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 (TEST DRUG)** IN COMPARISON WITH **KALETRA 200 MG/50 MG FILM KAPLI TABLET (REFERENCE DRUG)** IN HEALTHY MALE SUBJECTS UNDER FASTING CONDITIONS

CLINICAL STUDY PROTOCOL
"CONFIDENTIAL"

Principal Investigator: Prof. Dr. Muradiye Nacak

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Sponsor: World Medicine Ilaç San. ve Tic. A.Ş.
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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 treatment, four-period, full-replicated, cross-over trial to assess the bioequivalence of **Orvical 200 mg/50 mg Film Tablet (Test Drug)** in comparison with **Kaletra 200 mg/50 mg Film Kaplı Tablet (Reference Drug)** in healthy male subjects under fasting conditions
Study Code:	**NOV2020/01911**
Drugs:	**Test Drug***: "**Orvical 200 mg/50 mg Film Tablet**" containing 200 mg lopinavir and 50 mg ritonavir *(World Medicine-Turkey).* **: This drug is manufactured by World Medicine Ilaç San. ve Tic. A.Ş., Turkey.* **Reference Drug****: "**Kaletra 200 mg/50 mg Film Kaplı Tablet**" containing 200 mg lopinavir and 50 mg ritonavir *(AbbVie Tıbbi İlaçlar San. ve Tic. Ltd Şti-İstanbul, Turkey).* ***:This drug is manufactured by AbbVie Deutschland GmbH & Co. - Germany*
Dosage:	A single dose of Reference product containing **200 mg lopinavir and 50 mg ritonavir fixed dose combination** and a single dose of Test product containing **200 mg lopinavir and 50 mg ritonavir fixed dose combination** or vice versa; administered with 240 mL of water at room temperature, in each period.
Indication:	Bioequivalence study
Study Design:	Single-dose, open-label, randomised, two-treatment, four-period, full-replicated, 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:	World Medicine Ilaç San. ve Tic. A.Ş.-Turkey

Phase:	I (Bioequivalence study)
Planned Initiation:	2Q 2020 (inclusion of first subject)
Planned Duration:	13 days (approximately)
Primary Endpoint:	$AUC_{0\text{-}tlast}$ and C_{max} of **lopinavir and ritonavir**
Secondary Endpoint:	$AUC_{0\text{-}\infty}$, $t_{1/2}$, t_{max} of **lopinavir and ritonavir**
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 **lopinavir and ritonavir** 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 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 14.00, 24.00, 36.00** hours post-dose *(1 x 5 mL each; totally 21 blood sample points)*

*** Note:**
1. **Only in Period I; at t_0 the blood sample amount will be 12 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 lopinavir and ritonavir analysis *[for details see section 13.7 (Blood Sampling for Drug Analysis)]***

Wash-out duration:	At least 48 hours.
Acceptance Range:	If intra-subject coefficient of variation of reference product (CV_{WR}) is equal or less than 30%, acceptance range for C_{max} and $AUC_{0\text{-}tlast}$ is 80.00-125.00%. If CV_{WR} is more than 30% (the reference product exerts a highly variable drug product characteristic), the acceptance criteria for $\mathbf{C_{max}}$ will be widened to a maximum of **69.84 -143.19%** using scaled average bioequivalence (SABE) and for $AUC_{0\text{-}tlast}$ will be taken as **80.00-125.00%** regardless of variability

according to the EMA guideline (Guideline on the Investigation of Bioequivalence-CPMP/EWP/QWP/1401/98 Rev. 1/Corr, London 20 January 2010).

The other criteria for SABE: The geometric mean ratio should lie within the conventional acceptance range 80.00-125.00% **for C_{max} and $AUC_{0-tlast}$.**

1. THE PARTIES of PROJECT

Study Code: NOV2020/01911

Study Title: 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 (Test Drug)** in comparison with **Kaletra 200 mg/50 mg Film Kaplı Tablet (Reference Drug)** in healthy male subjects under fasting conditions

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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.

