completely in this **single-dose, two period, cross-over study** the following pharmacokinetic parameters will be calculated:

Primary pharmacokinetic parameters:

C_{max}: Maximum observed plasma concentration

$AUC_{0-tlast}$: Area under the plasma concentration-time curve from zero to the last measurable concentration, calculated by the linear log trapezoidal rule.

Secondary pharmacokinetic parameters:

$AUC_{0-\infty}$: Area under the plasma concentration-time curve, calculated by extrapolation to infinity.

t_{max}: Time to maximum observed plasma concentration

$t_{1/2}$: Terminal half-life

Additional pharmacokinetic parameters:

MRT: Mean residence time

λ_z: Terminal rate constant.

For pharmacokinetic calculations, the program package **Phoenix WinNonlin (Version 8.1, Certara L.P.)** or above will be employed. Phoenix WinNonlin will also be used to generate concentration/time plots.

19. STATISTICAL PROCEDURES

The statistical analysis of the pharmacokinetic data described in this section corresponds with provisions according to the ***EMA guideline for bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)- 2010***.

Statistical analysis will be performed as a valid case analysis including all volunteers in which no major protocol deviations occurred and all primary target variables are available for measurement.

If a volunteer is to be excluded from evaluation, this decision has to be justified in the Final Study Report. Statistical analysis will be performed by means of the program **Phoenix WinNonlin (Version 8.1, Certara L.P.)** or above.

19.1. Target Variables

19.1.1. Primary Target Variables

C_{max} and **$AUC_{0\text{-}tlast}$** are declared to be primary target variables.

19.1.2. Secondary Target Variables

$AUC_{0\text{-}\infty}$, t_{max} and **$t_{1/2}$** are declared to be secondary target variables. **MRT** and **λ_z** will be determined also.

In order to achieve a better approximation to a normal distribution C_{max} and AUCs data will be logarithmically transformed (base e) before analysis. The sources of variation will be treatments, periods, sequence and subjects (nested within sequence) in Analysis of variance (ANOVA). Evaluation of treatment, period, sequence and subject (nested within sequence) effects at 5% level of significance will be performed. From the result of this procedure, the two one-sided hypothesis at the 5% level of significance will be tested by constructing the 90% confidence interval for the geometric mean ratios test/reference products. The confidence interval is calculated by retransformation of the shortest confidence interval for the difference of the ln-transformed mean values. Differences in t_{max} will be evaluated non-parametrically.

Bioequivalence will be concluded if the 90% confidence intervals for the geometric mean ratios of the products (test/reference) are fully contained within the limits of acceptance of **80% - 125%** for C_{max} and $AUC_{0\text{-}tlast}$. For the secondary target variables, the 90% confidence intervals will be investigated for exploratory purposes.

Evaluating excluding values from statistical calculations, the criteria which are given in “Novagenix SOP-NOV-ENG-08-CQU5” will be applied.

These criteria are;

1. If a suspicious case about safety of blood samples such as in the absence of label, label is not read exactly or any confusion of sample, these samples are documented on “Protocol For Handing Over Receipt of Samples” form. These samples are analysed but not included in statistics.

2. After completing study analysis, reanalysis is done due to analytical reason according to SOP-NOV-ENG-08-TEC1 and SOP-NOV-ENG-08-CQU4. If the reanalysed data is still invalid for the analytical reason and there is insufficient plasma sample for reanalysis, that data should be excluded from statistical analyses. Any exclusion should be properly reported on final study report.

3. A subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of reference medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). That subject will be evaluated and may be excluded. Accordingly the two results are reported in final study report.

4. Subjects with non-zero baseline concentrations > 5% of C_{max}. Such subject should be excluded from statistical calculation.

5. Total number of subject should not be under 12 in the statistical calculation, whether not this study would be repeated from the clinic part.

19.1.3. Safety Evaluation

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (*e.g.* electrocardiogram, vital signs and special tests) will be considered as appropriate.

19.2. Calculation of Sample Size

The intra-individual variability of C_{max} is estimated as 17% according to only one literature. Since there is insufficient information for intra-individual variability, sample size has been choosen as **30 subjects** in order to demonstrate bioequivalence for a 2x2 crossover design.

19.3. Randomisation

The randomisation table will be provided by Novagenix. **30 subjects**, who will be included in the study, will be determined to receive either Test or Reference Product [In each study period, subjects will take different products (one dose of Test Drug or one dose of Reference Drug)] by a randomisation table.

30 subjects, who will be included in the study, will be determined to receive either Treatment A or Treatment B in Period I and Period II by a randomisation table generated by a computer programme. Which one of the Test or Reference administration will be Treatment A or Treatment B is randomised by the Investigator. All the analytical analyses are done without the knowledge of the Test and the Reference product. These products will be named and known as Treatment A or Treatment B by CRO. Then the form defining Treatment-Period relationship will be enveloped, sealed and sent to CRO by the Investigator. CRO will open the sealed envelope in the “Project Evaluation Meeting” which will be held after the laboratory analyses are completed. Once the seal is opened, no new reanalyse or no data change/exclusion will be allowed.

19.4. Documentation of the Data

Measured plasma concentrations will be listed per treatment for each volunteer and each sampling point. In addition, mean values, standard deviations and the standard error of the mean will be given per sampling point of each treatment.

For all pharmacokinetic parameters determined, the individual values per treatment will be tabulated with descriptive statistics (i.e. calculation of arithmetic means, standard deviation and standard error of the mean, geometric means, minimum, maximum, median and the number of evaluated values).

To display the time course of the plasma concentrations, individual concentration time curves as well as mean curves for each formulation will be plotted both in the linear and loglinear scale, using **Phoenix WinNonlin (Version 8.1, Certara L.P.)** or above.

All results will be summarized in tables and plots and will be reported and discussed in the Final Study Report.

Descriptive analysis of demographic and safety data reported in the CRFs will be included in the Clinical Raw Data.

19.5. Interim Evaluation

No interim evaluation is planned in the present trial.

20. ETHICAL CONSIDERATIONS

20.1. Ethical Conduct of the Study

The study will be performed in accordance with the relevant articles of the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West, RSA (1996), Edinburgh (2000), Washington (2002), Tokyo (2004) and Seoul (2008) and Fortaleza (2013).

20.2. Ethical, Legal and Administrative Aspects

Prior to the initiation of the study, the protocol, the volunteer information leaflet, the informed consent and other related documents will be submitted to the Ethics Committee (EC) and Ministry of Health (MoH) by NOVAGENIX for review and approval. The CRO project responsible and the Investigator must inform each other in writing that all ethical and/or legal requirements have been met before the first volunteer is enrolled into the study. In case of both two approvals, the study can be started immediately after the copies of approvals have been sent to the Sponsor. If protocol changes require the preparation of an amendment, this amendment has to be submitted to the EC and MoH for approval or only for notification provided that the amendment does not concern the safety and the well-being of the volunteers.

The study will only be performed when full approval of the study protocol has been obtained from the EC and MoH and copy of the certification has been received. A list of the members of the Ethics Committee will be attached, too.

Ethics Committee
Erciyes University
School of Medicine
38039 Kayseri, Turkey

Ministry of Health, Turkish Medicines and Medical Devices Agency
Söğütözü Mah. 2176 Sok. No:5
Çankaya, Ankara-Turkey

20.3. Volunteer Information and Informed Consent

Before being admitted to the clinical study, the volunteer must consent to participate in the study by signing the informed consent form on the day of screening as described in Appendix VII in response to a complete written and verbal explanation of the nature, scope and possible consequences of the clinical study explained in an understandable way for him/her by the physician.

The volunteers must be able to understand the full implications of their decision.

The **Volunteer Informed Consent Forms** will be prepared by NOVAGENIX and is given as attachment to this study protocol (see **Appendix IV**). It will explain the nature of the study, its objectives and potential risks and benefits. In addition, the following points must also be covered:

- a description of the aims of the study and how it will be organized
- the type of treatment and the way in which the volunteers will be allocated to treatment (e.g. by randomisation)
- the positive effects which can be expected of the study treatments
- any negative effects possibly attributable to the study treatments
- the freedom to ask for further information at any time
- the volunteer's right to withdraw from the clinical study at any time without giving reasons and without jeopardizing the further course of treatment
- the existence of volunteer insurance cover
- the right of the monitor and an independent authorized person to look into personal data.
- Personal information will be treated as strictly confidential and not be publicly available.

The **Volunteer Informed Consent Forms** (see **Appendix IV**) will be supplied by NOVAGENIX and will be also translated into Turkish. The translated forms will be used for confirmation of the volunteer's consent by the signature of the investigator and the volunteer.

The volunteers will be informed about this study by verbal and by reading the Volunteer Informed Consent Form from an authorized medical doctor who is in the clinical study team.

Each volunteer will give in writing his authorization that the study data may be given for review to the responsible Local and National Authorities.

The volunteer information and informed consent form will be provided in duplicate *[one signed version (original 1) will be left at the investigator; the other signed version (original 2) will be forwarded to the volunteer]*.

To ensure medical confidentiality and data protection, the signed informed consent forms remain with the investigator and must be kept there for at least **14 years** after the study has been completed. The investigator will allow these documents to be inspected on request and will affirm - by signing and dating - in the case report forms that informed consent has been obtained. The investigator will not undertake any investigations specifically required only for the clinical study until valid consent is obtained.

21. GOOD CLINICAL PRACTICE

21.1. Legal Requirements

This study will be conducted in accordance with the following:

- The Guidance for GCP, published by the Ministry of Health of Turkey. Circular, 13.11.2015.
- The Guidance on Safety Declaration of Clinical Trials , published by the Ministry of Health of Turkey, 13.11.2015.
- Regulation Amending the Regulation of Ministry of Health of Turkey for Clinical Trials. Official Journal, No: 29474; 13.09.2015.
- Regulation Amending the Regulation of Ministry of Health of Turkey for Clinical Trials. Official Journal, No: 29041; 25.06.2014.
- Regulation on Clinical Trials of Drugs and Biological Products. Official Journal, No: 28617; 13.04.2013.
- Regulation on the Principles of Good Laboratory Practice, Harmonisation of the Test Units, Supervision of Good Laboratory Practices and the Studies. Official Journal, No: 27516, 09.03.2010.
- Regulations on Evaluation of Bioequivalence and Bioavailability of Pharmaceutical Preparations. Official Journal, No: 21942; 27.05.1994.
- Guideline on Bioanalytical Method Validation, EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2, London, 21 July 2011.
- Guideline on The Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev.1/Corr., London, EMA, 20 January 2010.
- Bioanalytical Part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials: EMEA/INS/GCP/97987/2008, London, 28.05.2008.
- Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products- General Considerations. FDA, CDER, March 2003.
- Guidance for Industry. Statistical approaches to establishing bioequivalence. FDA, CDER, January 2001.
- ICH Topic E 9. Statistical Principles for Clinical Trials. September 1998 (CPMP/ICH/363/96).
- Guideline for good clinical practice E6(R2)-2017. EMA/CHMP/ICH/135/1995.
- Guidance for Industry. Bioanalytical Method Validation. FDA, CDER, May 2018.
- ICH Topic E3. Note for Guidance on Structure and Content of Clinical Study Reports. Step 4. Consensus Guideline from 30.11.1995 (CPMP/ICH/137/95).
- GLP Principles of Good Laboratory Practice as specified by international (OECD- Paris 1998.; Directive 2004/10/EC of the European Parliament and of the council of 11 February 2004)
- ICH Topic E2A. Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, November 1994 (CPMP/ICH/377/95).
- Declaration of Helsinki, Fortaleza, 2013.

21.2. Preventive Measures to Reduce Bias

The following measures are incorporated into the study in order to minimize bias:

- Volunteers are sequentially assigned to randomly ordered treatments,
- Volunteer enrollment is dependent on satisfactory fulfilment of the given list of inclusion criteria,
- The circumstances when individual volunteers withdraw prior to planned completion of the study are specified.

21.3. Investigator's Obligations

Prior to initiation of this study, the investigator will approve this protocol by signing the signature page. This signature confirms that the study will be performed in compliance with the protocol. The investigator must ensure that the Sponsor or the **ALPAN Farma** provides adequate documents (i.e. Product Information) giving information about the pharmacological and toxicological properties of the test product.

The investigator or his medically educated representative will review the CRFs for completeness and accuracy. The investigator will sign and date the CRFs and any changes in the CRF.

The signatures serve to attest that the information contained in the CRFs is true and has not been falsified. In case of a correction the reason for it shall also be given. It is the investigator's responsibility to assure completion of entries and to review and approve all CRFs. At all times the investigator has the final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the CRFs (section 16.2).

21.4. Adherence to the Protocol

Protocol violations are any deviations from the procedures outlined in this document, missing evaluations, incorrect timing of evaluations, non-compliance with study procedures and intake of prohibited medications.

After a volunteer has been enrolled, it is the investigator's responsibility to make a reasonable effort to avoid any protocol violations and to keep the subject in the study.

All protocol violations will be reported immediately to the Sponsor during the course of the study. The nature of these violations will be defined in written form. All protocol deviations will be listed and will be discussed with the Sponsor prior to the statistical analysis.

The investigator undertakes all reasonable measures to record data in adherence with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the investigator. All such deviations will be documented on the project records, together with the reason for their occurrence, and where appropriate, detailed in the study report.

21.5. Data Handling Procedures

The results from screening and data collected during the study will be recorded in the volunteer's Case Report Form (CRF) which will be designed and printed by NOVAGENIX. Each volunteer receives a code number. His personal identification remains in a separate confidential file that can be used only together with the investigator. Each CRF will be signed and dated by the investigator. All corrections in the CRFs are to be made legibly and signed by the investigator.

The investigator is responsible for the transfer of CRF and other required documents to ALPAN Farma. All CRFs are thereafter delivered to ALPAN Farma. Copies of all CRFs will be sent to NOVAGENIX by ALPAN Farma for Final Study Report writing.

In order to maintain volunteer confidentiality, all data recorded during the course of the study will only be identified by volunteer initials and volunteer study number. However, the investigator agrees to record the complete volunteer identification on the volunteer identification list. This list will be treated with strict adherence to confidentiality and will be filed in the Investigator's File.

