CLINICAL STUDY PROTOCOL

The name of the Protocol:	Multicenter open-label randomized parallel-group study of the efficacy and safety of TL-FVP-t compared to standard therapy in patients with mild to moderate coronavirus disease (SARS-CoV-2/COVID-19)
Protocol ID:	TL-FVP-t-01
Short name:	none
Date of drawing up of the Protocol:	May 08, 2020 (edited on May 19, 2020)
Number of the amendment to the Protocol:	Not applicable.
Date of adoption of the amendment to the Protocol:	Not applicable.
Protocol version:	1.0

Name and address of the clinical study sponsor (monitor):	Drugs Technology LLC Legal and postal address: 141400, Moscow region, Khimki, Rabochaya str., 2A, bldg. 31, room 21. Tel.: +7 (495) 225-62-00, Fax: +7 (495) 225-62-65. Email: info@drugsformulation.ru
Full Name, position of persons authorized to sign the Protocol and amendments to the Protocol on behalf of the sponsor:	Filon Olga Vladimirovna, Medical Director, Drugs Technology LLC Address: 141400, Moscow region, Khimki, Rabochaya str., 2A, bldg. 31, room 21. Tel.:, mobile: Email:
Full Name, position, address, and phone number of the sponsor's designated medical examiner for this study:	Nikolskaya Maria Viktorovna, Head of the Medical Information Department, Drugs Technology LLC Address: 141400, Moscow region, Khimki, Rabochaya str., 2A, bldg. 31, room 21. Phone: , mobile: . Email:

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SUBSCRIPTION LIST 1 (PRINCIPAL INVESTIGATOR)

to version No. 1.0 dated May 08, 2020 (as amended on May 19, 2020) of the Protocol ***"A multicenter open-label randomized study of the efficacy and safety of* TL-FVP-t *compared* with *standard therapy in parallel groups in patients with mild to moderate coronavirus disease* (SARS-CoV-2/COVID-19)"** (Protocol number: TL-FVP-t-01)

I, the undersigned, agree to the following:

1. I have fully read/understood the provisions of this Protocol, accept them, and undertake to conduct the study in accordance with this Protocol, as well as in accordance with the requirements of the ICH GCP, the Helsinki Declaration, and the requirements of state regulatory authorities of the Russian Federation and the Eurasian Economic Union.
2. I will not deviate from the Protocol without the prior written permission of the Sponsor, approved by the regulatory authorities and local ethics committees, except in cases where this is necessary to prevent any immediate danger to the subject.
3. I have a staff of qualified employees, the necessary equipment, and sufficient time to perform trial in accordance with this Protocol.
4. I will take all measures to ensure that all personnel involved in the study are adequately familiar with this Protocol and correctly perform their duties during the course of the study.
5. I agree with audit and inspection procedures in accordance with the rules established by the Sponsor and state regulatory authorities.
6. I understand that the text of this Protocol, as well as all other materials and research results, are confidential and are the property of the Sponsor. I undertake not to provide them to third parties, except in cases stipulated by the current legislation of the Russian Federation and the Eurasian Economic Union.

Principal Investigator:
Full name

_____

Position

_____ _____

Signature

Date

SUBSCRIPTION LIST 2 (SPONSOR)

to version No. 1.0 dated May 08, 2020 (as amended on May 19, 2020) of the Protocol **"A multicenter open-label randomized study of the efficacy and safety of TL-FVP-t compared with standard therapy in parallel groups in patients with mild to moderate coronavirus disease (SARS-CoV-2/COVID-19)"** (Protocol number: TL-FVP-t-01)

I, the undersigned, approve the Protocol of the study and undertake to conduct the study in accordance with all the requirements of the Protocol.

Sponsor:
Filon Olga Vladimirovna
Medical Director
Drug Technologies LLC

Signature

Date

LIST OF ABBREVIATIONS

AO	Aldehyde oxidase
AUC	Area Under the Curve, the total concentration of the drug in the blood plasma during the entire time of observation
$AUC_{0-\infty}$	The area under the pharmacokinetic concentration-time curve calculated from zero to infinity
AUC_{0-t}	The area under the pharmacokinetic concentration-time curve from zero to the last blood sampling at which the concentration of the drug is equal to or higher than the lower limit of quantitation
AUC_{ss}	Areas under the pharmacokinetic concentration-time curve in blood plasma after the drug reaches a steady state
CL/F	The total plasma clearance
C_{max}	The maximum concentration of the drug in blood plasma
$C_{max, ss}$	Average maximum plasma concentrations after reaching a steady state
COVID-19	An infection caused by the novel coronavirus SARS-CoV-2
CYP	Cytochrome P
CV	Coefficient of variation
FiO_2	Oxygen concentration in the respiratory mixture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IC_{50}	Inhibition concentration (IC_{50})
IL	Interleukin
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	Gene for specific potassium channels in the human heart
hURAT	Human uric acid transporter
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantitation
M1	Metabolite M1 hydroxy-favipiravir
MDCK	Madin-Darby Canine Kidney cells
MDR	Multidrug-resistant receptor
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
MSDS	Material Safety Data Sheet
NOAEL	No observed adverse effect level, the maximum dose of the drug that does not lead to the development of observed adverse effects