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4. LIST OF ABBREVIATIONS AND TERMS

AE / ADR	Adverse Event / Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT / AST	Alanin- / Aspartate Aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}tlast}$	Area under the plasma concentration-time curve from zero up to the last measurable concentration
$AUC_{0\text{-}\infty}$	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 treatment, four-period, full-replicated, cross-over trial to assess the bioequivalence of **Orvical 200 mg/50 mg Film Tablet (Test Drug)** in comparison with **Kaletra 200 mg/50 mg Film Kaplı 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 **lopinavir and ritonavir** from the test product (**Orvical 200 mg/50 mg Film Tablet, *World Medicine-Turkey***) in comparison with the reference product **(Kaletra 200 mg/50 mg Film Kaplı Tablet, *AbbVie Tıbbi İlaçlar Sanayi ve Ticaret Limited Şirketi-İstanbul, Turkey*)** under fasting conditions. The primary objective is to demonstrate the bioequivalence of test and reference products.
Test Drug*:	"**Orvical 200 mg/50 mg Film Tablet**" containing 200 mg lopinavir and 50 mg ritonavir *(World Medicine-Turkey).* **: This drug is manufactured by World Medicine Ilaç San. ve Tic., Turkey.*
Reference Drug**:	"**Kaletra 200 mg/50 mg Film Kaplı Tablet**" containing 200 mg lopinavir and 50 mg ritonavir *(AbbVie Tıbbi İlaçlar Sanayi ve Ticaret Limited Şirketi-İstanbul, Turkey).* ***: This drug is manufactured by AbbVie Deutschland GmbH & Co. - Germany*
Dosage:	A single dose of Reference product containing **200 mg lopinavir and 50 mg ritonavir fixed dose combination** and a single dose of Test product containing **200 mg lopinavir and 50 mg ritonavir fixed dose combination** or vice versa; administered with 240 mL of water at room temperature, in each period
Indication:	Bioequivalence study
Study design:	Single-dose, open-label, randomised, two-treatment, four-period, full-replicated, cross-over, study.
Variables:	**Pharmacokinetics:** Primary variables: $AUC_{0-tlast}$ and C_{max} of **lopinavir and ritonavir** Secondary variables: $AUC_{0-\infty}$, t_{max}, $t_{1/2}$ of **lopinavir and ritonavir** 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 <u>the clinical study period</u>: at pre-dose* and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 14.00, 24.00, 36.00 hours post-dose** ***(1 x 5 mL each; totally 21 blood sample points)***

*** Note:**

1. **Only in Period I; at t_0 the blood sample amount will be 12 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 lopinavir and ritonavir analysis** ***[for details see section 13.7 (Blood Sampling for Drug Analysis)]***

Route of Administration: Oral

Duration of Treatment: **13 days** (approximately)

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 lopinavir and 50 mg ritonavir** product *[either one tablet of the test drug or one tablet of the reference drug according to the randomisation table]*. Blood samples will be drawn immediately before the dosing and at **0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 14.00, 24.00, 36.00** hours after the dosing. In the **2nd, 3rd and 4th period** there will be the same procedure.

Analysis of Lopinavir and Ritonavir : Plasma concentrations of **lopinavir and ritonavir** 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: If intra-subject coefficient of variation of reference product (CVWR) is equal or less than 30%, acceptance range for C_{max} and $AUC_{0\text{-}tlast}$ is 80.00-125.00%.
If CVWR is more than 30% (the reference product exerts a highly variable drug product characteristic), the acceptance criteria for $\mathbf{C_{max}}$ will be widened to a maximum of **69.84 -143.19%** using scaled-average-bioequivalence (SABE) and for $AUC_{0\text{-}tlast}$ will be taken as **80.00-125.00%** regardless of variability according to the EMA guideline (Guideline on the Investigation of Bioequivalence-CPMP/EWP/QWP/1401/98 Rev. 1/Corr, London 20 January 2010).

	The other criteria for SABE: The geometric mean ratio should lie within the conventional acceptance range **80.00-125.00%** for C_{max} and $AUC_{0-tlast}$.
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 $AUC_{0-tlast}$ of lopinavir and ritonavir**.** 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 $AUC_{0-tlast}$ data for **lopinavir and ritonavir** 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:	World Medicine Ilaç San. ve Tic. A.Ş. Representative: Evrim Aksel
Protocol code:	NOV2020/01911
Phase:	I (Bioequivalence study)
Planned initiation:	2Q 2020 (inclusion of first subject)
Planned duration:	**13 days** (approximately)
Primary Endpoint:	$AUC_{0-tlast}$ and C_{max} of **lopinavir and ritonavir**
Secondary Endpoint:	$AUC_{0-\infty}$, $t_{1/2}$, t_{max} of **lopinavir and ritonavir**
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 + ½ month
- 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		PERIOD III		PERIOD IV		*Final examination
Study Days:	**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 ($t_{24.00}$ and $t_{36.00}$) Wash-out day (Day 2)**	**8th DAY 2nd dosing day and blood sampling (Day 3)**	**9th DAY blood sampling ($t_{24.00}$ and $t_{36.00}$) Wash-out day (Day 4)**	**10th DAY 3rd dosing day and blood sampling (Day 5)**	**11th DAY blood sampling ($t_{24.00}$ and $t_{36.00}$) Wash-out day (Day 6)**	**12th DAY 4th dosing day and blood sampling (Day 7)**	**13th DAY 24th and 36th hours blood (Day 8)**	**13th DAY Final examination**
Informed consent	●													
Covid-19 Rapid Test	●													
Covid-19 PCR Test	●				●									●
Inclusion	●				●									
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*** (0-36.00 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, during "study period" and "final examination".
** For amphetamines, cannabinoids, benzodiazepines, cocaine, opioids, and barbiturates.
***Blood sampling points (for each period): at pre-dose (12 mL only in Period I) and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 14.00, 24.00, 36.00 hours post-dose (*1 x 5 mL each; totally 21 blood sample points*)
Note:

1. Only in Period I; at t_0 the blood sample amount will be 12 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 lopinavir and ritonavir analysis. *[for details see section 13.7 (Blood Sampling for Drug Analysis)]*

****Adverse event questioning (in each period): at hospitalisation day, pre dose and 1.00, 4.00, 10.00, 24.00, 36.00 hours post-dose.

7. INTRODUCTION

7.1. Chemical and Pharmaceutical Properties

Lopinavir
Lopinavir is an antiviral agent chemically designated as [1S-[1R*,(R*),3R*,4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl] tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80 g/mol.

Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

Ritonavir
Ritonavir acts as a booster in this combination. It is chemically designated as 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95 g/mol.

Ritonavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

7.2. Pharmacological Properties

Lopinavir is an inhibitor of the HIV-1 and HIV-2 protease. Inhibition of HIV protease prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious virus. Lopinavir provides the antiviral activity of lopinavir/ritonavir combination. When lopinavir, an antiviral drug, is co-formulated with ritonavir, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

7.3. Pharmacokinetics

7.3.1.Absorption

Lopinavir
In a bioequivalence study, it is reported that the C_{max} and t_{max} of reference lopinavir product is 3.68±1.35 ng/mL and 4.3±0.9 h respectively, following single dose of 200 mg/50 mg of lopinavir/ritonavir tablets. According to the WHO's bioequivalence guidance for lopinavir/ritonavir combination, t_{max} of lopinavir was observed between 3 and 4 hours after a single dose. Multiple dosing with 400/100 mg lopinavir/ritonavir twice daily for 2 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 12.3 ± 5.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 113.2 ± 60.5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Ritonavir
In a bioequivalence study, it is reported that the C_{max} and t_{max} of reference ritonavir product is 173±82 and 4.3±0.9 h respectively, following single dose of 200 mg/50 mg of lopinavir/ritonavir tablets. According to the WHO's bioequivalence guidance for lopinavir/ritonavir combination, ritonavir peak plasma concentrations are observed after approximately 3-4 hours after oral administration.

7.3.2.Distribution

Lopinavir
At steady state, lopinavir is approximately 98 − 99% bound to serum proteins.

Ritonavir
The apparent volume of distribution (VB/F) of ritonavir is approximately 20-40 L after a single 600 mg dose. The protein binding of ritonavir in human plasma is approximately 98 - 99%.

7.3.3.Biotransformation

Lopinavir
Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir and therefore, increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir dose was due to parent active substance.

Ritonavir
Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform.

7.3.4.Elimination

Lopinavir
After a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4±2.3% and 82.6±2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and faeces, respectively. Unchanged lopinavir accounted for approximately 2.2% and 19.8% of the administered dose in urine and faeces, respectively. According to the WHO's bioequivalence guidance for lopinavir/ritonavir combination, the half-life was of 4-6 hours approximately, after a single dose administration. In a bioequivalence study, it is reported that $t_{1/2}$ of lopinavir is 4.3±0.9 h.

Ritonavir
Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. According to the WHO's bioequivalence guidance for lopinavir/ritonavir combination, ritonavir half-life when administered with lopinavir has been reported to be 5-6 hours. In a bioequivalence study, it is reported that $t_{1/2}$ of ritonavir is 6.3±1.6 h.

Some pharmacokinetics parameters of **lopinavir** are shown in the following table:

t_{max} (h)	Cmax (ng/mL)	Protein binding(%)	$t_{½}$ (h)	Excretion and metabolism
3-4.3	3.68±1.35 (*200 mg single dose*)	98-99	4-6	*mainly faeces*

Some pharmacokinetics parameters of **ritonavir** are shown in the following table:

t_{max} (h)	Cmax (ng/mL)	Volume of distribution (L)	$t_{½}$ (h)	Excretion and metabolism
4.3	173±82(*50 mg single dose*)	20-40 (*after a single 600 mg dose*).	5-6.3	*~mainly faeces*

This combination can be taken with or without food.