21.6. Monitoring

It is the responsibility of the investigator to assure that the study is conducted in accordance with the protocol and that valid data are entered into the CRF.

Monitoring and auditing of this study will be performed by **Sponsor's** authorized personnel in order to check the adherence to the protocol in compliance with Good Clinical Practice guidelines and to ensure international acceptability of the study data. In support of these measures, the investigator will make the records available to **ALPAN Farma** or **to the Sponsor** upon request at reasonable times. Case report forms will be checked for completeness and clarity.

Data verification is legally required and will be done by direct comparison with source documents in case of volunteer's respective consent with data on CRFs or by cross-checking with source documents in the presence of the investigator - always giving due consideration to data protection and medical confidentiality.

The investigator will permit a representative of Sponsor to monitor the study as frequently as necessary to determine that data recording and protocol adherence are satisfactory. The CRFs and related documents will be reviewed in detail in accordance with the Sponsor and Good Clinical Practice regulations.

Monitoring of this study will be performed by **Sponsor's** authorized personnel at suitable intervals throughout the study. These visits will be for the purpose of verifying adherence to the protocol and the completeness and exactness of the data entered on the Case Report Forms. The Sponsor is allowed to get any information about the state of the study. Case Report Forms will be transported from the investigator via **ALPAN Farma** to **the Sponsor** after completion of the trial.

It is the investigator's obligation to assure documentation of all relevant data in the volunteer's file, such as medical history / concomitant diseases, date of study enrolment, visit dates, results of examinations, administrations of medication and adverse events.

The investigator will affirm and uphold the principle of the subject's right to protection against the invasion of privacy. Throughout the study, all data will only be identified by volunteer number and volunteer initials. The data will be blinded correspondingly in all data analyses.

After completion of the study, all unused study medication and empty sachets will be collected by the **ALPAN Farma** and returned to the Sponsor.

21.7. Auditing

In order to guarantee that the performance of the study is in accordance with the GCP provisions, in-house and, if needed, on-site audits may be carried out. The auditor will be independent from the staff involved in the proceedings of this clinical study.

The investigator agrees to give the auditor access to all relevant documents for review. The same applies in case of an inspection of local or national authorities. In case of any inspection of FARMAGEN-Good Clinical Practice and Research Center by an outside authority, the Sponsor will be consulted before the Inspectors are permitted access to any of the project records.

After every on-site audit the investigator will receive an audit confirmation by the auditor. This has to be filed together with the study documentation and be made available to the local authorities in case of inspection. At the end of the study, an audit certificate will be included in the final report.

The NOVAGENIX Quality Assurance Unit (QAU) may conduct an inspection of the study procedures. The findings will be reported to the CRO Project Responsible.

21.8. Confidentiality

Volunteers will be informed that all study findings will be stored on computer and handled strictly confidential. Volunteers will be identified throughout documentation and evaluation by the individual volunteer number only, whereas all volunteer names will be kept secret by the investigator.

All information concerning study medication, all study materials and study drugs shall remain the property of the Sponsor. NOVAGENIX and the investigator are obliged to keep all data and information of the study confidential and to use those data only after permission of the Sponsor. It is understood that no study material or information developed in this trial in connection with **Favir 200 mg Film Tablet** by the Sponsor shall be made available to third parties, except for official representatives such as Regulatory Authorities.

21.9. Insurance

The volunteers will be insured by ALPAN Farma in accordance with the requirements and regulations for participants in a clinical trial. This insurance is taken out with **Mapfre Sigorta A.Ş**.

A copy of the Insurance Certificate for this study is included in **Appendix V** of this protocol.

21.10. Subject Payment

It will be paid by **ALPAN Farma** to the volunteers who will participate the clinical phase of the study for the loss of their working days and their expenditure during and for the trial *(e.g. transportation, communication, meal, accommodation, etc.)*. The amount is determined in the Budget Form in the EC and MoH submission files.

21.11 Qualification of the Investigator

By his signature of the study protocol, the investigator certifies that she/he has more than 5 years experience in the conduction of clinical trials. A signed and dated CV of the investigator containing this information will be submitted in **Appendix VI** of this study protocol.

22. PROTOCOL AMENDMENTS

22.1. Protocol Modifications

In order to ensure most comparable conditions during all phases of the trial and in the interests of valid statistical analysis neither the investigator nor NOVAGENIX or the Sponsor will alter the study conditions agreed upon and set out in this protocol.

Amendments should be made only in exceptional cases and by mutual agreement between the investigator, **NOVAGENIX, ALPAN Farma** and the **Sponsor**. Any amendment must be set out in writing, at the same time giving the reasons, and signed by all parties concerned. The amendment then becomes part of the study protocol.

Amendments which might have an impact on the safety and well-being of the subject such as the use of additional invasive examination methods require a new vote by the EC and MoH and a further Informed Consent Form that is to be signed by all subjects enrolled in the trial who are affected by the amendment. Other changes will only be submitted to the EC and MoH in a written form.

The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC and MoH approval opinion. As soon as possible, the implemented deviation or change, the reason for it, and if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the EC and MoH for review and approval opinion,

(b) to the Sponsor for agreement and if required,

(c) to the regulatory authority(ies).

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval opinion from EC and MoH of an amendment, except where necessary to eliminate an immediate hazard(s) to volunteers, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

If the approval by an EC and MoH is required for amendments, this must also be sought.

22.2. Protocol Violations

Protocol violations are major deviations from the procedures outlined in this document like missing evaluations, incorrect timing of evaluations, non-compliance with study medication and intake of prohibited medications. After a subject has been enrolled, it is the investigator's responsibility to make a reasonable effort to correct any protocol violations and to keep the subject in the study.

Protocol violations will be reported to the CRO Project Responsible during the course of the study in Monitoring Reports. All protocol violations with a possible influence on the aim of the trial will be listed and the evaluability of the subject concerned will be discussed in a blinded meeting with the CRO Project Responsible prior to the statistical analysis.

23. REPORTS

Prior to issuing the Final Study Report, NOVAGENIX will prepare a draft report according to the ICH guideline for approval by sponsor. The draft report will be submitted for a Quality Assurance audit and any findings or notifications will be appropriately considered in the final version. NOVAGENIX will prepare one Final Study Report with original signatures and send to sponsor both in paper and as CDs.

23.1. Archiving

ALPAN Farma will store all essential documents (i.e. original CRFs, Clinical Study Protocol, audit certificates, all written statements concerning the study etc.) and the Final Study Report at least **14 years.**

The investigator will keep the volunteer files and original data as long as possible and according to the local methods and facilities. The investigator should maintain the trial documents as specified in the ICH-GCP guideline (essential documents). The investigator must take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained for at least **14 years** after the completion of study. The subject identification codes list and subject's signed informed consent will be archived for at least **14 years**.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator when there is no further need to retain these documents.

Documents of a terminated study have to be archived accordingly at least **14 years** after termination of the study.

In case of any change concerning the archiving procedures the investigator/institution has to inform the Sponsor immediately.

24. COMMUNICATION OF STUDY RESULTS

Any publication requires the consent of the Sponsor.

By signing the protocol the investigator gives his/her consent that the trial results may be used for authorization purposes, for the compilation of information material and the publication. Results deriving from the present study can only be published by NOVAGENIX if both the Investigator, ALPAN Farma and the Sponsor give their consent.

25. CONTRACT AND COSTS

ALPAN Farma and the Investigator conclude an agreement on fees. This agreement considers the number of volunteers that are to be included and the costs determined by the visits performed for each volunteer, hospitalization and for laboratory analyses.

The expenditures of volunteers who are terminated their participation at an earlier point are paid according to the actual number of visits conducted, according to the provisions of the contract signed.

ALPAN Farma and Sponsor conclude an agreement on payments. This agreement covers the costs of clinic, analysis, biometrics and reporting.

Agreements on the amount and the methods of payment will be signed separately between the ALPAN Farma and the Investigator and Sponsor as well as between ALPAN Farma and Sponsor.

26. FINAL REGULATIONS

ALPAN Farma certifies that the information in this protocol is consistent with the current benefit-risk evaluation of the study medication, and the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (last revision).

Current versions of the SOPs will be used during the study.

The Sponsor will supply the Investigator and **ALPAN Farma** with details of any significant or new findings, including adverse events, relating to treatment with the study medication.

By signing the protocol the Investigator certifies that she/he has received the following documents:

- Product information
- Text of the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West, RSA (1996), Edinburgh (2000), Washington (2002), Tokyo (2004), Seoul (2008) and Fortaleza, 2013.
- Text of the ICH Guideline for Good Clinical Practice (2017)
- A sufficient number of volunteer information sheets, informed consent forms, CRFs and forms for reporting serious adverse events ("Serious adverse event in clinical study") to start the study
- Furthermore, by signing this protocol the investigator affirms that
- He has been adequately informed on the study drug and agrees that the study protocol contains all information required to perform the study as set out in the protocol.
- The first volunteer will not be included in the study until receipt of approval by the EC and MoH and/or until all legal requirements have been fulfilled.
- The study will be conducted in accordance with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (last revision), with ICH Guideline for Good Clinical Practice (2017) and the Turkish Drug Regulations.
- Informed consent to participate for all volunteers enrolled in the study will be obtained according to section 20.3 of this protocol, and that the consent forms as well all source data will be kept for 14 years.
- She/He will submit to the ALPAN Farma an up-to-date Curriculum Vitae.

27. REFERENCES

1. **Report on the Deliberation Results of Avigan Tablet 200 mg (Favipiravir), Pharmaceuticals and Medical Devices Agency (PMDA), 04.03.2014** https://www.pmda.go.jp/files/000210319.pdf

2. **Prescribing information of Avigan Tablets 200 mg, revised date 11.2017** https://health.tainan.gov.tw/warehouse/%7BEF3588B5-E673-41F4-88D8-B4CF30E9C27F%7D/%E5%85%AC%E8%B2%BB%EF%A7%8A%E6%84%9F%E6%8A%97%E7%97%85%E6%AF%92%E8%97%A5%E5%8A%91Avigan%E4%BD%BF%E7%94%A8%E6%96%B9%E6%A1%88.pdf

3. **EMA, CHMP Assessment Report, Medicinal Products under Development for the Treatment of Ebola, 03.02.2016 https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-medicinal-products-under-development-treatment-ebola_en.pdf**

4. **EMA, Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version.3 28.04.2020** https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

5. **MHRA, Advice for Management of Clinical trials in relation to Coronavirus, 12.03.2020** https://mhrainspectorate.blog.gov.uk/2020/03/12/advice-for-management-of-clinical-trials-in-relation-to-coronavirus/

6. **FDA, FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, updated :02.04.2020** https://www.fda.gov/media/136238/download

7. The Guidance for GCP, published by the Ministry of Health of Turkey. Circular, 13.11.2015.

8. The Guidance on Safety Declaration of Clinical Trials , published by the Ministry of Health of Turkey, 13.11.2015.

9. Regulation Amending the Regulation of Ministry of Health of Turkey for Clinical Trials. Official Journal, No: 29474; 13.09.2015.

10. Regulation Amending the Regulation of Ministry of Health of Turkey for Clinical Trials. Official Journal, No: 29041; 25.06.2014.

11. Regulation on Clinical Trials of Drugs and Biological Products. Official Journal, No: 28617; 13.04.2013.

12. Regulation on the Principles of Good Laboratory Practice, Harmonisation of the Test Units, Supervision of Good Laboratory Practices and the Studies. Official Journal, No: 27516, 09.03.2010.

13. Regulations on Evaluation of Bioequivalence and Bioavailability of Pharmaceutical Preparations. Official Journal, No: 21942; 27.05.1994.

14. Guideline on Bioanalytical Method Validation, EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2, London, 21 July 2011.

15. Guideline on The Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev.1/Corr., London, EMA, 20 January 2010.

16. Bioanalytical Part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials: EMEA/INS/GCP/97987/2008, London, 28.05.2008.

17. Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products- General Considerations. FDA, CDER, March 2003.

18. Guidance for Industry. Statistical approaches to establishing bioequivalence. FDA, CDER, January 2001.

19. ICH Topic E 9. Statistical Principles for Clinical Trials. September 1998 (CPMP/ICH/363/96).

20. Guideline for good clinical practice E6(R2)-2017. EMA/CHMP/ICH/135/1995.

21. Guidance for Industry. Bioanalytical Method Validation. FDA, CDER, May 2018.

22. ICH Topic E3. Note for Guidance on Structure and Content of Clinical Study Reports. Step 4. Consensus Guideline from 30.11.1995 (CPMP/ICH/137/95).

