OPEN-LABEL, RANDOMISED, SINGLE ORAL DOSE, TWO-PERIOD, CROSS-OVER TRIAL TO ASSESS THE BIOEQUIVALENCE OF **FAVICOVIR 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"

Principal Investigator: Prof. Dr. Muradiye Nacak

Clinical Center: Gaziantep Üniversitesi FARMAGEN GCP Center, Gaziantep –Turkey

Sponsor: Atabay Kimya San. ve Tic. 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

STUDY SYNOPSIS

Study Title:	Open-label, randomised, single oral dose, two-period, cross-over trial to assess to bioequivalence of **Favicovir 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:	**NOV2020/01917**
Drugs:	**Test Drug*:** "**Favicovir 200 mg Film Tablet**" containing 200 mg favipiravir *(Atabay-Turkey).* *****: *This drug is manufactured by Atabay Kimya San. ve Tic. 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 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: $AUC_{0\text{-}tlast}$ and C_{max} Secondary variables: $AUC_{0\text{-}\infty}$, 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:	Atabay Kimya San. ve Tic. 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: NOV2020/01917

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

Sponsor:
Atabay Kimya San. ve Tic. A.Ş.
Acıbadem Köftüncü Sok. No:1 34718
Kadıköy, İstanbul-Turkey
Phone: +90 216 339 69 03
Fax: +90 216 326 18 08

CRO:
Alpan Farma Ltd.Şti.
Istanbul Subesi
Bomonti Business Center No:4 Şişli/İstanbul-Turkey
Phone: +90 536 216 27 21

Contracted Analytical Laboratory:
Novagenix Bioanalytical Drug R&D Centre
Esenboğa Yolu 25. Km. 06970 Akyurt, Ankara-Turkey
Phone: +90 312 398 10 81
Fax: +90 312 398 07 18

Clinical Facility:
Gaziantep Üniversitesi FARMAGEN GCP Center
Gaziantep Üniversitesi Teknoloji Geliştirme Bölgesi (Teknopark),
Burç Yolu, Şahinbey 27260, Gaziantep-Turkey
Phone: +90 342 360 62 62
Fax: +90 342 360 64 57

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:

Prof. Dr. Muradiye Nacak
FARMAGEN GCP Center
Phone: +90 342 360 62 62
Fax: +90 342 360 64 57
E-mail: m.nacak@farmagenarge.com
Date and Signature:

CRO Representative (Project Manager):	Prof. Dr. Aydın Erenmemişoğlu **Alpan Farma Ltd.Şti.** Address: 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:

Sponsor Representative:	Vildan Tüzer, Chem. Eng. **Atabay Kimya San. ve Tic. A.Ş.** **Addresses:** Acıbadem Köftüncü Sok. No:1 34718 Kadıköy/İstanbul Phone: +90 216 339 69 03 Fax: +90 216 326 18 08 E-mail: vtuzer@atabay.com **Date and Signature**

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:

⌊_____⌋

Data Management Responsible:

Erkin Alkan
Novagenix Bioanalytical Drug R&D Centre
Phone: +90 312 398 10 81/126
Fax: +90 312 398 07 18
Date and Signature:

⌊_____⌋

Statistical Calculation Responsible:

Emel Doğan Kurtoğlu, PhD.
Novagenix Bioanalytical Drug R&D Centre
Phone: +90 312 398 10 81/127
Fax: +90 312 398 07 18
Date and Signature:

⌊_____⌋

Quality Assurance Manager:

Çiğdem Özer
Novagenix Bioanalytical Drug R&D Centre
Phone: +90 312 398 10 81/125
Fax: +90 312 398 07 18
Date and Signature:

⌊_____⌋

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 **Favicovir 200 mg FilmTablet (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 (**Favicovir 200 mg Film Tablet, *Atabay-Turkey***) in comparison with the reference product **(Avigan 200 mg Film Tablet, *Toyama Chemical Industry Co Ltd.-Japan*)** under fasting conditions. The primary objective is to demonstrate the bioequivalence of test and reference products.
Test Drug*:	"**Favicovir 200 mg Film Tablet**" containing 200 mg favipiravir *(Atabay-Turkey).* **: This drug is manufactured by Atabay Kimya San. ve Tic., 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 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:	Atabay Kimya San. ve Tic. A.Ş. Representative: Vildan Tüzer
Protocol code:	NOV2020/01917
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 **.**

