

Subject Screening Number:

INFORMED CONSENT FORM

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

Dear Volunteer,

The drugs tested in this trial is **Favira 200 mg Film Kaplı Tablet (Test Drug)** containing **200 mg favipiravir** of Novelfarma İlaç San. ve Tic. Ltd. Şti. It is a medication used orally and it could be valuable in the treatment of the diseases caused by highly pathogenic influenza viruses

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

After the “Covid-19 PCR Test*” to be applied to you, your screening examinations will be carried out at the FARMAGEN GCP Center based on your negative test result. Screening tests will be done before the beginning of the study and will include standard clinical and laboratory research. Standard clinical research includes your medical history, a complete clinical examination, drug abuse screening, alcohol breath test, **Covid-19 PCR test***, standard ECG, and measurement of your height, weight, body temperature, blood pressure, and heart rate after five minutes of rest in the supine position. Depending on the suitability of your clinical examination and laboratory results, you will be transferred to Gaziantep University Hotel where you will be during the isolation period for clinical study. Your isolation period will be provided for 4 nights in single rooms reserved for you at Gaziantep University Hotel. During this time, breakfast, lunch, dinner and snacks will be served to your room. In addition, fever, blood pressure and heart rate will be measured in every morning. It will be important that the volunteers participating in the study do not come into contact with each other during the isolation and that the rules of isolation are followed. On Day 5 **Covid-19 PCR test*** will be applied. You will be transferred to FARMAGEN GCP Center for clinical study in suitable isolation conditions according to your test result and general condition.

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

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

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

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

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

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

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

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

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

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

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

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

Blood samples for drug analysis (8 mL at most each time, only in Period I; at pre-dose (t_0) the blood sample amount will be 20 mL) will be drawn at the following times in each study period: **before the drug is administered**, and then **10, 15, 30, 45.minutes and 1.00, 1.33, 1.66, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 14.00, 24.00** hours after the drug is administered. Blood samples will be drawn using a catheter during the time period passed at the Clinic. The total volume of blood to be drawn during the entire study is expected to be approximately **358 mL**, including blood samples for initial and the heparinised discarded blood at determined blood sampling points each of approximately 0.5 mL and final laboratory controls. **An amount of blood loss could provoke; dizziness, faintness, sweating, thirst, weak and rapid pulse, rapid respiration, orthostatic hypotension and eventual decrease in some laboratory parameters such as hemoglobin and hematocrit. Having in mind that the blood loss in the present trial will take place over a period of several weeks, the risk for the volunteers to experience one of the upper side effects is relatively low.**

The collected blood samples will be transferred to NOVAGENIX Bioanalytical Drug R&D Centre in Ankara- Turkey to determine the level of drug in blood. These samples will be used to only for this study and in accordance with study objectives and any remaining material will be destroyed.

You can decide at any time whether your samples can be used for the analysis of determine the level of drug in blood or should be destroyed. If you decide that your blood samples shall not be subjected to analysis, you will have to inform the investigator about your decision in **a written form**.

However, the samples can be stored for monitoring, inspection and audit activities of the relevant health authorities for the aim of verifying the information on clinical studies.

Samples can not be used as a source of commercial gain in any way. However, intellectual property and patent rights are exempted from this condition.

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

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

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

Side effects:

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

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

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

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

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

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

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

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

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

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

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Data Protection:

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

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

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

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

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

1. Health-related issues that occur due to the treatment and/or administration of drugs with the decision and approval of the conducting physician during the research,
 2. Any problem that may occur regarding your health due to the clinical study is immediately reported to your investigating physician and insurer by you or your relatives.
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Subject's paraph	
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Screening Number:

Test Drug: Favira 200 mg Film Kaplı Tablet (Novelfarma -Turkey)**Reference Drug: Avigan 200 mg Film Tablet (Toyama Chemical Industry Co Ltd.-Japan)**

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

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

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

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

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

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

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

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

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

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

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

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

Subject's:

NAME

DATE OF BIRTH

SIGNATURE.....

DATE

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

Doctor Who Is Responsible For Informed:

NAME.....

SIGNATURE.....

DATE.....

This Informed Consent Form includes 5 pages.

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