23. GLP Principles of Good Laboratory Practice as specified by international (OECD- Paris 1998.; Directive 2004/10/EC of the European Parliament and of the council of 11 February 2004)

24. ICH Topic E2A. Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, November 1994 (CPMP/ICH/377/95).

25. Declaration of Helsinki, Fortaleza, 2013.

28. LOCATION OF STUDY DOCUMENTATION

The following documents are kept in the Project File at **FARMAGEN** and **ALPAN FARMA** with coded **NOV2020/01919** as printout and/or electronically in server:

1. The Approved and Originally Signed Protocol and Its Amendments, as well as Other Relevant Signature Documents *
2. Announcement of The Trial to The Central Authorities *
3. Announcement of The Trial to The Local Authorities *
4. Agreement(s) with The Investigator(s)
5. The Ethics Committee Approval Notice **,
6. The Ministry of Health Approval Notice **
7. The Correspondence with The Sponsor, Investigator, Ethics Committee, Ministry of Health and Personnel Involved in The Study
8. Curricula Vitae for Key Clinical Personnel ***
9. Copy of The Sample Volunteer Information Document and Informed Consent Form
10. Copy of the CRF and Additional Related Documents (Form for SAE)
11. Personnel Assignment List with Signatures **
12. Randomisation List
13. Trial Medication Documents (Record of The Receipt **, Dispensing and Disposal of Drug Supplies **, Analytical Certificates, Copy of The Labelling of Trial Medication)
14. Laboratory Reference Ranges and Laboratory Certificate **
15. Audit Certificates (if available) **
16. Volunteer's Insurance
17. Screening-log, Identification***- and/or Enrolment-log of Volunteers
18. Monitoring Reports **
19. Documentation of Data Handling, Plausibility Checks, Data Base Codes and Closure
20. CRFs of all Volunteers Including Query Forms *
21. Reports on Serious and/or Unexpected Adverse Events (Adverse Drug Reactions) *
22. Publications
23. Records of any Deviation From Planned Procedures

* ***original;***
** ***copy will be sent to the Sponsor***
*** ***only in clinical center***

29. APPENDICES

Appendix 1: Table of Body Mass Index

Appendix 2: Case Report Form

Appendix 3: Analytical Study Plan

Appendix 4: Volunteer Informed Consent Form

Appendix 5: Copy of Insurance Certificate

Appendix 6: Curriculum Vitae for key CRO and Clinical Personnel and Dietitian

Appendix 7: Isolation procedure due to Covid-19 pandemic

APPENDIX 1: TABLE OF BODY MASS INDEX

BODY MASS INDEX

BODY WEIGHT IN KILOGRAMS ACCORDING TO HEIGHT AND BODY MASS INDEX[#]

	Body Mass Index (kg/m^2)													
	19.0	20.0	21.0	22.0	23.0	24.0	25.0	26.0	27.0	28.0	29.0	30.0	35.0	40.0
Height (cm)	Body Weight (kg)													
140.0	37.2	39.2	41.2	43.1	45.1	47.0	49.0	51.0	52.9	54.9	56.8	58.8	68.6	78.4
142.0	38.3	40.3	42.3	44.4	46.4	48.4	50.4	52.4	54.4	56.5	58.5	60.5	70.6	80.7
144.0	39.4	41.5	43.5	45.6	47.7	49.8	51.8	53.9	56.0	58.1	60.1	62.2	72.6	82.9
146.0	40.5	42.6	44.8	46.9	49.0	51.2	53.3	55.4	57.6	59.7	61.8	63.9	74.6	85.3
148.0	41.6	43.8	46.0	48.2	50.4	52.6	54.8	57.0	59.1	61.3	63.5	65.7	76.7	87.6
150.0	42.8	45.0	47.3	49.5	51.8	54.0	56.3	58.5	60.8	63.0	65.3	67.5	78.8	90.0
152.0	43.9	46.2	48.5	50.8	53.1	55.4	57.8	60.1	62.4	64.7	67.0	69.3	80.9	92.4
154.0	45.1	47.4	49.8	52.2	54.5	56.9	59.3	61.7	64.0	66.4	68.8	71.1	83.0	94.9
156.0	46.2	48.7	51.1	53.5	56.0	58.4	60.8	63.3	65.7	68.1	70.6	73.0	85.2	97.3
158.0	47.4	49.9	52.4	54.9	57.4	59.9	62.4	64.9	67.4	69.9	72.4	74.9	87.4	99.9
160.0	48.6	51.2	53.8	56.3	58.9	61.4	64.0	66.6	69.1	71.7	74.2	76.8	89.6	102.4
162.0	49.9	52.5	55.1	57.7	60.4	63.0	65.6	68.2	70.9	73.5	76.1	78.7	91.9	105.0
164.0	51.1	53.8	56.5	59.2	61.9	64.6	67.2	69.9	72.6	75.3	78.0	80.7	94.1	107.6
166.0	52.4	55.1	57.9	60.6	63.4	66.1	68.9	71.6	74.4	77.2	79.9	82.7	96.4	110.2
168.0	53.6	56.4	59.3	62.1	64.9	67.7	70.6	73.4	76.2	79.0	81.8	84.7	98.8	112.9
170.0	54.9	57.8	60.7	63.6	66.5	69.4	72.3	75.1	78.0	80.9	83.8	86.7	101.2	115.6
172.0	56.2	59.2	62.1	65.1	68.0	71.0	74.0	76.9	79.9	82.8	85.8	88.8	103.5	118.3
174.0	57.5	60.6	63.6	66.6	69.6	72.7	75.7	78.7	81.7	84.8	87.8	90.8	106.0	121.1
176.0	58.9	62.0	65.0	68.1	71.2	74.3	77.4	80.5	83.6	86.7	89.8	92.9	108.4	123.9
178.0	60.2	63.4	66.5	69.7	72.9	76.0	79.2	82.4	85.5	88.7	91.9	95.1	110.9	126.7
180.0	61.6	64.8	68.0	71.3	74.5	77.8	81.0	84.2	87.5	90.7	94.0	97.2	113.4	129.6
182.0	62.9	66.2	69.6	72.9	76.2	79.5	82.8	86.1	89.4	92.7	96.1	99.4	115.9	132.5
184.0	64.3	67.7	71.1	74.5	77.9	81.3	84.6	88.0	91.4	94.8	98.2	101.6	118.5	135.4
186.0	65.7	69.2	72.7	76.1	79.6	83.0	86.5	89.9	93.4	96.9	100.3	103.8	121.1	138.4
188.0	67.2	70.7	74.2	77.8	81.3	84.8	88.4	91.9	95.4	99.0	102.5	106.0	123.7	141.4
190.0	68.6	72.2	75.8	79.4	83.0	86.6	90.3	93.9	97.5	101.1	104.7	108.3	126.4	144.4
192.0	70.0	73.7	77.4	81.1	84.8	88.5	92.2	95.8	99.5	103.2	106.9	110.6	129.0	147.5
194.0	71.5	75.3	79.0	82.8	86.8	90.3	94.1	97.9	101.6	105.4	109.1	112.9	131.7	150.5
196.0	73.0	76.8	80.7	84.5	88.4	92.2	96.0	99.9	103.7	107.6	111.4	115.2	134.5	153.7
198.0	74.5	78.4	82.3	86.2	90.2	94.1	98.0	101.9	105.9	109.8	113.7	117.6	137.2	156.8
200.0	76.0	80.0	84.0	88.0	92.0	96.0	100.0	104.0	108.0	112.0	116.0	120.0	140.0	160.0

[#]Each entry gives the body weight in kilograms (kg) for a person of a given height and body mass index (kg/m^2)

DESIRABLE BODY MASS INDEX RANGE IN RELATION TO AGE:

Age Group (yr)	Body Mass Index (kg/m^2)	Age Group (yr)	Body Mass Index (kg/m^2)
19 - 24	19 - 24	45 - 54	22 - 27
25 - 34	20 - 25	55 - 64	23 - 28
35 - 44	21 - 26	65 +	24 - 29

Reference: Mahan LK (Ed)
Krause's Food, Nutrition and Diet Therapy, 8th edition
Appendix 19. Determination of Body Mass Index
Philadelphia : WB Saunders Company, 1992 824

APPENDIX 2: CASE REPORT FORM

"Open-label, randomised, single oral dose, two-period, cross-over trial to assess to bioequivalence of **Favir 200 mg Film Tablet(Test Drug)** in comparison with **Avigan 200 mg Film Tablet (Reference Drug)** in healthy male subjects under fasting conditions"

CASE REPORT FORM (CRF)

(Stamp of Investigator)

Screening No : _____

Random No : _____

Clinical Center Code : _____

The volunteer is:

Only screened ☐

☐ **Not eligible**

☐ **Reserve volunteer**

☐ **Volunteer did not come to hospitalisation**

☐ **Other: .....**

Study completed ☐

Drop-out ☐

Replacement for a drop-out -NA-

Note: According to Clinical Study Protocol; if drop-out exists, then these dropouts <u>WILL NOT BE</u> replaced.

STUDY FLOW CHART

	SCREENING AND ISOLATION				PERIOD I			PERIOD II		*Final examination
Study Day:	1st DAY screening	2nd DAY (isolation)	3rd DAY (isolation)	4th DAY (isolation)	5th DAY Hospitalization day (Day 0)	6th DAY 1st dosing day and blood sampling (Day 1)	7th DAY blood sampling ($t_{24.00}$) Wash-out day/ (Day 2)	8th DAY 2nd dosing day and blood sampling (Day 3)	9th DAY blood sampling ($t_{24.00}$) (Day 4)	9th DAY Final examination
Informed consent	●									
Covid-19 PCR Test#	●				●					●
Inclusion criteria	●									
Demography (Birth date, ethnic group, gender, height, weight, BMI)	●									
"Medical/Surgical history	●									
HBsAg, anti-HCV, HIV	●									
ECG	●									●
Clinical examination (Physical examination)	●									●
Clinical chemistry, haematology, urinalysis	●									●
Blood pressure, pulse rate	●	●	●	●	●		●			●
Body temperature°	●	●	●	●	●	●	●	●	●	●
Drug abuse screening**	●									
Alcohol breath test	●									
Check of restrictions, diet					●	●	●	●		
Exclusion criteria and Withdrawal of volunteers	●	●	●	●	●	●	●	●	●	
Hospitalization day					●					
Randomisation	●									
Drug administration						●		●		
Blood sampling*** (0-24.00 h)						●	●	●	●	
Adverse event questioning****	●	●	●	●	●	●	●	●	●	

* The final examination will be carried out on the day of last blood sampling .

Two Covid-19 PCR tests will be applied on screening day.

° Body temperature monitoring will be performed at the following times: at "screening/isolation days", "hospitalisation day (Day 0)", "during study period" and "final examination".

** For **amphetamines, cannabinoids, benzodiazepines, cocaine, opioids, and barbiturates**.

***Blood sampling points (for each period): **at pre-dose (20 mL only in Period I)** 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, 24.00 hours post-dose** (*1 x 8 mL each; totally 19 blood sample points*)

Note:

1. Only in Period I; at t_0 the blood sample amount will be 20 mL.
2. Not to have difficulty to draw blood through catheter; the cannula will be kept patent by injecting approximately 0.5 mL of 5 IU/mL of heparin in normal saline solution at determined blood sampling points. In such cases, before collecting the blood samples at the first blood sampling points after heparin administration, first 0.5 mL blood will be discarded. The aim of this procedure is to eliminate the possible effect of heparin on **favipiravir** analysis.

****Adverse event questioning**: at "screening/isolation days", hospitalisation day (Day 0) and at pre-dose**, 1.00, 4.00, 8.00, 14.00, 24.00** hours post-dose in each period.

GENERAL INSTRUCTION

Enter all data in capital letters and avoid writing outside the space provided.

Always use a blue ballpoint pen.

Abbreviations to be used

ND: If not done,
NA: If not applicable or not available,
NK: If not known.

Example:

N	A	0	1	2	0	1	0

dd / mm / yyyy

Sign and date forms, where requested.

Information must be immediately written in the CRF and in the source document.

Completion of CRF data items:

No ❒ Yes ❒

Errors:

- Cross out the error with a single horizontal line and write any correction next to it.
- Do not use correcting fluid.
- Make sure that the error, although crossed out, remains legible
- Sign and date the correction.
- Give reason for correction, if not self-explanatory.

Please sign each completed page of this CRF.

ENTRY EXAMINATION
1st DAY (screening)

Date of examination

I__I__I I__I__I I__I__ I__I__I
dd / mm / yyyy

Approval Date of Informed Consent

I__I__I I__I__I I__I__ I__I__I
dd / mm / yyyy

Covid-19 PCR Test

☐ Positive	☐ Negative	*If "positive" please specify:*

Demographic Data	
Birth date:	I__I__I I__I__I I__I__ I__I__I dd / mm / yyyy
Ethnic group:	Caucasian ❒ Other ❒ *please specify*……..
Gender:	Male ❒ Female ❒
Height:	I__ I__I__I cm
Weight (Incl. Indoor clothing without shoes)	I__ I__I__I. I__I kg
Body mass index (between 18.5 and 30.0)	I__I__I. I__I kg/m^2

……..
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY
(screening)

Medical and surgical history / Life style			
			If yes, or abnormal, please specify:
Hyper/ Hypotension	❒ No	❒ Yes	
Allergy	❒ No	❒ Yes	
Other diseases	❒ No	❒ Yes	
Major surgery	❒ No	❒ Yes	
Micturition	❒ Normal	❒Abnormal	
Defecation	❒ Normal	❒Abnormal	
Sleep	❒ Normal	❒Abnormal	

……..
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY
(screening)

Life style and habits			
Alcohol	❒ No	❒ Yes	Units: I__I /day (Unit equals = 0.5 L beer, 200 mL Wine or 50 g spirits)
Nicotine	❒ No	❒ Yes	Cigarette or equivalent: I__I__I /day
Consumption of food and beverages containing methylxanthines per day	❒ No	❒ Yes	*If yes, please specify below:*
	Coffee I__I__I cups of 150 mL x 100 mg methylxanthines = I__I__ I__I__I mg/day		
	Tea I__I__I cups of 150 mL x 50 mg methylxanthines =I__I__ I__I__I mg/day		
	Hot Chocolate I__I__I cups of 150 mL x 200 mg methylxanthines =I__I__ I__I__I mg/day		
	Cola I__I__I glasses of 200 mL x 25 mg methylxanthines =I__I__ I__I__I mg/day		
	Energy drinks I__I__I cans of 250 mL x 80 mg methylxanthines=I__I__ I__I__I mg/day		
	Chocolate I__I__I bars of 100 g x 400 mg methylxanthines =I__I__ I__I__I mg/day		
	Total calculated methylxanthines (caffeine, theophylline, theobromine) per day: *-Daily maximum 500 mg methylxanthines intake is allowed for the study-* **I__I__ I__I__I mg/day**		
Special diet	❒ No	❒ Yes	*If yes, please specify:*
History of drug abuse	❒ No	❒ Yes	*If yes, please specify:*

.....
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY
(screening)

Clinical investigation	
Body temperature:	I__I__I. I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Orthostatic hypotension ***(if it deemed necessary by the investigator)*** *If a decrease of* ***SBP more than 20 mmHg or DBD more than 10 mmHg*** *occurs between sitting/supine to standing position subject will be excluded.* ❒ No / ❒ Yes ❒ NA	<u>Sitting position</u> Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg <u>Standing position</u> Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Signature of investigator	

.....
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY
(screening)