7.4. Indications

Lopinavir/Ritonavir combination is indicated in combination with other antiretroviral agents for the treatment of HIV1 infection in adults and pediatric patients.

7.5. Contraindications

- Hypersensitivity to the active substances or to any of the excipients in both products. Severe hepatic insufficiency.
- Lopinavir/Ritonavir tablets both of which are inhibitors of the P450 isoform CYP3A. Lopinavir/ritonavir should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include:

Medicinal product class	Medicinal products within class	Rationale
Concomitant medicinal product levels increased		
Alpha1-adrenoreceptor antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension.
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions
Antiarrhythmics	Amiodarone, dronedarone	Increased plasma concentrations of amiodarone and dronedarone. Thereby, increasing the risk of arrhythmias or other serious adverse reactions
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid. The concomitant administration with fusidic acid is contraindicated in dermatological infections

Anticancer	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase
Anti-gout	Colchicine	Increased plasma concentrations of colchicine. Potential for serious and/or lifethreatening reactions in patients with renal and/or hepatic impairment
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life threatening reactions
	Pimozide	Increased plasma concentrations of pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from this agent
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated
Ergot alkaloids	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia
GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent
Hepatitis C virus direct acting antivirals	Elbasvir/grazoprevir	Increased risk of alanine transaminase (ALT) elevations
	Ombitasvir/paritaprevir/ritonavir with or without dasabuvir	Increased plasma concentrations of paritaprevir; thereby, increasing the risk of alanine transaminase (ALT) elevations
HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis
Phosphodiesterase (PDE5) inhibitors	Avanafil	Increased plasma concentrations of avanafil
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafilassociated adverse events

		(which include hypotension and syncope).
	Vardenafil	Increased plasma concentrations of vardenafil
Sedatives/hypnotics	Oral midazolam, triazolam	Increased plasma concentrations of oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents.
Lopinavir/ritonavir medicinal product level decreased		
Herbal products	St. John's wort	Herbal preparations containing St John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of lopinavir and ritonavir

7.6. Adverse Reactions

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 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 disorders	Common	Erectile dysfunction, menstrual disorders - amenorrhoea, menorrhagia

7.7. Cautions and precautions

Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of lopinavir/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized byCYP3A or initiation of medications metabolized by CYP3A in patients already receiving lopinavir/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of lopinavir/ritonavir, respectively. These interactions may lead to:

• Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.

• Clinically significant adverse reactions from greater exposures of lopinavir/ritonavir.

• Loss of therapeutic effect of lopinavir/ritonavir and possible development of

resistance.
Consider the potential for drug interactions prior to and during lopinavir/ritonavir therapy; review concomitant medications during lopinavir/ritonavir therapy, and monitor for the adverse reactions associated with the concomitant medications.

Pancreatitis
Pancreatitis has been observed in patients receiving lopinavir/ritonavir therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to lopinavir/ritonavir has not been established, marked triglyceride elevations are a risk factor for development of pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and lopinavir/ritonavir and/or other antiretroviral therapy should be suspended as clinically appropriate.

Hepatotoxicity
Patients with underlying hepatitis B or C or marked elevations in transaminase prior to treatment may be at increased risk for developing or worsening of transaminase elevations or hepatic decompensation with use of lopinavir/ritonavir.
Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days after the initiation of lopinavir/ritonavir in conjunction with other antiretroviral agents.
Appropriate laboratory testing should be conducted prior to initiating therapy with lopinavir/ritonavir and patients should be monitored closely during treatment. Increased AST/ALT monitoring should be considered in the patients with underlying chronic hepatitis or cirrhosis.

QT Interval Prolongation
Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.

PR Interval Prolongation
Lopinavir/ritonavir prolongs the PR interval in some patients. Lopinavir/ritonavir should be used with caution in patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.
The impact on the PR interval of co-administration of lopinavir/ritonavir with other drugs that prolong the PR interval has not been evaluated. As a result, co-administration of lopinavir/ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A.

Diabetes Mellitus/Hyperglycemia
New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Consider monitoring for hyperglycemia, new onset diabetes mellitus or an exacerbation of diabetes mellitus in patients treated with lopinavir/ritonavir.

Immune Reconstitution Syndrome
During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections which may necessitate further evaluation and treatment.
Autoimmune disorders have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Lipid Elevations
Treatment with lopinavir/ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating lopinavir/ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with lopinavir/ritonavir and HMG-CoA reductase inhibitors.

Fat Redistribution
Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Patients with Hemophilia
Increased bleeding, including spontaneous skin hematomas and hemarthrosis have been reported in patients with hemophilia type A and B treated with protease inhibitors. A causal relationship between protease inhibitor therapy and these events has not been established.