NADPH	Nicotinamide adenine dinucleotide phosphate
$PaCO_2$	Partial pressure of carbon dioxide in the blood
PaO_2	Partial pressure of oxygen in the blood
P-gp	P-glycoprotein
PEEP	Positive End Expiratory Pressure, constantly positive airway pressure
pKa	Dissociation constant
PvO_2	Oxygen tension in venous blood
SARS-CoV	The coronavirus that caused the outbreak of severe acute respiratory syndrome
SARS-CoV-2	The novel coronavirus caused the outbreak of infection in 2019–2020.
$T_{1/2}$	Apparent elimination half-life
T_{max}	Time to reach maximum concentration
TNF	Tumor necrosis factor
XO	Xanthine oxidase
α	Boundary value problem of the first kind (significance level)
β	Boundary value problem of the second kind
δ	Half-width of the equivalence zone
ε	The observed difference between the average
$\sigma_{l,1}$	Standard deviation for a between-subject comparison
BP	Blood pressure
ACE	Angiotensin-converting enzyme
ALT	Alanine transaminase
AST	Aspartate transaminase
ATPase	Adenosine triphosphatase
APTT	Activated partial thromboplastin time
BCP	Blood chemistry panel
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
WHO	World Health Organisation
HPLC	High performance liquid chromatography
HPLC-MS/MS	High-performance liquid chromatography and tandem mass spectrometry
GA	Glatiramer acetate
GGT	Gamma-glutamyl transpeptidase
GTP	Guanosine triphosphate
DHM	Department of Health of Moscow
RF	Respiratory failure
DNA	Deoxyribonucleic acid
ALV	Artificial lung ventilation (mechanical ventilation)
BMI	Body mass index

IFN	Interferon
IL	Interleukin
CBT	Clinical blood test
CrCl	Creatinine clearance
MP	Medicinal product
LD_{50}	Lethal dose, which causes the death of 50% of animals
LDL	Low-density lipoproteins
MDS	Myelodysplastic syndrome
MoH of Russia	Ministry of Health of the Russian Federation
PBMC	Human peripheral blood mononuclear cells
MLD	Minimum lethal dose
INN	International nonproprietary name
LIE	Local irritant effect
NIV	Non-invasive ventilation
ADR	Adverse drug reactions
LMWH	Low molecular weight heparins
NSAIDs	Non-steroidal anti-inflammatory drugs
LLOQ	Lower Limit of Quantitation
HT	Serotonin receptors
IEC	Independent ethics Committee
AE/SAE	Adverse event/serious adverse event
CBC	Complete blood count
UA	Urinalysis
ARF	Acute respiratory failure
ARVI	Acute respiratory viral infection
ARDS	Acute respiratory distress syndrome
ICU	Intensive care unit
LLC	Limited liability company
HR	Hazard ratio
LLC	Limited liability company
HR	Hazard ratio
PCR	Polymerase chain reaction
PTT	Prothrombin time
RNA	Ribonucleic acid
RCT	Randomized controlled trial
RF	Russian Federation
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
USA	United States of America
SARS	Severe acute respiratory syndrome

TSH	Thyroid-stimulating hormone
PK	Pharmacokinetics
RR	Respiratory rate
HR	Heart rate
AP	Alkaline phosphatase
ECG	Electrocardiography
ECMO	Extracorporeal membrane oxygenation