12-lead electrocardiogram	
Date:	I__I__I / I__I__I / I__I__ I__I__I dd mm yyyy
Findings:	N ❒ Y ❒ *If "yes", please specify code* * I__I__I
Result:	Normal ❒ Abnormal ❒ *If "abnormal" please specify below* Not clinically significant ❒ Clinically significant ❒

*

01= Sinus bradycardia
02= Sinus tachycardia
03= Sinus arrhythmia
04= AV Block, 1^0
05= AV Block, 2^0 (type 1)
06= AV Block, 2^0 (type 2)
07= AV Block, 3^0
08= AV Block, variable
09= Sinoatrial exit block
10= Atrial premature complexes
11= Ventricular premature complexes
12= Atrial tachicardia (regular sustained, 1:1 condition)
13= Atrial tachicardia, repetitive (short paroxysms)
14= Atrial tachicardia, multifocal (chaotic atrial tachicardia)
15= Supraventricular tachicardia, unspecified
16= Supraventricular tachicardia, paroxysmal
17= AV Junctional premature complexes
18= AV Junctional escape complexes
19= AV Junctional rhythm, accelareted
20= AV Junctional rhythm
21= Ventricular tachycardia (≥3 consecutive complexes)
22= Right atrial enlargement
23= Left atrial enlargement
24= Low voltage QRS complex, limb leads only
25= Low voltage QRS complex, limb and precordial leads
26= Poor R-wave progression
27= Left ventricular hypertrophy
28= Left anterior hemiblock
29= Left posterior hemiblock
30= LBBB, complete
31= Right ventricular hypertrophy
32= RBBB, incomplete
33= RBBB, complete
34= Prolonged QT interval
35= ST-depression
36= U-wave
37= Non specific T change
38= Non specific ST-change

39= I_____I

.....
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY (screening)

Physical examination:			
General state:			
Pathologies in any system	❒ No	❒ Yes	
Endocrine / Metabolic			
Allergies / Drug sensitivity			
Head			
Neck			
Eyes			
Ear-nose-throat			
Heart			
Respiratory system			
Gastrointestinal system			
Hepatic, biliary			
Urogenital system			
Musculoskeletal system			
Vascular system			
Lymph nodes			
Skin			
Neurological			
Psychiatric			
Other			
Examination Performed	Name-Surname: Signature of investigator:		

If abnormal findings present are they clinically relevant? ❒ No ❒ Yes

If yes, this is to be regarded as an exclusion criteria!

.....
Signature of investigator

ENTRY EXAMINATION -*cont.*-
1st DAY (screening)

Additional information:

Illness within the last 4 weeks prior start of the trial:	❒ No ❒ Yes	If yes, please , specify the diagnose below	
		Start of illness	**End of illness**
		|__|__| /|__|__|/|__|__|__|__| dd mm yyyy	|__|__|/|__|__|/|__|__|__|__| dd mm yyyy
Last administration of any medication:	|__|__| /|__|__|/|__|__|__|__| dd mm yyyy	*or* within 12 months ❒	*or* not administrated ❒

In case that any medication was administered within **4 weeks**, please specify:

Drug (generic name)	Dosage	Start of treatment	End of treatment
1.		|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**	|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**
2.		|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**	|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**
3.		|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**	|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**
4.		|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**	|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**
5.		|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**	|__|__| /|__|__|/|__|__|__|__| **dd mm yyyy**

	Date		
Last participation in any clinical trial or experimental drug intake:	|__|__| /|__|__|/|__|__|__|__| dd mm yyyy	*or* more than 12 months ago ❒	*or* none ❒
Last donation of blood or plasma:	|__|__| /|__|__|/|__|__|__|__| dd mm yyyy	*or* more than 12 months ago ❒	*or* none ❒

.....
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY (screening)

LABORATORY INVESTIGATION
Clinical chemistry, haematology, virology

(**Note:** blood must be taken in the morning under fasting conditions) **Please add the copy of the Laboratory Results for the entry examination** and comment if any parameter is outside the normal range and clinically relevant, copy must be signed and dated by the investigator who assessed the laboratory findings.

Laboratory Investigation of blood and urine	
Hematology:	Hemoglobin, hematocrit, leukocytes, erythrocytes and platelet count
Electrolytes:	Sodium, chloride, potassium, calcium
Substrates:	Creatinine, eGFR, total protein, total bilirubin, blood glucose, BUN, uric acid,
Enzymes	AST, ALT, GGT, ALP
Serological Findings	HIV-Ab, HbsAg and Anti HCV
Urine	pH, leukocytes, nitrites, protein, glucose, ketones, urobilinogen, bilirubin, specific gravity, blood (Ery) and microscopic examination of sediment

For values outside the normal range the clinical relevance should be evaluated on the print-out as follows:

NCR: Not Clinically Relevant.

CR: Clinically Relevant

In case of values judged as clinically relevant (CR) please comment below.

.....
.....
.....
.....
.....
.....

Please note: Any values rated CR are considered as an exclusion criterion

.....
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY (screening)

DRUG ADDICTION SCANNING IN THE URINE (with urine kit)

Test	Reference range	Result
Amphetamines	>1000 ng / mL (positive) <1000 ng / mL (negative)	Positive ❒ Negative ❒
Barbiturates	>300 ng / mL (positive) <300 ng / mL (negative)	Positive ❒ Negative ❒
Benzodiazepines	>300 ng / mL (positive) <300 ng / mL (negative)	Positive ❒ Negative ❒
Cannabinoids	>50 ng /mL (positive) <50 ng / mL (negative)	Positive ❒ Negative ❒
Cocaine	>300 ng / mL (positive) <300 ng / mL (negative)	Positive ❒ Negative ❒
Opioids	>300 ng / mL (positive) <300 ng / mL (negative)	Positive ❒ Negative ❒

ALCOHOL BREATH TEST

Alcohol	❒ Positive	❒ Negative	Units: I__I /day (Unit equals = 0.5 L beer, 200 mL Wine or 50 g spirits)

Covid-19 PCR Test

❒ Positive	❒ Negative	*If "positive" please specify:*

.....
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY
(screening)

Inclusion criteria		
Please check all following criteria. If one criterion is answered with "No" the volunteer is not eligible for this study	**Y**	**N**
Volunteer('s)		
1) Healthy Caucasian male subjects aged between **20 and 40 years**	☐	☐
2) Non smokers or smoking maximum 5 cigarettes a day, those who won't smoke or drink coffee during the study period,	☐	☐
3) **Two Negative Covid-19 PCR test results,**	☐	☐
4) Negative alcohol breath test results	☐	☐
5) Normal physical examination at screening visit	☐	☐
6) Having the Body Mass Index ranged between **18.5-30 kg/m^2** which is in the desirable range according to age (see Study Protocol - Appendix I)	☐	☐
7) Ability to communicate adequately with the investigator himself or his/her representatives	☐	☐
8) Ability and agreement to comply with the study requirements	☐	☐
9) Normal blood pressure and heart rate measured under stabilised conditions at the screening visit after at least 5 minutes of rest under supine position: SBP within 100 to 140 mmHg, DBP within 60 to 90 mmHg and HR within 50 to 90 bpm	☐	☐
10) Normal/Acceptable 12-lead electrocardiographic results at least after 5 minutes of rest	☐	☐
11) Laboratory results within normal range or clinically non-significant (CBC, glucose, urea, uric acid, creatinine, *estimated GFR (eGFR)*, total bilirubin, sodium, potassium, calcium, chloride, SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase, total protein and urinalysis), drug addiction scanning in urine results in negative (amphetamine, barbiturate, benzodiazepine, cannabinoid, cocaine, opiate).	☐	☐
12) Understanding of the study and agreement to give a written informed consent	☐	☐
13) **Understanding of that he and his partner will use a practice adequate contraception during the study and at least 7 days after the study.**	☐	☐

.....
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY
(screening)

Exclusion criteria *Please check all following criteria.* *If one criterion is answered with "yes" the volunteer is not eligible for this study*		
Volunteer('s)	**Y**	**N**
1) Who have atopic constitution or asthma or known allergy for favipiravir and/or any other ingredients of the products.	❒	❒
2) Who have positive Covid-19 PCR test result.	❒	❒
3) Any history or presence of clinical relevance of cardiovascular, neurological, musculoskeletal, haematological, hepatic, gastrointestinal, renal, pulmonary, endocrinological, metabolism or psychiatric disease, any type of porphyria.	❒	❒
4) Symptomatic or asymptomatic orthostatic hypotension at screening or before the first drug administration defined by a decrease of SBP more than 20 mmHg or DBD more than 10 mmHg occurs between sitting/supine to standing position subject will be excluded (if it deemed necessary by the investigator).	❒	❒
5) Presence or history of malabsorption or any gastrointestinal surgery except appendectomy or except herniotomy.	❒	❒
6) Subjects who have given more than 400 mL blood within the last two months before the first drug administration and subjects who have participated to any drug research within the last two months before the first drug administration.	❒	❒
7) Subjects suspected to have a high probability of non-compliance to the study procedure and/or completion of the study according to the investigator's judgement.	❒	❒
8) Subjects who used any of prescribed systemic or topical medication (including OTC medication) within 2 weeks (or six elimination half lives of this medication, whichever is longer) before the initiation of the study (except single doses of analgesics which have no drug interaction with study product).	❒	❒
9) Use of any vitamins or herbal products within 7 days prior to the initial dose of the study medication.	❒	❒
10) History of allergic response to heparin		
11) Subjects who have any chronic disease which might interfere with absorption, distribution, metabolism or excretion of the drug,	❒	❒
12) Subjects who regular consumed of beverages or food containing methylxanthines (e.g. coffee, tea, cola, caffeine, chocolate, sodas,) equivalent to more than 500 mg methylxanthines per day,	❒	❒
13) Subjects who has taken any grapefruit or grapefruit juice during 7 days prior to drug administration, during the study.	❒	❒
14) History of drug abuse.	❒	❒

15) History of alcohol abuse and/or regular use of more than 2 units of alcohol per day or 10 units per week and/or positive alcohol breath test results (Note: one unit of alcohol equals 250 mL beer, 125 mL wine or 25 mL spirits)	❒	❒
16) Positive blood test for HBV, HCV and HIV.	❒	❒
17) Who have relationship to the investigator.	❒	❒
18) Who are not suitable to any of inclusion criteria.	❒	❒
19) History of difficulty of swallowing.	❒	❒
20) Intake of depot injectable solutions (including study medications) within 6 months before start of the study.	❒	❒
21) Intake of enzyme-inducing, organotoxic or long half-life drugs within 4 weeks before start of the study.	❒	❒
22) Special diet due to any reason, e.g. vegetarian	❒	❒

Decision on subject enrolment		
Based upon my review of the subject's data I find this subject eligible to participate in the present clinical trial	❒No	❒Yes
I__I__I__I__I__I__I__I__I (DD) (MM) (YYYY)	**Signature of Investigator** ……	

……
Signature of investigator

ENTRY EXAMINATION *-cont.-*
1st DAY
(screening)

EVALUATION OF AVAILABILITY OF VOLUNTEER FOR RANDOMISATION

	No	Yes
Is volunteer available for randomisation?	❒	❒

If not randomised, please comment:
.....
.....
.....
.....

Date I__I__I /I__I__I/I__I__I__I__I
dd mm yyyy

.....
Signature of investigator

2nd DAY
(isolation)

Clinical investigation	
Body temperature:	I__I__I. I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Signature of investigator	

Check of adverse events and exclusion criteria	
Any adverse event occurred until?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

3rd DAY
(isolation)

Clinical investigation	
Body temperature:	I__I__I. I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Signature of investigator	

Check of adverse events and exclusion criteria	
Any adverse event occurred until?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

4th DAY
(isolation)

Clinical investigation	
Body temperature:	I__I__I. I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Signature of investigator	

Check of adverse events and exclusion criteria	
Any adverse event occurred until?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

5th DAY
(isolation)

Clinical investigation	
Body temperature:	I__I__I. I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Signature of investigator	

Covid-19 PCR Test

❒ Positive	❒ Negative	*If "positive" please specify:*

.....
Signature of investigator

5th DAY *-cont.-*
(isolation)

Check of adverse events and exclusion criteria	
Any adverse event occurred until?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

DAY 0 IN PERIOD I (Hospitalisation)- *Cont.*-
(5th Day in study)

Hospitalisation Beginning	
Date	I__I__I /I__I__I/I__I__I__I__I dd mm yyyy
Daytime	I__I__I I__I__I hh mm

Questioning concerning diet and restrictions at hospitalisation	Y	N
Was the volunteer identified by means of ID card and study identification card?	❒	❒
Did the luggage of the volunteer contain any not allowed items (i.e. foods, cigarettes, drugs…)?	❒	❒
Did the volunteer drink alcohol from 7 days prior to dosing until the moment of questioning?	❒	❒
Did the volunteer drink / eat grapefruit products from 7 days prior to dosing until the moment of questioning?	❒	❒
Did the volunteer drink / eat food or beverages containing caffeine/ other methylxanthines and fruit juices from 2 days prior to dosing until the moment of questioning?	❒	❒
Did the volunteer take any medication since the last visit (screening) until this moment of questioning (except single doses of analgesics which have no drug interaction with study products)?	❒	❒

.....
Signature of investigator

DAY 0 IN PERIOD I (Hospitalisation Day)- *Cont.-*
(5th Day in study)

Clinical investigation	
Body temperature:	I__I__I.I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Signature of investigator	

Check of adverse events and exclusion criteria	
Any adverse event occurred untl hospitalisation?	❒ No ❒ Yes
Any exclusion criteria met at the present visit?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

DAY I IN PERIOD I (1st medication day)
(6th Day in study)

1st medication day	
Date	I__I__I I__I__I I__I__ I__I__I **dd / mm / yyyy**

Questioning concerning diet and restrictions before dosing		
*If one criterion is answered with **(Yes)** the volunteer is not eligible for this trial.*	❒ No	❒ Yes
Did the volunteer chew any chewing gum since hospitalisation?	❒	❒
Did the volunteer drink water less than 1 hour prior to each dosing on medication day?	❒	❒
Did the volunteer eat or drink anything other than water from 21:00 on the evening before dosing?	❒	❒

Body temperature:	I__I__I.I__I ^{0}C

Check of adverse events and exclusion criteria before dosing	
Any new adverse event occurred until the medication?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

DAY 1 IN PERIOD I (1st medication day) - *Cont.*-
EVALUATION OF AVAILABILTY OF VOLUNTEER FOR MEDICATION
(6th Day)

	No	Yes
Is volunteer available for medication?	❒	❒

If not available, please comment:
.....
.....
.....
.....

