Subject Screening Number: .....

INFORMED CONSENT FORM

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"Open-label, randomised, single oral dose, two-treatment, four-period, full replicated, cross-over trial to assess the bioequivalence of Orvical 200 mg/50 mg Film Tablet'in (Test Drug) in comparison with Kaletra 200 mg/50 mg Film Kaplı Tablet (Reference Drug) in healthy male subjects under fasting conditions"

Dear Volunteer,

The drug tested in this trial is ***Orvical 200 mg/50 mg Film Tablet***, containing **200 mg lopinavir and 50 mg ritonovir of World Medicine İlaç San. ve Tic. A.Ş.** It is a medication used orally and it could be valuable in the treatment of HIV1 infection in adults and pediatric patients in combination with other antiretroviral agents.

The purpose of the present research study is to investigate the bioequivalence of orally administered test drug containing **200 mg lopinavir and 50 mg ritonovir** ***(Orvical 200 mg/50 mg Film Tablet)*** and on the other orally administered reference drug containing **200 mg lopinavir and 50 mg ritonovir** ***(Kaletra 200 mg/50 mg Film Tablet)***. The **reference drug** is already registered and commercially available for years in **Turkey** as ***Kaletra 200 mg/50 mg Film Tablet***. The company responsible for placing the reference product on the market is ***AbbVie Tıbbi İlaçlar San. ve Tic. Ltd Şti-İstanbul, Turkey***. 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 drug. Therefore, this drug will be used as reference and will establish the basis of comparison to be used for the test drug (***Orvical 200 mg/50 mg Film Tablet***). (***Orvical 200 mg/50 mg Film Tablet*** is manufactured by **World Medicine İlaç San. ve Tic.A.Ş.** in Turkey.) The comparison will be based on the measurement of the concentrations of the active ingredients 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 Rapid Test (with a drop of blood from your fingertip)*****" 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. Laboratory research includes whole blood and urine tests. 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 IKU Center for clinical study in suitable isolation conditions according to your test result and general condition.

In this 4 period trial, each **30 subjects** who enrolled into the trial will be given orally a single dose of one tablet of the **test drug (T) in two periods** and a single dose of one tablet of the **reference drug (R) in two periods** ***(200 mg lopinavir and 50 mg in each time)*** **under fasting conditions** according to randomization table and there will be a wash-out of **at least 48 hours**. You will take a total of **4 doses (4x200 mg=800 mg lopinavir and 4x50=200 mg ritonovir)** during the trial. 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 **13 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. Laboratory research includes whole blood and urine tests. Also, **Covid-19 PCR*** test will be applied in the final examination.

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

Approximately **32 mL** blood sample *(20[#] mL for entry examination and 12 mL for final examination)* is going to be collected for the standard laboratory tests on entry and final examination with HIV (AIDS) and hepatitis tests at only entry examination. The blood samples collected for laboratory (entry and final examination) tests will be sent to GAMA Medical Laboratories (GAMA Tıp Laboratuvarları) which is located in Gaziantep-Turkey, and will be used exclusively for this research, specifically for it's purpose. *Covid-19 PCR test analyzes will be carried out in Gaziantep University Şahinbey Research Hospital, Molecular Genetic Diagnosis, Hematology and Tissue Typing Laboratory. 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 on entry examination.

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You will come to the clinic the day before study period around **18:00** and will stay in the clinic for **8 days**. **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 temperature will be measured in the mornings during the study period. F*inal examination and laboratory tests will be done on the day of last blood sampling in the* ***4th 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 each 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 on the evening of hospitalization 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 two days before the initial screening tests and lasting until the last laboratory test in the final check up is performed.

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

One tablet of test drug or one tablet of reference drug will be taken with 240 mL of water -as a whole in sitting position and this will be followed by mouth check. The drug will be administered approximately at 08:00 a.m.

You should sit without lying in your bed during 5 hours after the drug administration. In this interval ($t_{0.50}$-$t_{5.00}$); the blood collections will be performed in bed; lunch will be provided on bed.

The following day of drug administration, a standard breakfast, lunch, dinner and a light breakfast will be served at around 21.30 in the evening. 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. The same procedure will be applied in the 3rd and 4th Period drug administration. In the 4th period drug application, after the last blood sample is taken ($t_{36.00}$), final examination and laboratory tests will be performed.