° **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)]*

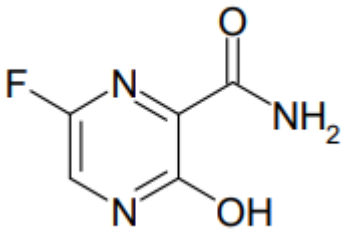
****Adverse event questioning**: at hospitalisation day (Day 0) and at pre-dose**, 1.00, 4.00, 8.00, 14.00, 24.00** hours post-dose in each period.

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 **(Favicovir 200 mg Film Tablet, Atabay-Turkey)** in comparison with Reference Drug **(Avigan 200 mg Film Tablet, *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: "Favicovir 200 mg Film Tablet" is manufactured by Atabay Kimya San. ve Tic. A.Ş., Turkey and is will be licensed by Atabay Kimya San. ve Tic. A.Ş., Turkey.

Reference Drug: "Avigan 200 mg Film Tablet" is manufactured and licenced by 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),

    *** SGOT (AST), SGPT (ALT), GGT and uric acid levels should be within normal range.**
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.**

[#]*One of the Covid-19 PCR test will be applied on examination day, the other will be applied on the 5th isolation day*

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. 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**.**
3. 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)***,
4. Presence or history of malabsorption or any gastrointestinal surgery except appendectomy or except herniotomy.
5. 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.
6. 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.
7. 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).
8. Use of any vitamins or herbal products within 7 days prior to the initial dose of the study medication.
9. History of allergic response to heparin.
10. Subjects who have any chronic disease which might interfere with absorption, distribution, metabolism or excretion of the drug.
11. 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.
12. Subjects who has taken any grapefruit or grapefruit juice during 7 days prior to drug administration, during the study.
13. History of drug abuse.
14. 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).
15. Positive blood test for HBV, HCV and HIV.

16. Who have relationship to the investigator.
17. Who are not suitable to any of inclusion criteria.
18. History of difficulty of swallowing.
19. Intake of depot injectable solutions (including study medications) within 6 months before start of the study.
20. Intake of enzyme-inducing, organotoxic or long half-life drugs within 4 weeks before start of the study.
21. 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, **Atabay Kimya San. ve Tic. 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 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:	Atabay Kimya San. ve Tic. A.Ş. - Turkey
Marketing Authorisation Holder:	Atabay Kimya San. ve Tic. –Turkey
Batch Number:	FATA-P01
Expiry Date:	03.2022
Trade name:	**Favicovir 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:	Toyama Chemical Industry Co.Ltd./Japan
Marketing Authorisation Holder:	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 Atabay Kimya San. ve Tic. 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".

**** SGOT (AST), SGPT (ALT), GGT and uric acid levels should be within normal range for entry examination.***

 # 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).

SGOT (AST), SGPT (ALT), GGT and uric acid levels should be within normal range.

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; Favicovir 200 mg Film Tablet *(Atabay-Turkey)*

Reference Drug; Avigan 200 mg Film Tablet *(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 # : **NOV01917**	
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 **Atabay Kimya San. ve Tic. 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 **Atabay Kimya San. ve Tic. 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 Atabay Kimya San. ve Tic. A.Ş.** as soon as possible.

The responsible sites for the upper procedure are:

Atabay Kimya San. ve Tic. A.Ş. **Contact Person**	**Alpan Farma Ltd.Şti.** **Contact Person**
Vildan Tüzer, Chem. Phone: (+90) 216 339 69 03 Fax: +90 216 326 18 08 GSM: +90 533 301 82 62 E-mail: vtuzer@atabay.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 **Favicovir 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.2 27.03.2020** 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 **NOV2020/01917** 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