Date I__I__I /I__I__I/I__I__I__I__I
dd mm yyyy

.....
Signature of investigator

DAY 1 IN PERIOD-I (1st medication day)
FORM FOR BLOOD SAMPLING
(6th Day in study)

Day 1		Date |_____|_____|_____| DD / MM / YYYY			
Sample No	Time p.a. (hour)	Actual time (hh.min)	Deviation (min)	*Reason for Deviation	Signature
1	0.00		NA		

*The drug will be taken under fasting conditions with **240 mL water** in the room temperature in oral route*

DRUG →	Please stick the Period I Drug Label into this area.	**Randomisation correct:** ❒Yes ❒No **Mouth check performed:** ❒Yes ❒No Signatures: ..... (administered) ..... (controlled)

Drug Administration Time	|__|__| |__|__| hh mm	

2	0.17				
3	0.25				
4	0.50				
5	0.75				
6	1.00				
7	1.33				
8	1.66				
9	2.00				
10	2.50				
11	3.00				
12	3.50				

p.a.: Pre Administration

.....
Signature of investigator

DAY 1 AND DAY 2 IN PERIOD-I *FORM FOR BLOOD SAMPLING*

-cont.-

(6th and 7th Day in study)

Sample No	Time (hour)	Actual time (hh.min)	Deviation (min)	*Reason for Deviation	Signature
13	4.00				
14	5.00				
15	6.00				
16	8.00				
17	10.00				
18	14.00				
Day 2					
19	24.00				

***: Reason For Deviation:**
A: Difficulty with blood sampling
B: Taken by Venepuncture
C: Due to AEs
D: Due to technical reasons
E: Subject did not show up at scheduled
F: Subject did not come to the blood sampling
G: Other; *please explain shortly*

.....
Signature of investigator

REGISTRATION OF EXCLUSION CRITERIA DURING PERIOD I
(6th and 7th Day in study)

Any exclusion criteria occurred until?*			
PERIOD I	**No**	**Yes**	**Signature**
Day 0	❒	❒	
Day 1	❒	❒	
Day 2	❒	❒	

***: See The Drop-out Sheet**

REGISTRATION OF ADVERSE EVENTS DURING PERIOD I

Any adverse events occurred until?*			
PERIOD I	**No**	**Yes**	**Signature**
Pre-dose	❒	❒	
1.00	❒	❒	
4.00	❒	❒	
8.00	❒	❒	
14.00	❒	❒	
24.00	❒	❒	

***: See The Adverse Events Form**

.....
Signature of investigator

7th DAY IN STUDY

Clinical investigation	
Body temperature:	I__I__I.I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__I__ I__I mmHg Diastolic: I__I__ I__I mmHg
Signature of investigator	

Check of adverse events and exclusion criteria	
Any new adverse event occurred until?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

DAY I IN PERIOD II (2nd medication day)
(8th Day in study)

2nd medication day	
Date	I__I__I I__I__I I__I__ I__I__I **dd / mm / yyyy**

Questioning concerning diet and restrictions before dosing		
*If one criterion is answered with **(Yes)** the volunteer is not eligible for this trial.*	❒ No	❒ Yes
Did the volunteer chew any chewing gum since hospitalisation?	❒	❒
Did the volunteer drink water less than 1 hour prior to each dosing on medication day?	❒	❒
Did the volunteer eat or drink anything other than water from 22:00 on the evening before dosing?	❒	❒

Body temperature:	I__I__I.I__I ^{0}C

Check of adverse events and exclusion criteria before dosing	
Any adverse events occurred until?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

DAY 1 IN PERIOD-2 (2nd medication day)
FORM FOR BLOOD SAMPLING
(8th Day in study)

Day 1	Date |_____|_____|_____| DD / MM / YYYY

Sample No	Time p.a. (hour)	Actual time (hh.min)	Deviation (min)	*Reason for Deviation	Signature
1	0.00		NA		

*The drug will be taken under fasting conditions with **240 mL water** in the room temperature in oral route*

DRUG ➡	Please stick the Period II Drug Label into this area.	**Randomisation correct:** ❒Yes ❒No **Mouth check performed:** ❒Yes ❒No Signatures: ..... (administered) ..... (controlled)
Drug Administration Time	|__|__| |__|__| hh mm	

2	0.17				
3	0.25				
4	0.50				
5	0.75				
6	1.00				
7	1.33				
8	1.66				
9	2.00				
10	2.50				
11	3.00				
12	3.50				

p.a.: Pre Administration

.....
Signature of investigator

DAY 1 AND DAY 2 IN PERIOD-II *FORM FOR BLOOD SAMPLING*

-cont.-

(8th and 9th Day in study)

Sample No	Time (hour)	Actual time (hh.min)	Deviation (min)	*Reason for Deviation	Signature
13	4.00				
14	5.00				
15	6.00				
16	8.00				
17	10.00				
18	14.00				
Day 2					
19	24.00				

***: Reason For Deviation:**
A: Difficulty with blood sampling
B: Taken by Venepuncture
C: Due to AEs
D: Due to technical reasons
E: Subject did not show up at scheduled
F: Subject did not come to the blood sampling
G: Other; *please explain shortly*

.....
Signature of investigator

REGISTRATION OF EXCLUSION CRITERIA DURING PERIOD II
(8th and 9th Day in study)

Any exclusion criteria occurred until?*			
PERIOD II	**No**	**Yes**	**Signature**
Day 1	❒	❒	
Day 2	❒	❒	

***: See The Drop-out Sheet**

REGISTRATION OF ADVERSE EVENTS DURING PERIOD II

Any adverse events occurred until?*			
PERIOD II	**No**	**Yes**	**Signature**
Pre-dose	❒	❒	
1.00	❒	❒	
4.00	❒	❒	
8.00	❒	❒	
14.00	❒	❒	
24.00	❒	❒	

***: See The Adverse Events Form**

.....
Signature of investigator

9th DAY IN STUDY

Clinical investigation	
Body temperature:	I__I__I.I__I ^{0}C
Signature of investigator	

Check of adverse events and exclusion criteria	
Any new adverse event occurred until?	❒ No ❒ Yes
Any exclusion criteria occurred until?	❒ No ❒ Yes → if yes, specify below …… …… …… ……

……
Signature of investigator

FINAL EXAMINATION

(The final examination will be carried out on the day of last blood sampling)

Date of examination	
	I__I__I I__I__I I__I__ I__I__I **dd / mm / yyyy**

Clinical investigation:	
Body temperature:	I__I__I.I__I ^{0}C
Heart rate: (after 5 min supine rest)	I__I__I / min
Blood pressure: (after rest)	Systolic: I__ I__I__I mmHg Diastolic: I__ I__I__I mmHg

Covid-19 PCR Test

❒ Positive	❒ Negative	*If "positive" please specify:*

.....
Signature of investigator

FINAL EXAMINATION - *cont.*-

(The final examination will be carried out on the day of last blood sampling)

12-lead electrocardiogram	
Date:	I__I__I / I__I__I / I__I__ I__I__I dd mm yyyy
Findings:	N ❒ Y ❒ *If "yes", please specify code* * I__I__I
Result:	Normal ❒ Abnormal ❒ *If "abnormal" please specify below* Not clinically significant ❒ Clinically significant ❒

*

01= Sinus bradycardia
02= Sinus tachycardia
03= Sinus arrhythmia
04= AV Block, 1^0
05= AV Block, 2^0 (type 1)
06= AV Block, 2^0 (type 2)
07= AV Block, 3^0
08= AV Block, variable
09= Sinoatrial exit block
10= Atrial premature complexes
11= Ventricular premature complexes
12= Atrial tachicardia (regular sustained, 1:1 condition)
13= Atrial tachicardia, repetitive (short paroxysms)
14= Atrial tachicardia, multifocal (chaotic atrial tachicardia)
15= Supraventricular tachicardia, unspecified
16= Supraventricular tachicardia, paroxysmal
17= AV Junctional premature complexes
18= AV Junctional escape complexes
19= AV Junctional rhythm, accelareted
20= AV Junctional rhythm
21= Ventricular tachycardia (≥3 consecutive complexes)
22= Right atrial enlargement
23= Left atrial enlargement
24= Low voltage QRS complex, limb leads only
25= Low voltage QRS complex, limb and precordial leads
26= Poor R-wave progression
27= Left ventricular hypertrophy
28= Left anterior hemiblock
29= Left posterior hemiblock
30= LBBB, complete
31= Right ventricular hypertrophy
32= RBBB, incomplete
33= RBBB, complete
34= Prolonged QT interval
35= ST-depression
36= U-wave
37= Non specific T change
38= Non specific ST-change

39= I_____I

.....
Signature of investigator

FINAL EXAMINATION - *cont.* -

(The final examination will be carried out on the day of last blood sampling)

Physical examination: Did any new findings or changes in comparison to pre-study exam occure? ❒ No ❒ Yes If yes, please enter only **new findings** or **changes** in the following table			
General state:			
Pathologies in any system	❒ No	❒ Yes	
Endocrine / Metabolic			
Allergies / Drug sensitivity			
Head			
Neck			
Eyes			
Ear-nose-throat			
Heart			
Respiratory system			
Gastrointestinal system			
Hepatic, biliary			
Urogenital system			
Musculoskeletal system			
Vascular system			
Lymph nodes			
Skin			
Neurological			
Psychiatric			
Other			
Examination Performed	Name-Surname: Signature of investigator:		

.....
Signature of investigator

FINAL EXAMINATION *–cont.-*
(The final examination will be carried out on the day of last blood sampling)

LABORATORY INVESTIGATION
Clinical chemistry, haematology, virology

(**Note:** blood must be taken in the morning under fasting conditions) **Please add the copy of the Laboratory Results for the final examination** and comment if any parameter is outside the normal range and clinically relevant, copy must be signed and dated by the investigator who assessed the laboratory findings.

Laboratory Investigation of blood and urine	
Hematology:	Hemoglobin, hematocrit, leukocytes, erythrocytes and platelet count
Electrolytes:	Sodium, potassium, calcium, chloride
Substrates:	Creatinine, eGFR, total protein, total bilirubin, blood glucose, BUN, uric acid
Enzymes	AST, ALT, GGT, ALP
Serological Findings	-
Urine	pH, leukocytes, nitrites, protein, glucose, ketones, urobilinogen, bilirubin, specific gravity, blood (Ery) and microscopic examination of sediment

For values outside the normal range the clinical relevance should be evaluated on the print-out as follows:

NCR: Not Clinically Relevant.

CR: Clinically Relevant

In case of values judged as clinically relevant (CR) please comment below.

.....
.....
.....
.....
.....
.....

Any values rated clinically relevant (CR) are considered as an adverse event.

.....
Signature of investigator

FINAL EXAMINATION *-cont. -*

(The final examination will be carried out on the day of last blood sampling)

Occurrence of adverse events after the last PK-blood sampling of last period	❒ **No**	❒**Yes**	If "yes", please fill in the "adverse event form" of the CRF
Clinical findings at final examination	❒ **No**	❒**Yes**	
If abnormal findings at final examination present, are these clinically relevant?	❒ **No**	❒**Yes**	If Clinically Relevant, please specify …… …… …… ……
Control examination	(If any pathological finding in at least one of the clinical and or laboratory final examinations is found) …… …… …… …… ……		

……
Signature of investigator

CONCOMITANT MEDICATION

Concomitant Medication	YES	NO
Was any concomitant medication used?	❒	❒
If yes, is this evaluated as a restriction?	❒	❒

Please specify all concomitant medication:

Drug (brand/ generic name)	Active Substances	Dosage per Administration	Due to AE?	Start and end of treatment
1.			❒ No ❒Yes if yes, please give No. of AE: |__|__|	Start of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min End of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min
2.			❒ No ❒Yes if yes, please give No. of AE: |__|__|	Start of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min End of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min
3.			❒ No ❒Yes if yes, please give No. of AE: |__|__|	Start of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min End of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min

.....
Signature of investigator

CONCOMITANT MEDICATION *(Continued)*

Drug (brand/ generic name)	Active Substances	Dosage per Administration	Due to AE?	Start and end of treatment
4			❒ No ❒Yes if yes, please give No. of AE: |__|__|	Start of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min End of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min
5			❒ No ❒Yes if yes, please give No. of AE: |__|__|	Start of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min End of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min
6			❒ No ❒Yes if yes, please give No. of AE: |__|__|	Start of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min End of treatment: |__|__|__|__|__|__|__| (DD) (MM) (YYYY) |__|__|: |__|__| Hours min

.....
Signature of investigator

DROP-OUT SHEET

Please fill in this sheet if a premature discontinuation of the trial in a volunteer occurs

Date of discontinuation			
I __I__I / I__I__I / I__I__ I__I__I dd mm yyyy			
Medical reason	❒**No**	❒**Yes**	If "yes", following: …… …… …… …… …… ……
Associated with the trial?	❒**No**	❒**Yes**	
Sheet for adverse events completed	❒**No**	❒**Yes**	
Non-medical reason	❒**No**	❒**Yes**	If "yes", following: …… …… …… …… …… ……
Volunteer replaced? **-NA-*** ***If drop-out exists, then these dropouts <u>WILL NOT BE</u> replaced.***	❒**No**	❒**Yes**	If "yes", which number and administration sequence were used for the additional volunteer

No. of additional volunteer -NA- ***If drop-out exists, then these dropouts <u>WILL NOT BE</u> replaced.***	**Treatment received (T= test; R= reference)**	
	PERIOD 1	**PERIOD 2**
I_____I	I_____I	I_____I

……
Signature of investigator

CONTROL EXAMINATION

Results of control examination	
....	
Examination performed by: *Name of investigator in block letters*	*Signature*

....
Signature of investigator

FORM FOR MEAL INGREDIENTS

The standardised Dinner was served no later than 21:00 on day 0 of study following composition:

Soup.....	Carbohydrates: 165.……g
Chicken.....	Proteins: 45……g
Rice	Fats: 40……g
Yoghurt.....	**Total caloric value: 1200……..kcal**
Bread (1 - 4 slices)	

Standardised lunch will be served at Day 1, Day 2, Day 3, Day 4 has following composition:

Soup.....	Carbohydrates: 165……g
Meatball (4 pieces).....	Proteins: 45……..g
Rice.....	Fats: 40……..g
Bread (1 - 4 slices).....	**Total caloric value: 1200….. kcal**
Apple.....	