Resistance/Cross-resistance
Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in lopinavir/ritonavir-treated patients, it is unknown what effect therapy with lopinavir/ritonavir will have on the activity of subsequently administered protease inhibitors.

7.8. Interactions

Potential for Lopinavir/ritonavir to Affect Other Drugs
Lopinavir/ritonavir is an inhibitor of CYP3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. co-administration of lopinavir/ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring. Additionally, lopinavir/ritonavir induces glucuronidation. Published data suggest that lopinavir is an inhibitor of OATP1B1.

Potential for Other Drugs to Affect Lopinavir
Lopinavir/ritonavir is a CYP3A substrate; therefore, drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce therapeutic effect of lopinavir/ritonavir. Although not observed in the lopinavir/ritonavir /ketoconazole drug

interaction study, co-administration of lopinavir/ritonavir and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Established and Other Potentially Significant Drug Interactions
Some members of the following pharmacological groups provide an established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended concomitant use of lopinavir/ritonavir with the member of these groups.

- HIV-1 Protease Inhibitors
- HIV CCR5 Antagonists
- Non-nucleoside Reverse Transcriptase Inhibitors
- Nucleoside Reverse Transcriptase Inhibitors
- Antiarrhytmics
- Anticancer agents
- Anticoagulants
- Anticonvulsants
- Antidepressants
- Antiinfectives
- Antifungals
- Antigouts
- Antimycobacterials
- Antiparasitics
- Antipsychotics
- Sedative/hypnotics
- Contraceptives
- Corticosteroids
- Dihydropyridine Calcium Channel Blockers
- Endothelin Receptor Antagonists
- Hepatitis C direct acting Antivirals
- HMG-CoA Reductase Inhibitors
- Immunosuppressants
- Inhaled or Intranasal Steroids
- Long-acting beta-adrenoceptor Agonists
- Narcotic Analgesics
- PDE5 inhibitors

8. OBJECTIVE OF THE TRIAL

The aim of this study is to evaluate the pharmacokinetic profiles and the relative bioavailability of **lopinavir and ritonavir** from the Test Drug **(Orvical 200 mg/50 mg Film Tablet, World Medicine-Turkey)** in comparison with Reference Drug **(Kaletra 200 mg/50 mg Film Kaplı Tablet**, **AbbVie Tıbbi İlaçlar San. ve Tic. Ltd Şti-İstanbul, Turkey**) under **fasting** conditions. The primary objective is to demonstrate the bioequivalence of both 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-sequence, two treatment, four-period, full-replicated, cross-over study, **30 healthy** male subjects (intention to treat population) will receive one single oral dose of **200 mg lopinavir and 50 mg ritonavir** ***[either one tablet of the test drug or one tablet of the reference drug according to the randomisation table]*** under fasting conditions, according to a sequence determined by randomisation [in Period II and Period IV, the subjects will be administered by the other drug that they will not administered in the Period I and Period III].

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

Test Drug: "Orvical 200 mg/50 mg Film Tablet" is manufactured by World Medicine Ilaç San. ve Tic. A.Ş., Turkey and is will be licensed by World Medicine Ilaç San. ve Tic. A.Ş., Turkey.

Reference Drug: "Kaletra 200 mg/50 mg Film Kaplı Tablet" is manufactured by AbbVie Deutschland GmbH & Co. Germany and is licensed by AbbVie Tıbbi İlaçlar Sanayi ve Ticaret Limited Şirketi-İstanbul, Turkey

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 7**.

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 **lopinavir and ritonavir** plasma concentrations will be drawn at specified time points. After taking the last blood sample and carried out the post-study 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. **Negative Covid-19 Rapid Test results and two Negative Covid-19 PCR test results**,
4. Negative alcohol breath test results,
5. Normal physical examination at screening visit,
6. Having the Body Mass Index ranged between **18.5-30 kg/m^2** (see Appendix I) which is in the desirable range according to the age,
7. Ability to communicate adequately with the investigator himself or his representatives,
8. Ability and agreement to comply with the study requirements,
9. Normal blood pressure and heart rate measured under stabilised conditions at the screening visit after at least 5 minutes of rest under supine position: SBP within 100 to 140 mmHg, DBP within 60 to 90 mmHg and HR within 50 to 90 bpm,
10. Normal/ acceptable 12-lead electrocardiographic results at least after 5 minutes of rest,
11. Laboratory results within normal range or clinically non-significant (CBC, glucose, urea, uric acid, creatinine, *estimated GFR (eGFR)*, total bilirubin, sodium, potassium, calcium, chloride, SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase, total protein and urinalysis), drug addiction scanning in urine results in negative (amphetamine, barbiturate, benzodiazepine, cannabinoid, cocaine, opiate),
12. Understanding of the study and agreement to give a written informed consent according to section 20.3.