Blood samples for drug analysis *(5 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 **30 minute and 1, $1^{1/2}$, 2, $2^{1/2}$, 3, $3^{1/3}$, $3^{2/3}$ 4, $4^{1/33}$,$4^{2/3,}$ 5, $5^{1/2}$, 6, 7, 8, 10, 14, 24, 36.** 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 **479 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.

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 adverse effects are classified below by system organ class according to the following convention: Very common (≥1/10), Common (≥1/100 to < 1/1.000), Uncommon (≥1/1.000 to < 1/1.000), Rare (≥1/10,000 to < 1/1,000), Very rare, including isolated reports (<1/10.000), Not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infection
	Common	Lower respiratory tract infection, skin infections including

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		cellulitis, folliculitis and furuncle
Blood and lymphatic system disorders	Common	Anaemia, leucopenia, neutropenia, lymphadenopathy
Immune system disorders	Common	Hypersensitivity including urticaria and angioedema
	Uncommon	Immune reconstitution inflammatory syndrome
Endocrine disorders	Uncommon	Hypogonadism
Metabolism and nutrition disorders	Common	Blood glucose disorders including diabetes mellitus, hypertriglyceridaemia, hypercholesterolemia, weight decreased, decreased appetite
	Uncommon	Weight increased, increased appetite
Psychiatric disorders	Common	Anxiety
	Uncommon	Abnormal dreams, libido decreased
Nervous system disorders	Common	Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia
	Uncommon	Cerebrovascular accident, convulsion, dysgeusia, ageusia, tremor
Eye disorders	Uncommon	Visual impairment
	Uncommon	Tinnitus, vertigo
Cardiac disorders	Uncommon	Atherosclerosis such as myocardial infarction, atrioventricular block, tricuspid valve incompetence
Vascular disorders	Common	Hypertension
	Uncommon	Deep vein thrombosis
Gastrointestinal disorders	Very common	Diarrhoea, nausea
	Common	Pancreatitis, vomiting, gastrooesophageal reflux disease, gastroenteritis and colitis, abdominal pain (upper and lower), abdominal distension, dyspepsia, haemorrhoids, flatulence
	Uncommon	Gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastritis and rectal haemorrhage, stomatitis and oral ulcers, faecal incontinence, constipation, dry mouth
Hepatobiliary disorders	Common	Hepatitis including AST, ALT and GGT increases
	Uncommon	Hepatic steatosis, hepatomegaly, cholangitis, hyperbilirubinemia
	Not known	Jaundice
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular rash, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritus
	Uncommon	Alopecia, capillaritis, vasculitis
	Not known	Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	Common	Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and spasms
	Uncommon	Rhabdomyolysis, osteonecrosis
Renal and urinary disorders	Uncommon	Creatinine clearance decreased, nephritis, haematuria
Reproductive system and breast	Common	Erectile dysfunction, menstrual disorders -

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disorders		amenorrhoea, menorrhagia

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

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).**

Drug contains lactose monohydrate. Who has rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorptionshould not take this medicine.

As with all prescription drugs, other unpredictable side effects or life-threatening events can occur in addition to the above mentioned side effects**.**

Your participation of this study will be finished after the last blood sampling at 36th 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.***

Data Protection:

Only Screening Number 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 **(World Medicine İlaç San. ve Tic. A.Ş.)** or the Contract Research Organisation **(ALPAN Farma Ltd. Şti.)**, 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 **(World Medicine İlaç San. ve Tic. A.Ş.)** and the principal investigator, ALPAN Farma insured all participants **for the cases of study-related loss of function or cases, where hospitalization or surgical intervention is required, death, or permanent disability due to this study. In case of your request a copy of the insurance policy will be given to you by investigator.**

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

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

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Screening Number: ……..

Test drug: ***Orvical 200 mg/50 mg Film Tablet, World Medicine- Turkey***
Reference drug: ***Kaletra 200 mg/50 mg Film Tablet, AbbVie Tıbbi İlaçlar - Turkey***

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

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

I promise to report any deterioration of my well being or my health, as well as the occurrence of any unexpected/unusual symptoms to the researchers immediately, to work in collaboration with the researchers, and to follow the instructions provided during the study. 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 ……

Doctor Who Is Responsible For Informed:

NAME……..
SIGNATURE……..
DATE……..

This Informed Consent Form includes 5 pages.

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