Standardised dinner will be served at Day 1, Day 2, Day 3 has following composition:

Soup.....	Carbohydrates: 165.……g
Chicken.....	Proteins: 45……g
Rice	Fats: 40……g
Yoghurt.....	**Total caloric value: 1200……..kcal**
Bread (1 - 4 slices)	

……
Signature of investigator

FORM FOR MEAL INGREDIENTS - *cont.*-

Standardised breakfast will be served on Day 2, Day 4 has following composition:

2 slices of bread (50 g)……	Protein.....29,9 g
50 g feta cheese ……..	Carbohydrate…….. 41,2 g
75 g cucumber (raw)…	Fats.....21,0 g
80 g green tomato (raw) …	**Total caloric value: 473,1 kcal**
200 millilitre of semi-skimmed milk ……..	
1 boiled eggs (50 g)……	
35 g black olives ……	

The light breakfast will be served approximately 21:30 p.m (Day 1, Day 2, Day 3) has following composition:

Sandwich bread (50 g)……	Protein.....23,3 g
50 g feta cheese ……	Carbohydrate…….. 39,1 g
75 g cucumber (raw)……..	Fats.....12,7 g
80 g green tomato (raw) ……	**Total caloric value: 370,3 kcal**
200 millilitre of buttermilk……	

……
Signature of investigator

FORM FOR MEAL INGREDIENTS - *cont.*-

Time points of intake of standard dinner (Day 0 in study, *between 18:00 to 21:00*)	
Standard dinner Taken on:	I__I__I__I__I__I__I__I__I DD MM YYYY
Between:	I___I I___I toI___I I___I Hour Minute Hour Minute

Standardised lunch will be served at Day 1, Day 2, Day 3, Day 4.		
	Day 1	**Day 2**
Standard lunch Taken on:	I__I__I__I__I__I__I__I__I DD MM YYYY	I__I__I__I__I__I__I__I__I DD MM YYYY
Between:	I___I I___I toI___I I___I Hour Minute Hour Minute	I___I I___I toI___I I___I Hour Minute Hour Minute
	Day 3	**Day 4**
Standard lunch Taken on:	I__I__I__I__I__I__I__I__I DD MM YYYY	I__I__I__I__I__I__I__I__I DD MM YYYY
Between:	I___I I___I toI___I I___I Hour Minute Hour Minute	I___I I___I toI___I I___I Hour Minute Hour Minute

.....
Signature of investigator

FORM FOR MEAL INGREDIENTS - *cont.*-

Standardised dinner will be served at Day 1, Day 2, Day 3		
	Day 1	**Day 2**
Standard dinner Taken on:	|__|__|__|__|__|__|__|__| DD MM YYYY	|__|__|__|__|__|__|__|__| DD MM YYYY
Between:	|___| |___| to|___| |___| Hour Minute Hour Minute	|___| |___| to|___| |___| Hour Minute Hour Minute
	Day 3	
Standard dinner Taken on:	|__|__|__|__|__|__|__|__| DD MM YYYY	
Between:	|___| |___| to|___| |___| Hour Minute Hour Minute	

.....
Signature of investigator

FORM FOR MEAL INGREDIENTS - *cont.*-

Standardised breakfast will be served on Day 2, Day 4.		
	Day 2	**Day 4**
Standard breakfast Taken on:	|__|__|__|__|__|__|__|__| DD MM YYYY	|__|__|__|__|__|__|__|__| DD MM YYYY
Between:	|___| |___| to|___| |___| Hour Minute Hour Minute	|___| |___| to|___| |___| Hour Minute Hour Minute

.....
Signature of investigator

FORM FOR MEAL INGREDIENTS - *cont.*-

The light breakfast will be served approximately 21:30 p.m (Day 1, Day 2, Day 3)		
	Day 1	**Day 2**
light breakfast Taken on:	|__|__|__|__|__|__|__|__| DD MM YYYY	|__|__|__|__|__|__|__|__| DD MM YYYY
Between:	|___| |___| to|___| |___| Hour Minute Hour Minute	|___| |___| to|___| |___| Hour Minute Hour Minute
	Day 3	
light breakfast Taken on:	|__|__|__|__|__|__|__|__| DD MM YYYY	
Between:	|___| |___| to|___| |___| Hour Minute Hour Minute	

.....
Signature of investigator

RECONCILIATION FORM
for CRF pages

- ***Instructions for filling in the form:***

- Place an "X" through the page numbers of those pages that have NO INFORMATION OF ANY KIND recorded on them (empty pages). If a subject is a screening failure or a drop-out whole blocks of pages may be crossed together.
- In case of additional pages which are filled in, please enter the page number in the empty boxes.

18	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
28	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**
38	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**
48	**49**	**50**							

……

Signature of investigator

STATEMENT OF THE INVESTIGATOR

I hereby confirm that the clinical trial was conducted in accordance with the protocol, the principles of the declaration of Helsinki and GCP-guidelines and the data in this case report form is to the best my knowledge, a truthful and correct representation of the source data and the results of the trial.

Date I__I__I__I__I__I__I__I__I Signature of Principal Investigator
DD MM YYYY

Date I__I__I__I__I__I__I__I__I Signature of Quality Control
DD MM YYYY

Appendix to CRF

I____I forms for Adverse Event (AE) registration (Amount)

I____I forms for Serious Adverse Event (SAE) registration (Amount)

(Empty forms for registration of AE and SAE are in the investigator's file)

Please attach the original completed AE and SAE forms after this last CRF page!

APPENDIX 3: ANALYTICAL STUDY PLAN

QUANTITATIVE DETERMINATION
OF
FAVIPIRAVIR IN HUMAN PLASMA

ANALYTICAL STUDY PLAN

"CONFIDENTIAL"

Sponsor: Koçak Farma İlaç ve Kimya San. A.Ş.
İstanbul-Turkey

Contract Research Organisation (CRO): ALPAN Farma Ltd.Şti.
Kayseri- Turkey

Contracted Analytical Laboratory: Novagenix Bioanalytical Drug R&D Centre,
Ankara - Turkey

CONTENTS

DEFINITION OF PARTS

Investigator:

Prof. Dr. Muradiye Nacak
FARMAGEN GCP Center
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Fax: +90 342 360 64 57
E-mail: m.nacak@farmagenarge.com
Date and signature:

08.05.2020

Sponsor Representative:

Cem Koçak
Koçak Farma İlaç ve Kimya San. A.Ş.
Addresses: Mahmutbey Mah. 2477 Sok.
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E-mail: ckocak@kocakfarma.com
Date and Signature:

Alpan Farma Representative (Project Manager):

Prof. Dr. Aydın Erenmemişoğlu
Alpan Farma Ltd.Şti.
Addresses: Istanbul Subesi Bomonti Business Center No:4 Şişli/İstanbul-Turkey
Phone: +90 536 216 27 21
Fax: NA
E-mail: erenmemis@gmail.com
Date and signature:

08-05-2020

Contracted Analytical Laboratory
Bioanalytical Laboratory Manager:

Berrak Güney
Novagenix Bioanalytical Drug R&D Centre
Phone: +90 312 398 10 81/138
Fax: +90 312 398 07 18
Date and Signature:

08.05.2020 Bgüney

DATES:

The start of analysis:	Approximately in 4 weeks after samples receipt.
The completion of analysis:	Approximately 6 weeks after starting analysis of samples.
The final analytical report(draft):	Approximately 2 weeks after completion of analysis.

1. QA DECLARATION

Novagenix Bio Analytical Drug R&D Centre Quality Assurance Department declares that Novagenix will execute the project coded as **NOV2020/01919** with respect to Good Clinical Practice (GCP), Good Laboratory Practice (GLP), FDA, EMA regulations and internal Standard Operation Procedures of Novagenix and makes the audit plan according to SOP-NOV-ENG-10-CQU5 (Title: Quality Assurance Programme). Audit programme will be given in the analytical study report.

Çiğdem Özer
Quality Assurance Manager

06-05-2020
Date

2. TITLE OF THE STUDY

Open-label, single oral dose, two-period, cross-over trial to assess to bioequivalence of Favir 200 mg Film Tablet (Test Drug) in comparison with Avigan 200 mg Film Tablet (Reference Drug) in healthy male subjects under fasting conditions.

3. PURPOSE OF THE STUDY

Determination of favipiravir in human plasma to assess to bioequivalence of Favir 200 mg Film Tablet (Test Drug) in comparison with Avigan 200 mg Film Tablet (Reference Drug) in healthy male subjects under fasting conditions.

The determination of favipiravir in human plasma will be carried out in accordance with Novagenix's Standard Operating Procedures and in accordance with the following national and international codes, regulations and guidances.

1. The Guidance for GCP, published by the Ministry of Health of Turkey. Circular, 13.11.2015.
2. Regulation Amending the Regulation of Ministry of Health of Turkey for Clinical Trials. Official Journal, No: 29474; 13.09.2015.
3. Regulation Amending the Regulation of Ministry of Health of Turkey for Clinical Trials. Official Journal, No: 29041; 25.06.2014.
4. Regulation on Clinical Trials of Drugs and Biological Products. Official Journal, No: 28617; 13.04.2013.
5. Regulations for Principles of GLP, Harmonisations of Test Laboratories, Auditing of GLP and Studies, Official Journal, No:27516; 09.03.2010.
6. Regulations on Evaluation of Bioequivalence and Bioavailability of Pharmaceutical Preparations. Official Journal, No: 21942; 27.05.1994.
7. Guideline on Bioanalytical Method Validation, EMEA/CHMP/EWP/192217/2009 Rev.1Corr.2, 21 July 2011.
8. Guideline on The Investigation of Bioequivalence. CPMP/QWP/EWP/1401/98 Rev.1/Corr., London, EMA, 20 January 2010.
9. Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products- General Considerations. FDA, CDER, March 2003.
10. Bioanalytical Method Validation. Guidance for Industry. FDA.CDER. May 2018.
11. Guideline for good clinical practice E6(R2)-2017. EMA/CHMP/ICH/135/1995.
12. GLP Principles of Good Laboratory Practice as specified by international (OECD- Paris 1998; Directive 2004/10/EC of the European Parliament and of the council of 11 February 2004).

4. SUBJECT SAMPLES

Subject's plasma samples generated from the clinical study according to the study protocol will be packed in dry ice with data logger and sent to NOVAGENIX.

The duplicate set of samples will be delivered similarly under seperate cover after receipt of the original set.

At the site samples will be stored in a temperature-monitored freezer set nominally at -70ºC until analysis is completed.

5. ANALYTICAL METHOD

Plasma levels of favipiravir will be determined by a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method.

Plasma concentrations of favipiravir will be determined for 8 calibration levels, which will include the expected concentration range of the study, using interpolation from the line of best fit for calibration standards. The regression algorithm will be least square linear regression based on analyte to internal standard peak-area ratio. Stable isotope labelled favipiravir will be used as internal standard.

LLOQ is the lowest concentration of the calibration curve.

Reference substance: Favipiravir (Supplier, batch number and certificate of analysis will be given in the Final Study Report)

Internal standard: Stable isotope labelled favipiravir (Supplier, batch number and certificate of analysis will be given in the Final Study Report)

Calibration standards and quality control samples will be prepared by spiking human plasma with stock and working solutions of favipiravir. Calibration standards and quality control samples will be prepared from seperately weighed stocks.

Quality control samples in subject batch will be prepared as four concentration (low, medium, medium2, high) and analyzed at least twice.

6. BEFORE THE STUDY VALIDATION

Prior to starting analysis of study samples, the method protocol for favipiravir will be validated by the determination of its LLOQ, Specificity, Stability, Precision and Accuracy according to FDA and EMA recommendations (1,2). A complete validation report containing statistical calculation and full analytical data obtained from the validation run will be provided with the Final Study Report.

7. IN-STUDY CONTROL LIMITS

Acceptance limits for in-study control of quality control samples and calibration standards will be determined from the validation data and expressed in terms of percent accuracy. They are based on commonly recommended ranges (1, 2) and as per Novagenix SOP-NOV-ENG-08-TEC1.

In process control limits for calibration standards and quality control samples containing favipiravir that will be used in routine analysis are shown below.

In-Study Control Ranges for Favipiravir Plasma Calibration Standard

Accuracy for LLOQ ±% 20, for the other ±% 15.

In-Study Control Ranges for Favipiravir Plasma Quality Control Samples

Accuracy for quality control sample concentrations (Low, medium, medium2, high) ±% 15.

Precision (CV)(%) for LLOQ ≤ 20%, for the others ≤ 15%

7.1. ACCEPTANCE AND REJECTION CRITERIA

1. As a criterion for acceptance of the calibration curve, the back calculated concentrations of the calibration standards should be within ± 15% of the nominal value, except for the LLOQ for which it should be within ± 20%. At least 75% of the calculated concentrations of the calibration curve should fulfil the acceptance criteria (at least 6 non-zero samples). While excluding the out of range calibration standards (ST), first of all the highest deviate ST is excluded and calibration curve is re-evaluated. Only in validation batches the lowest ST and the highest ST cannot be excluded from calibration curve. Otherwise batch will be reanalysed.

2. In validation, the mean concentration should be within 15% of the nominal values for the QC samples, except for the LLOQ which should be within 20% of the nominal value. CV should be ± 15% (for LLOQ ±20%). Two third of the QC samples at each concentration should fulfil the acceptance criteria.