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 lopinavir and ritonavir or any other ingredients of the products.**
2. **Who have hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.**
3. Any history or presence of clinical relevance of cardiovascular **(myocardial infarction/ ischaemia and/or QT prolongation etc.)**, neurological, musculoskeletal, haematological, hepatic, gastrointestinal, renal, pulmonary, endocrinological, metabolism or psychiatric disease, any type of porphyria**.**
4. **Baseline ECG should be performed at screening. Exclude subjects having a QTc > 440 ms**
5. 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)***,
6. Presence or history of malabsorption or any gastrointestinal surgery except appendectomy or except herniotomy.
7. 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.
8. 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.
9. 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).
10. Use of any vitamins or herbal products within 7 days prior to the initial dose of the study medication.
11. Subjects who have any chronic disease which might interfere with absorption, distribution, metabolism or excretion of the drug.
12. Subjects who regular consumed of beverages or food containing methylxanthines (e.g. coffee, tea, cola, caffeine, chocolate, sodas,) equivalent to more than 500 mg methylxanthines per day.
13. Subjects who has taken any grapefruit or grapefruit juice during 7 days prior to drug administration, during the study.
14. History of allergic response to heparin.

15. History of drug abuse.
16. 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).
17. Positive blood test for HBV, HCV and HIV.
18. Who have relationship to the investigator.
19. Who are not suitable to any of inclusion criteria.
20. History of difficulty of swallowing.
21. Intake of depot injectable solutions (including study medications) within 6 months before start of the study.
22. Intake of enzyme-inducing, organotoxic or long half-life drugs within 4 weeks before start of the study.
23. 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, **World Medicine Ilaç San. ve Tic. A.Ş.-Turkey.** The packaging and labelling will be done according to the GMP and GCP requirements.

The reference drug marketing authorisation holder is A**bbVie Tıbbi İlaçlar Sanayi ve Ticaret Limited Şirketi-İstanbul,Turkey**. 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:	Lopinavir and ritonavir
Formulation:	Film Tablets for oral administration
Strength:	200/50 mg
Manufacturer:	World Medicine Ilaç San. ve Tic. A.Ş. - Turkey
Marketing Authorisation Holder:	World Medicine Ilaç San. ve Tic. -Turkey
Batch Number:	00400892
Expiry Date:	04.2022
Trade name:	**Orvical 200 mg/50 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:	Lopinavir and ritonavir
Formulation:	Film Tablets for oral administration
Strength:	200/50 mg
Manufactured:	AbbVie Deutschland GmbH & Co. - Germany
Marketing Authorisation Holder:	AbbVie Tıbbi İlaçlar San. ve Tic. Ltd Şirketi-İstanbul-Turkey
Batch Number:	1121788
Expiry Date:	07.2022
Trade name:	**Kaletra 200 mg/50 mg Film Kaplı 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 **tablet** [Test or Reference] in study. Also, the subjects will have the information about the **tablets** 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 in each period once daily either test drug or reference drug as 200 mg lopinavir and 50 mg ritonavir (*in Period II and Period IV, the subjects will be administered by the other drug that they will not administered in the Period I and*

Period III).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 **ALPAN Farma** 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 World Medicine Ilaç 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 (paracetamol etc.) 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 original package to protect from light and moisture in a dry place at room temperature below 25°C, 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 7** 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 7**. 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 Rapid Test and Covid-19 PCR test.**

Clinical laboratory tests will be performed using the auto analyser at a contracted and certified laboratory **(GAMA Tıp Merkezi-G.Antep)**. **Covid-19 PCR test will be performed at "Gaziantep University Şahinbey Research Hospital, Molecular Genetic Diagnosis, Hematology and Tissue Typing Laboratory".**

**** 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 Covid-19 PCR test result is positive, the volunteer(s) 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 **four 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) normally until taking the last blood sample in 4^{th} 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 7,** at approximately **18:00** on the day before the treatment (Day 0) of study and will remain there for **8 days**. 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 examination and final examination and laboratory tests on the day of last sampling in **fourth 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 7.

Study drugs will be administered on the Day 1, Day 3, Day 5 and Day 7. 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** in bed for **5 hours** after drug administration without lying in bed for each period. ***In this interval ($t_{0.5}$-$t_{5.00}$); 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 7**. 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, haematology, HB_sAg, HIV-Ab, HCV-Ab, **Covid-19 PCR**, drug screening, alcohol breath test, urinalysis).