3. In study, the accuracy values of the QC samples should be within ±15% of the nominal values. At least 67% of the QC samples and at least 50% at each concentration level should comply with this criterion. In case these criteria are not fulfilled the analytical run should be rejected, and the study samples re-extracted and analysed.

4. Should any system failure lead to abort the run in progress, the analysis of the interrupted batch will be restarted via partial sequence or reinjection after the problem is solved provided that the stability of the samples has been proven for the duration of the failure.

8. CRITERIA FOR REASSAYS OF STUDY SAMPLES

The reasons for the reanalysis of study samples are established according to SOP-NOV- ENG-08-CQU4 and are following categories.

a. Rejection of an analytical run because the run did not fulfil the acceptance criteria with regard to accuracy and precision of the calibration standards and/or QC samples,
b. Internal standard response significantly different from the response for the calibration standard and QC samples,
c. Improper sample injection or malfunction of equipment,
d. The obtained concentration is above the ULOQ or below the run's LLOQ, in runs where the lowest standard sample has been rejected from a calibration curve, resulting in a higher LLOQ compared with other run's,
e. Identification of sample analyte in pre-dose samples or placebo sample,
f. Poor chromatography.
g. Sample prossesing error.

9. INCURRED SAMPLES RENALYSIS

Incurred sample reanalysis (ISR) will be performed by choosing sampling points according to SOP-NOV-ENG-08-CQU4.

The difference between the study samples' and incurred samples' values obtained should be within 20% of the mean for at least 67% of the repeats according to Guidance on Validation of Bioanalytical Methods, 2011, EMA.

10. RESULTS

All of the analytical results will be delivered to statistical department for the determination of the comparative pharmacokinetic behaviours of the generic and the reference drugs:

The following parameters will be determined from the results of the analysis of study samples and will serve for the determination of the comparative pharmacokinetic behaviours of the generic and the reference drugs:

C_{max}

$AUC_{0\text{-}tlast}$

$AUC_{0\text{-}\infty}$

t_{max}

$t_{1/2}$

λ_z

MRT

11. ARCHIVING

Raw data generated during this study such as chromatograms and spreadsheets and all other documents are stored in-house in hard copy and electronic format as mentioned in SOP-NOV-ENG-10-CQU4. The study logbook together with a copy of the Final Study Report is filled in fireproof cabinets on-site. The minimum period of archiving will be 14 years.

All plasma samples will be stored in a temperature-monitored freezer set nominally at -20ºC for a period of at least six months after the final date of analysis. Extended storage beyond this period will be subjected to negotiation between sponsor and Novagenix.

All plasma samples will be disposed end of six months by the approval of sponsor and according to "Çevre ve Orman Bakanlığı Tehlikeli Atıklar Bertaraf Yönetmenliği *(Hazardous Waste Control Direction,Turkish Ministry of Environment and Forest, Ankara, 14.03.2005)* " and SOP-NOV-ENG-08-LOG9.

12. STUDY PLAN AMENDMENTS

Different equipment, lower limit of quantification (LLOQ), column, chemicals, detector, extraction, concentration range, internal standard can be applied in process of method development and study, if there is need. But this different parameters would be validated.

They would be documented in the validation report and final study report.

13. STUDY PLAN DEVIATIONS

Study plan deviations will be documented in the final study report.

14. REFERENCES

1. Guidance for Industry . Bioanalytical Method Validation. FDA, May 2018.
2. Guideline on Bioanalytical Method Validation,

   EMEA/CHMP/EWP/192217/2009Rev.1Corr.2, London, 21 July 2011.
3. Shah VP. Kamal K. Midha KK et al. Bioanalytical method validation- a revisit with a decade of progress (Conference report). *Pharm Res 2000; 17(12): 1551-1557.*
4. The United States Pharmacopiea, XXIV Edition. Validation of Compendial Methods, USP Convention Inc. Rockville. 2000, pp. 2149.
5. SOP-NOV-ENG-10-CQU5
6. SOP-NOV-ENG-08-TEC1.
7. SOP- NOV- ENG-08-CQU4
8. SOP-NOV-ENG-08-LOG9.

APPENDIX 4: INFORMED CONSENT FORM

Subject Screening Number: .....

INFORMED CONSENT FORM

Principal Investigator: Prof. Dr. Muradiye Nacak
Gaziantep Üniversitesi FARMAGEN GCP Center
Gaziantep Üniversitesi Teknoloji Geliştirme Bölgesi (Teknopark)
Burç Yolu, Şahinbey 27260, Gaziantep-Turkey
Telephone : +90 342 360 62 62
GSM: +90 505 252 54 69

"Open-label, randomised, single oral dose, two-period, cross-over trial to assess to bioequivalence of Favir 200 mg Film Tablet(Test Drug) in comparison with Avigan 200 mg Film Tablet (Reference Drug) in healthy male subjects under fasting conditions"

Dear Volunteer,

The drugs tested in this trial is ***Favir 200 mg Film Tablet (Test Drug)*** containing **200 mg favipiravir of Koçak Farma İlaç ve Kimya San. A.Ş.** *It is a medication used orally and it could be valuable in the treatment of the diseases caused by highly pathogenic influenza viruses*

The purpose of the present research study is to investigate the bioequivalence of orally administered test drug containing **200 mg favipiravir *(Test drug)*** and on the other orally administered reference drug containing **200 mg favipiravir *(Avigan 200 mg Film Tablet).*** The **reference drug** is already registered and commercially available for years in ***Japan*** as ***Avigan 200 mg Film Tablet***. The company responsible for placing the reference product on the market is **Fuji Film Toyama Chemical Industry Co Ltd.-Japan .** The efficacy and safety of this reference drug has been proven through the clinical studies that were carried out in order to obtain the license for the drugs. Therefore, this drug will be used as reference and will establish the basis of comparison to be used for the test drug. (**test drug is** manufactured by **Koçak Farma İlaç ve Kimya San. A.Ş.** in Turkey.) The comparison will be based on the measurement of the concentrations of the active ingredient of the drugs in blood. In addition, the safety of the test product will be compared to the safety of the reference products based on the evaluation of adverse events.

After the "Covid-19 PCR Test*" to be applied to you, your screening examinations will be carried out at the FARMAGEN GCP Center based on your negative test result. Screening tests will be done before the beginning of the study and will include standard clinical and laboratory research. Standard clinical research includes your medical history, a complete clinical examination, drug abuse screening, alcohol breath test, **Covid-19 PCR test***, standard ECG, and measurement of your height, weight, body temperature, blood pressure, and heart rate after five minutes of rest in the supine position. Depending on the suitability of your clinical examination and laboratory results, you will be transferred to Gaziantep University Hotel where you will be during the isolation period for clinical study. Your isolation period will be provided for 4 nights in single rooms reserved for you at Gaziantep University Hotel. During this time, breakfast, lunch, dinner and snacks will be served to your room. In addition, fever, blood pressure and heart rate will be measured in every morning. It will be 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 are followed. On Day 5 **Covid-19 PCR test*** will be applied. You will be transferred to FARMAGEN GCP Center for clinical study in suitable isolation conditions according to your test result and general condition.

Under fasting condition in this 2 period trial, each of **30 subjects** who enrolled into trial will be given a single dose of **Test Drug (200 mg favipiravir)** in one period and a single dose of **Reference Drug** (**200 mg favipiravir)** in one period and there will be a wash-out of at least **48 hours.** You will take a total of **2** drugs ***[(Test Drug) / (Reference Drug)]*** during the trial **(total 400 mg favipiravir)**. The drugs will be assigned randomly. Therefore, you will have an equal chance of receiving either drug. The total duration of the trial including isolation period will be approximately **9 days.**

The final examination will be carried out on the day of last blood sampling in the last period and will include standard clinical and laboratory research. Standard clinical research includes a complete clinical examination, standard ECG, body temperature, blood pressure, and heart rate after five minutes of rest in the supine position. Also, **Covid-19 PCR*** test will be applied in the final examination.

** Covid-19 PCR screening tests will be made by taking a swab from your throat and nose. Volunteers who have positive results in Covid-19 screening tests will be taken to Gaziantep University Research Hospital Emergency Department under appropriate conditions.*

Approximately **32 mL** blood sample *(20 mL[#] for entry examination and 12 mL for final examination)* is going to be collected for the standard laboratory tests on entry and final examination with HIV (AIDS) and hepatitis tests at only entry examination. The blood samples collected for laboratory (entry and final examination) tests will be sent to GAMA Medical Laboratories (GAMA Tıp Laboratuvarları) which is located in Gaziantep-Turkey, and will be used exclusively for this research, specifically for it's purpose. Covid-19 PCR test analyzes will be carried out at FARMAGEN GCP Center. *An amount of blood sample will be needed if any Clinical Laboratory Tests occur which need to be repeated.*

[#] *8 mL of 20 mL of entry examination blood sample will be used for analytical studies of this project.*

Approximately 30 mL urine sample is going to be collected for the standard laboratory tests on entry and final examination with drug abuse tests.

You will come to the clinic the day before study period around **18:00** and will stay in the clinic for **90** hours. **But according to your health situation, the investigator and/or co-investigator will be decided whether you can leave the clinic at that time or not**. Your body

Subject's paraph	

temperature will be measured in the mornings during study period. *Final examination and laboratory tests will be done on the day of last blood sampling in the **2. period***

You **should not consume alcohol and cigarette** during the trial. You will not be allowed to **chewing gum** on the day of drug administration. You will not be allowed to consume **food or drink** (coffee, tea, cola, hot chocolate, etc.) and fruit juices **that contain caffeine or other methylxanthines** starting two days before administration and lasting until the last blood sample for that period is drawn. **Grapefruit products** should not be consumed starting seven days before the first dose is administered and lasting until the last blood sample is drawn. No food and beverages will be consumed starting the evening before the drug is administered, i.e. 22:00 in the evening and lasting until the lunchtime (approximately 4 hours after drug administration) in each study period. Not allowed to drink water between 1 h before to 1 h after administration, except while dosing in each period. No vigorous physical activity is allowed starting with the initial screening tests and lasting until the last laboratory test in the final check up is performed.

Dinner on the day before drug application will be served no later than 21:00. A typical lunch will be served approximately 4 hours after the drug is administered and a typical dinner will be served approximately 10 hours after the drug is administered. Light breakfast will be served at around 21.30 in the evening. The total amount of water to be consumed on the day of drug administration is maximum 1.5 litters and water consumption will begin 1 hour after the administration of the drug.

The following day of drug administration, a standard breakfast, lunch, dinner and a light breakfast (at around 21.30 in the evening)will be served. From 22.00 in the evening, no food or drink other than water will be consumed until 4 hours after the 2nd Period drug application. Standard lunch will be given approximately 4 hours after the medication and standard dinner will be given approximately 10 hours after the drug. A light breakfast will be served at around 21.30 in the evening. In the 2nd period drug application, after the last blood sample is taken (t24.00), final examination and laboratory tests will be performed.

A test drug or reference drug will be taken with 240 mL of water -as a whole in sitting position and this will be followed by mouth check. ***You should sit without lying in your bed during 4 hours after the drug administration. In this interval ($t_{0.17}$-$t_{4.00}$); the blood collections will be performed in bed; lunch will be provided on bed.*** **The drug will be administered approximately at 08:00 a.m.**

Blood samples for drug analysis *(8 mL at most each time, only in Period I; at pre-dose (t_0) the blood sample amount will be 20 mL)* will be drawn at the following times in each study period: **before the drug is administered**, and then **10, 15, 30, 45.minutes and 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, 24.00** hours after the drug is administered. Blood samples will be drawn using a catheter during the time period passed at the Clinic. The total volume of blood to be drawn during the entire study is expected to be approximately **358 mL**, *including blood samples for initial and the heparinised discarded blood at determined blood sampling points each of approximately 0.5 mL and final laboratory controls.* **An amount of blood loss could provoke; dizziness, faintness, sweating, thirst, weak and rapid pulse, rapid respiration, orthostatic hypotension and eventual decrease in some laboratory parameters such as hemoglobin and hematocrit. Having in mind that the blood loss in the present trial will take place over a period of several weeks, the risk for the volunteers to experience one of the upper side effects is relatively low.**

The collected blood samples will be transferred to NOVAGENIX Bioanalytical Drug R&D Centre in Ankara- Turkey to determine the level of drug in blood. These samples will be used to only for this study and in accordance with study objectives and any remaining material will be destroyed.
You can decide at any time whether your samples can be used for the analysis of determine the level of drug in blood or should be destroyed. If you decide that your blood samples shall not be subjected to analysis, you will have to inform the investigator about your decision in a written form.
However, the samples can be stored for monitoring, inspection and audit activities of the relevant health authorities for the aim of verifying the information on clinical studies.
Samples can not be used as a source of commercial gain in any way. However, intellectual property and patent rights are exempted from this condition.

To monitor your compliance with the study, all the rooms and the corridors are being observed continuously by video cameras during the time in the clinic. All the records will be deleted after the study.

On admission to the clinic (hospitalization day in study) the luggage of all volunteers will be checked for not allowed items (food, beverages, cigarettes, chewing-gum, and any drugs). A security service personnel or clinical personnel will perform a security check on your body and on your luggage by a hand on admission to the clinic and before the start of hospitalization.

To monitor your compliance with the study, all the rooms and the corridors are being observed continuously by video cameras during the time in the clinic. All the records will be kept for 2 months after completion of the clinical period, and all records will be deleted at the end of this period.

Subject's paraph	

Side effects:
The main adverse events of favipiravir seen during the development of the product for influenza include mild to moderate diarrhoea, abdominal pain, headache and asymptomatic elevations of blood uric acid, decrease of neutrophil count, increase of AST (GOT), increase of ALT (GPT).

Adverse reactions observed in Japanese clinical studies and the global phase III clinical study (studies conducted with dose levels lower than the approval dosage) are shown in the table below with frequency.