  * Clinical screening and examination wiil be carried out after negative "Covid-19 Rapid Test" results

Period 1- Period 2- Period 3-Period 4:

- Interview (possible presence of exclusion criteria and/or adverse events)
- Standardised dinner will be served before first dosing on day 0 *(between 18:00 p.m. to 21:00 p.m.)*
- Blood samples will be collected before dosing with separation of plasma.
- Treatments will be given according to randomised administration [single oral dose of one tablet of the **Test Drug** or one tablet of the **Reference Drug**]* with compliance check ***(approximately 08:00 a.m.)***
- Blood sampling (0.50-36.00 hours) will be done after drug administration with separation of plasma

- Standardised lunch will be served at 4 hours after the dosing (Day 1, Day 3, Day 5 and Day 7).
- Standardised dinner will be served at 10 hours after the dosing (Day 1, Day 3, Day 5 and Day 7)
- Standardised light breakfast will be served at approximately 21.30 pm (Day 1, Day 3, Day 5 and Day 7).
- Questioning for and registration of adverse events **at hospitalisation_day, pre dose and 1.00, 4.00, 10.00, 24.00, 36.00 hours** post-dose.
- Standard breakfast, standard lunch, standard evening meal and a standardised light breakfast will be served in Day 2, Day 4 and Day 6. In 8th day of the study standard breakfast lunch and dinner will be served.
- Discharge from the clinic (after final examinations).

At the end of the 4th period, subjects will have taken 2 tablets of Test Drug and 2 tablets of Reference Drug totally in whole study according to the full-replicated design (TRTR/ RTRT).

Final examination:

- The final examination will be carried out on the day of last blood sampling of the **4th 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 **36 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 either 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 lunch time on the following day, i.e. until 4 hours post dose.*(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 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; Orvical 200 mg/50 mg Film Tablet *(World Medicine-Turkey)*

Reference Drug; Kaletra 200 mg/50 mg Film Kaplı Tablet *(AbbVie Tıbbi İlaçlar Sanayi ve Ticaret Limited Şirketi-İstanbu-Turkey)*

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 one tablet of the test drug or one tablet of the reference drug (***200 mg lopinavir and 50 mg ritonavir in each case***) with 240 mL water, **under fasting conditions**. ***After the washout period; in Period II and Period IV, the subjects will be administered by the other drug that they will not administered in the Period I and Period III.***

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 **5 hours** after drug administration without lying in bed for each period. In this interval ($t_{0.5}$-$t_{5.00}$); the blood samples will be performed in bed and lunch will be provided on bed. Dosing will commence at approximately **08:00 a.m.**

13.6. Dietary Regimen

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

In treatment days (Day 1, Day 3, Day 5 and Day 7);

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

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

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

In treatment days (Day 2, Day 4, Day 6 and Day 8);

Also standard breakfast, standard lunch, standard evening meal and a standardised light breakfast will be served in Day 2, Day 4 and Day 6. In 8th day of the study standard breakfast lunch and dinner 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
1-2-3-4	1	$t_{0.00}$	P01
		$t_{0.50}$	P02
		$t_{1.00}$	P03
		$t_{1.50}$	P04
		$t_{2.00}$	P05
		$t_{2.50}$	P06
		$t_{3.00}$	P07
		$t_{3.33}$	P08
		$t_{3.66}$	P09
		$t_{4.00}$	P10
		$t_{4.33}$	P11
		$t_{4.66}$	P12
		$t_{5.00}$	P13
		$t_{5.50}$	P14
		$t_{6.00}$	P15
		$t_{7.00}$	P16
		$t_{8.00}$	P17
		$t_{10.00}$	P18
		$t_{14.00}$	P19
	2	$t_{24.00}$	P20
		$t_{36.00}$	P21

** 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.*

5 mL blood samples will be drawn at predetermined sampling times during the clinical study to determine plasma **lopinavir and rotinavir** concentrations.

*** Note:**

1. Only in Period I; at t0 the blood sample amount will be 12 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 lopinavir and ritonavir analysis [for details see section 13.7 (Blood Sampling for Drug Analysis)] 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 **479 mL**. *[Including "The Heparinised Discarded Blood (approximately 20 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"].*

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:

Lopinavir; Ritonavir	
Study # : **NOV01911**	
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 **lopinavir and ritonavir**

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

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 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 Covid-19 PCR test result is positive, the volunteer(s) will be dropped out from 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 1 day after 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 **hospitalization day, pre dose and $t_{1.00}$, $t_{4.00}$, $t_{10.00}$, $t_{24.00}$, $t_{36.00}$** hours after the drug administrations. 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 **World Medicine Ilaç 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 **World Medicine Ilaç 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 World Medicine Ilaç San. ve Tic. A.Ş.** as soon as possible.