	≥ 1%	%0.5 - < 1	< 0.5%
Hypersensitivity		Rash	eczama, pruritus
Hepatic	AST (GOT) increased,ALT (GPT) increased, γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea (4.79%)	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic	Neutrophil count decreased, white blood cell count decreased		White blood cell count increased, reticulocyte count decreased, monocyte increased
Metabolic disorders	Blood uric acid increased (4.79%), blood triglycerides increased	Glucose urine Present	Blood potassium decreased
Respiratory			Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others			Blood CK (CPK) increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo, supraventricular extrasystoles

Clinically significant adverse reactions such as, shock, anaphylaxis, pneumonia, hepatitis fulminant, hepatic dysfunction, jaundice, toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute kidney injury decrease of white blood cell, neutrophil count and platelet count, neurological and psychiatric symptoms (consciousness disturbed, abnormal behavior, deliria, hallucination, delusion, convulsion, etc.) haemorrhagic colitis have been reported with other anti-influenza virus agents.

(**Also, a verbal explanation will be made about the unexpected side effects by the investigator.)**

You and your partner need to practice adequate contraception for 7 days after the study.

Please ask the informing physician about any terms you do not understand. If any side effect will occur, report to the study investigator immediately. You can ask additional questions any time during the trial about additional information not provided in this form**. Investigator and authorised personnel have to be reachable 7/24 during the entire clinical study (see the phone number given in the first page).**

As with all prescription drugs, other unpredictable side effects or life-threatening events can occur in addition to the above mentioned side effects**.** ***Do not drive or operate machine on medication day.***

Your participation of this study will be finished after the last blood sampling at 24. hours for pharmacokinetic purpose in the last period and the following post-study examination and laboratory tests and /or in the cases of the drop-out or occurring a serious adverse event.

Because of participating the clinical phase of the study, a payment will be done to you with a receipt/voucher or a signed minute for the loss of your working days and the some private expenditures (e.g. transportation, communication, meal, accommodation etc.). ***Except these, you will not have any payment for the use of blood samples obtained from clinical study or other purposes. If you violate the procedures of the study or of your own health protection, you may be withdrawn from the study before its completion or the amount of the money which will be paid to you may reduced.***

Subject's paraph	

Data Protection:

Only the birth dates and initial letters of subject names will be used as identity markers in study records. Your identity will be kept confidential. Study records will only be used for scientific purposes and will be delivered to the sponsor of this study. To ensure a fair study in accordance with the rules, the authorized study monitors of the drug firm **(Koçak Farma İlaç ve Kimya San. A.Ş.)** or the Contract Research Organisation **(Alpan Farma)**, inspectors, ethics committees, and legal authorities are permitted to access your medical records. Individuals working with the study have been specially trained in this area and must adhere to occupational guidelines. They can only be given access to your personal data not including your name.

The privacy of your records will always be respected. The data protection law will be followed.

You can withdraw from the study without explanation and without risking clinical treatment that might be needed in the future. Your signature under the informed consent form does not entitle you to complete the study.

All subjects participating in this study are insured. By mutual agreement between the clinical study sponsor **(Koçak Farma İlaç ve Kimya San. A.Ş.)** and the principal investigator, ALPAN Farma insured all participants **for the cases of study-related loss of function or cases, where hospitalization or surgical intervention is required, death, or permanent disability due to this study. In case of your request a copy of the insurance policy will be given to you by investigator.**

The insurer is responsible for health-related problems that may occur only under the following conditions:

1. Health-related issues that occur due to the treatment and/or administration of drugs with the decision and approval of the conducting physician during the research,

2. Any problem that may occur regarding your health due to the clinical study is immediately reported to your investigating physician and insurer by you or your relatives.

Subject's paraph	

Screening Number: ……..

Test Drug: Favir 200 mg Film Tablet ***(Koçak -Turkey)***
Reference Drug: Avigan 200 mg Film Tablet ***(Fuji Film Toyama Chemical Industry Co Ltd.-Japan)***

II, ……., agree to take part voluntarily in the above research conducted by **ALPAN Farma (Contract Research Organisation) on behalf of Koçak Farma İlaç ve Kimya San. A.Ş. (Sponsor)** of my own free will. I have been informed about the structure of the study, its possible duration, risks and about my responsibilities by the physician whose name is given below. I have read and understood the above explanations. Physician who is responsible for informed have advised me about possible disorders and side effects. I have also read the informing document about all aspects and details of the study. Finally, I have understood and accepted all the information, explanations, and recommendations provided.

I have reported my previous and current illnesses along with the treatments and drugs I received in the last three months and all the information about any consultations with a doctor in the last six months and the drug treatments I am planning to take.

I promise to report any deterioration of my well being or my health, as well as the occurrence of any unexpected/unusual symptoms to the researchers immediately, to work in collaboration with the researchers, and to follow the instructions provided **during the study and isolation period**. If I violate the rules, my participation to the clinical trial will be ended by the investigator(s). I have given explicit information about the previous studies in which I participated. I have been told that this research is reviewed and approved by an ethics committee. I was also told that I can ask any further questions I might have to those individuals.

I understand that I am free to withdraw from the study anytime, without giving any explanation.

I am aware that although this study can contribute to the development of medical knowledge, it will not be of direct help to my health and I might even harm myself by participating in this study if I am not honest with the information I provide or if I do not follow the instructions given to me.

I promise not to behave in any way that is likely to affect the results of the study. I also understand that I will be notified immediately in case any information that might affect my participation is discovered during the course of the study.

I am not stipulating any restrictions for the use of study results. I accept that the results will be given to authorized people and corporations. I accept that the data recorded during the study will be delivered to the sponsor firm and later to health authorities. I understand and consent that study results will be evaluated by computer, keeping the identities of participants confidential.

I understand that all the subjects participating in this study are insured. The sponsor drug firm approves that the compensation fee will be paid by insurance in case I suffer from any important disorder in my health or wellbeing due to my participation in this study.

I accept that any damage that occurs to my health at my own fault and/or for disobeying the instructions of the researcher will not be covered by insurance. I have understood and accepted that damages will not be covered by insurance in case my health deteriorates due to any drugs or treatments I receive outside of the researcher's permission or knowledge. I have understood and accepted that the insurer can cover the damages that may occur due to drugs used during and for the purposes of the study, the applied procedures, or another medical treatment administration carried out by the consent of the conducting physician.

The maximum compensation fee to be paid in such a situation is up to the amount mentioned in the insurance policy in case the liability is accepted.

I know that some private insurance companies accept participating in medical studies as an issue to be reported in insurance claim demands and I will check if my participation in the study will affect current policies in case of such an insurance claim demand or application for renewal.

I or my relatives will notify the insurer and the study doctors in case any deterioration occurs in my health. **I have been informed about content, structure, aim and risks of this clinical study by verbal and by Volunteer Informed Consent Form document from an authorized medical doctor who is in the clinical study team.** Also, I have read and understood this informed subject consent and study-related subject information form and accepted with my own free will, signed, and received one copy of it.

Subject's:

NAME ……..

DATE OF BIRTH ……..

SIGNATURE……

DATE ……

As the responsible physician, I am convinced that the subject understood all the written and verbal explanations provided, read and understood the given information, and agreed to participate in the study of his/her own free will.

Doctor Who Is Responsible For Informed:

NAME……..

SIGNATURE……..

DATE……..

This Informed Consent Form includes 5 pages.

Subject's paraph	

APPENDIX 5: COPY OF INSURANCE CERTIFICATE

MAPFRE Sigorta

SİGORTA SERTİFİKASI / INSURANCE CERTIFICATE

Poliçe Numarası / Policy Number	:	5602000000254
Poliçe Vadesi / Policy Term	:	06-03-2020- 06-03-2021
Sigortalı Adı ve Adres / Insured and Adress	:	Novagenix Bio Analitik İlaç Araştırma Geliştirme Merkezi San.Tic. A.Ş. / Esenboğa Yolu 25. km 06970 Akyurt, Ankara-Türkiye Novagenix Bioanalytical Drug R&D Centre / Esenboğa Yolu 25. km 06970 Akyurt, Ankara-Turkey
Teminat Türü / Type of Coverage	:	İş bu sertifika , Sigortalı tarafından, yapılan onaylanmış klinik çalışmalara katılan Gönüllü'nün ölüm, daimi sakatlık , cerrahi müdahale gerektiren durumlar ve kalıcı hastalık dahil bedensel ve ruhsal zarara uğraması hali veya uygulanabilir herhangi bir ek keşif devresinde yapılacak tüm hasarlar (örneğin işlev kaybı ya da hospitalizasyon sakatlık talepleri ile ilgili maruz kalınan tüm harcama ve masraflar) için poliçe hüküm ve şartları dahilinde verilmiş teminatı teyid etmektedir. / This certificate evidences covarege for the Bodily Injury, including death, permanent disability , situations that require surgical intervention and permanent illness or during the insurance term or during any applicable additional term of exploration (e.g. loss function or cases, where hospitalization or surgical intervention is required) of the Participants enrolled in the approved clinical trial made by the insured under the policy. İş bu sertifika konusu teminat, poliçe hüküm ve şartları çerçevesinde , Sigortalının mahalli mevzuat ve/veya kararlara uygun olarak gerçekleştirdiği tüm ticari faaliyetlerini içine alacak şekilde genişletilir. / Coverage under the Certificate is extended to include all of the Insured's business activities in accordance with the local legislation and/or ruling, subject to the terms and conditions of the policy. İş bu sertifika gönüllüler ile gerçekleştirilecek Biyoyararlanım/Biyoeşdeğerlik çalışması faaliyetini kapsamaktadır. This certificate covers bioavailability/bioequivalence studies to be carried out with volunteers.
Çalışma Protokol Numarası / Study Protocol Number	:	NOV2020/01919

Teminat Limitleri / Limit of Liability	:	,	**Kişi Başı / Olay Başı (per person / per occurence)**	**Yıllık Toplam (aggregate)**
		Klinik Deneyler / Clinical Trials :	EUR 150.000	EUR 750.000

Poliçe Muafiyeti / Deductible	:	NIL / yok
Çalışma Başlığı / Study Protokol Title	:	Favir 200 mg Film Tablet'in (Test İlaç), Avigan 200 mg Film Tablet'e (Referans İlaç) göre; sağlıklı erkek katılımcılarda, açık-etiketli, randomize, oral tek doz, iki periyotlu, çapraz geçişli uygulama ile açlık koşullarında biyoeşdeğerlik çalışması Open-label, randomised, single oral dose, two-period, cross-over trial to assess to bioequivalence of Favir 200 mg Film Tablet(Test Drug) in comparison with Avigan 200 mg Film Tablet (Reference Drug) in healthy male subjects under fasting conditions
Kapsam Bölgesi / Coverage Territory	:	Turkey
Çalışma Süresi / Study Period	:	06-03-2020- 06-03-2021
Katılımcı Sayısı / Number of Participanst	:	30

This certificate is issued as a matter of information only and confers no rights upon the certificate the holder. This certificate does not affirmatively or negatively amend, extend or alter the coverage afforded by the policies above.
İşbu sertifika; asıl geçerliliği olan, Sigortalı tarafından meydana gelen hasarları teminat altına alan,kayıt ve şartları hüküm süren 5602000000254 nolu poliçenin ayrılmaz bir parçasıdır.
This certificate, which is an Inseparable part of the Policy numbered 5602000000254 that prevails, covers losses and damages claimed by the insured parties, as defined in the Policy, subject to the Policy terms and conditions.
"İlgili çalışma sırasında söz konusu olabilecek bir tazminat talebi halinde, ödemenin yapılabilmesi için gerekli olan bilgi ve belgeler yürürlükteki mevzuat çerçevesinde sigortacıya bildirilecektir"
"In case of being a claim during the study, required information and documents will be reported to the insurer within the scope of the

Tanzim Tarihi / Date of issuance : 6.05.2020

TEB ARTI SİGORTA ve REASÜRANS BROKERLİĞİ A.Ş.
Mustafa Kemal Mah. 2147 Sokak No: 3 Kat 1
Çankaya/ANKARA
Mersis No: 0853050900000019

APPENDIX 7: ISOLATION PROCEDURE DUE TO COVID-19 PANDEMIC

Appendix-7: Isolation procedure due to Covid-19 pandemic

Due to the outbreak of Corona virus (Covid-19), which is progressing at an international level, volunteer recruitment to the clinical trial will be done as stated below.

- Volunteers, who are invited to participate in the study (informed to be in fasted conditions), will be informed at gathering area near the building of the Gaziantep University FARMAGEN GCP Center (paying attention to the social distance rules, which are one of the epidemic measures). Volunteers will be kept under surveillance, from the initial screening to the final examination, after the briefing.
- "Rapid Covid-19 Test*" will be applied to the volunteers.
- Volunteers who have negative results from the "Rapid Covid-19 Test" will be screened in small groups in FARMAGEN GCP Center, including the Covid-19 PCR test*, as specified in the protocol.
- Volunteers who fulfill the inclusion criteria written as protocol will be transferred to Gaziantep University Hotel under appropriate conditions and each volunteer will be placed in the Hotel in a separate room.
- Volunteers will be accommodated in the hotel for 4 nights in isolation.
- In isolation period;
    - Body temperature, blood pressure and pulse rate monitoring will be performed once a day, in the morning.
    - Standardized breakfast, lunch and dinner will be served to the volunteers in their separate rooms.

- On 5th day of isolation, samples will be taken for Covid-19 PCR Test*.
- Volunteers who have negative Covid-19 test results will be transferred to FARMAGEN GCP Center under appropriate conditions approximately at 18.00 pm.
- Volunteers will remain in Farmagen GCP Center throughout the study period as stated in the protocol.
- After the last blood sampling, the final examinations, including the Covid-19 PCR test*, will be carried out.
- Volunteers, whose final examinations are done (after receiving Covid-19 PCR test results), will be taken to their homes with appropriate conditions.
- Medical staff assigned during the voluntary screening period and clinical study, will also be screened for Covid-19. Precautions will be taken with the necessary protective equipments by medical staff.

**Volunteers who have positive results in Covid-19 screening tests will be taken to Gaziantep University Research Hospital Emergency Department under appropriate conditions.*