The responsible sites for the upper procedure are:

World Medicine Ilaç San. ve Tic. A.Ş. **Contact Person**	**Alpan Farma Ltd.Şti.** **Contact Person**
Evrim Aksel Phone: (+90) 212 474 70 50 Fax: +90 212 474 09 01 E-mail: evrim.aksel@worldmedicine.com.tr	**Prof. Dr. Aydın Erenmemişoğlu** Phone: +90 352 2242322 Fax: +90 352 2242322 GSM: +90 532 5510082 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 **lopinavir and ritonavir** 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 16 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 **lopinavir and ritonavir** 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, four-period, full-replicated, 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 given by the CPMP guideline CPMP/EWP/QWP/1401/98 Rev. 1 dated 20 January 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.

19.1.3. Criteria for Bioequivalence

Bioequivalence of **Test Drug** in comparison with **Reference Drug** will be evaluated (T vs R) and concluded if the 90% confidence intervals for the geometric mean ratios of the treatments are fully contained within acceptance ranges for C_{max} and $AUC_{0\text{-}tlast}$ for **lopinavir** and **ritonavir**.

The acceptance ranges for C_{max} will be widened to a maximum of 69.84 -143.19% using scaled-average-bioequivalence (SABE) and for $AUC_{0\text{-}tlast}$ will be taken as 80.00-125.00% regardless of variability according to the EMA guideline (Guideline on the Investigation of Bioequivalence-CPMP/EWP/QWP/1401/98 Rev. 1/Corr, London 20 January 2010).

The extent of the widening is defined, as below, based upon the intra-subject coefficient of variation of Reference Drug (CV_{WR}):

- If CV_{WR} for C_{max} is greater than 30%:

  Acceptance ranges will be determined using scaled-average-bioequivalence **(**SABE) according to: [U, L] = exp [±k· s_{wr}], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760, and s_{WR} is the intra-subject standard deviation of the log-transformed values of C_{max} of the Reference product. s_{WR} will be obtained from Linear Mixed Effects model including only data for the Reference product with the subject effect (nested within sequence), the period at which it is given, the sequence in which each product is received as fixed effects.

  Before CV_{WR} calculation for C_{max}, to show the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers, outlier analysis using studentized intrasubject residual will be applied to reference product data.

The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology;

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$* CV(\%) = 100\sqrt{e^{s^2_{WR}} - 1}$$

The other criteria for SABE: The geometric mean ratio should lie within the conventional acceptance range 80.00- 125.00% for C_{max} and $AUC_{0\text{-tlast}}$.

- If CV_{WR} is equal or less than 30%:

Assessment of bioequivalence will be determined using average bioequivalence methods. 80.00-125.00% acceptance range will be used for the assessment of bioequivalence.

For both conditions, 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 terms to be used in Analysis of Variance (ANOVA) model are sequence, subject within sequence, period and treatment.

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 intervals for the ratios test versus reference preparation. The confidence intervals are calculated by retransformation of the shortest confidence intervals for the difference of the ln-transformed mean values.

Differences in t_{max} will be evaluated non-parametrically.

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.

19.1.4. 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-subject variability is estimated between 30-35% for C_{max} and $AUC_{0\text{-}tlast}$ for both **lopinavir** and **ritonavir** according to literatures. A total number of **30 subjects** is estimated in order to demonstrate bioequivalence with a power of 80% and a test/reference parameter ratio between 0.90 and 1.10**.**

19.3. Statistical Code and 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 by a randomisation table. ***[at the end of the 4th period, subjects will have taken 2 tablets of Test product and 2 tablets of Reference product totally in whole study according to the replicated design (TRTR/RTRT)].***

30 subjects, who will be included in the study, will be determined to receive either Treatment A or Treatment B in each period by a randomisation table generated with a computer programme (***in Period II and Period IV, the subjects will be administered by the other drug that they will not administered in the Period I and Period III).***

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 7** 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).
- ICH E6 (R2)- Guideline for good clinical practice, 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 **Lopinavir; Ritonavir 200 mg/50 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. **FDA, Label of Lopinavir/Ritonavir** **https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021251s052_021906s046lbl.pdf**
2. **Summary of Product Characteristics of Lopinavir/Ritonavir** **https://www.ema.europa.eu/en/documents/product-information/lopinavir/ritonavir-mylan-epar-product-information_en.pdf**
3. **Summary of Product Characteristics Ritonavir** **https://www.ema.europa.eu/en/documents/product-information/norvir-epar-product-information_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.
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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. ICH E6 (R2)- Guideline for good clinical practice, 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

NOV2020/01911 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