GLOSSARY OF TERMS

Term	Definition
Investigational product	A concept that includes an investigational medicinal product, a reference product, or a placebo. This is a finished dosage form of an active substance or placebo that is being studied or used for control in a clinical study, including an authorized medicinal product if the method of use differs from the approved one, as well as when it is used for a new indication or to obtain additional information on an approved indication.
Study/test product/drug	A finished dosage form, the properties of which are being examined in this study.
Comparator/reference product/drug	Active control or placebo, used as a control in the clinical study in order to reduce bias in evaluations, maintain a blind mode with respect to the study drug, evaluate the internal validity of the study and/or the comparative effects of the study drug.
Case Report Form (CRF)	A document in paper or electronic format intended for entering all the information required by the Protocol and referable to the sponsor for each subject of the study
Investigator's Brochure	Summary of the results of preclinical and clinical studies of the test product, significant for investigation in humans.
Subject identification code/subject ID |__|__|-|__|__|__|	A unique code assigned by the investigator to each subject and used to identify them throughout the study to ensure the confidentiality of their personal data, and used instead of the subject's name in all data related to the study. This code usually consists of a two-digit study center number and a three-digit number indicating the order of enrollment of patients in the study.
Screening number |__|__|-|__|__|	A unique number assigned to each patient who signed the informed consent (IC), consisting of a two-digit site number and a two-digit number indicating the order in which patients were enrolled.
Randomization number |__|__|__|	A unique number assigned to each patient included in the study (randomized) and encoding a specific type of treatment. This number is not used anywhere after randomization.
Evaluation	The procedure used to obtain the data required in this study.

Term	Definition
Enrolment	The time point at which randomization and distribution to a particular therapy group is performed.
Early retirement of a patient	The time point at which the patient leaves the study before the planned end of the study therapy and/or evaluations; at this time, the study therapy is discontinued, and no further evaluations are planned.
End of participation in the study	The time point at which the patient's final evaluation session occurs.
Study treatment	Includes any drug (study or comparison/reference drug) used in any study group as part of the study procedures.
Variable	An identifier used in data analysis; obtained directly or indirectly from data collected during specified estimates at specified time points.

DOCUMENT HISTORY

Not applicable.

Full Names and positions of investigators responsible for conducting the study, and addresses and phone numbers of study sites (clinical centers)

Information about investigators conducting the study and medical institutions (study sites), where we expect to conduct clinical studies, provided in the document "Information on medical institutions where it is expected to conduct the clinical study of the medicinal product for human use."

Full Name, position, address and phone number of the qualified physician responsible for making medical decisions

Full Name of the qualified physician responsible for making medical decisions	Position	Address:	Phone, email
Nikolskaya Maria Viktorovna	Head of the Medical Information Department, Drugs Technology LLC		

Names and addresses of clinical and other medical and/or technical services and/or organizations involved in the study

No.	Name of the organization	Role in the study	Full Name of the responsible person	Address of the organization	Phone, Fax, email

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The identifier of the Protocol	TL-FVP-t-01
Name of the study	Multicenter open-label randomized parallel-group study of the efficacy and safety of TL-FVP-t compared to standard therapy in patients with mild to moderate coronavirus disease (SARS-CoV-2/COVID-19)
Abbreviated name of the study	Not applicable
Phase	Phase 3
Type of the study:	Interventional
The sponsor of the study:	Drugs Technology LLC Legal and postal address: 141400, Moscow region, Khimki, Rabochaya str., 2a, bldg. 31, room 21. Tel.: +7 (495) 225-62-00, Fax: +7 (495) 225-62-65. Email: info@drugsformulation.ru.
Study drug:	The internal code of the medicinal product: TL-FVP-t Name: FAVIPIRAVIR-TL Dosage form: film-coated tablet INN: Favipiravir Dosage: 200 mg Manufacturer: R-Pharm JSC, Moscow, Russia MA Holder: Drugs Technology LLC, Moscow, Russia
Comparison therapy:	A "standard" etiotropic therapy recommended according to the current version at the time of the study of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19) for patients with mild to moderate symptoms. In the comparison group, patients will receive either umifenovir in combination with interferon-alpha, or chloroquine, or its derivatives (chloroquine/hydroxychloroquine or mefloquine) using standard regimens and dosages according to the Guidelines.
Concomitant therapy:	Concomitant therapy is a treatment against which it is planned to use the study drug and comparison therapy. Concomitant therapy is prescribed at the discretion of the study physician and is determined by the actual condition and needs of a patient. It involves symptomatic therapy,
	pathogenetic therapy and antibiotic therapy (in cases of complicated infections) recommended according to the current version at the time of the study of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment coronavirus disease (COVID-19) for patients with mild to moderate symptoms, as well as the relevant standards adopted in the study site. Symptomatic therapy includes: • Relief of fever (antipyretic drugs; the recommended drug is acetaminophen, it is permissible to use NSAIDs,

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	for example, ibuprofen). • Complex therapy of rhinitis and/or rhinopharyngitis (moisturizing/irrigation drugs, nasal decongestants); • Complex therapy of bronchitis (mucoactive drugs, broncholytic drugs, and other). Pathogenetic therapy may include antithrombotic and anti-inflammatory drugs.
The study sites:	The multicenter clinical study, it is planned to include about 5–10 sites in the Russian Federation.
Central laboratory:	The study will include a central laboratory where PCR testing (smears) for the SARS-CoV-2 virus and general clinical laboratory tests will be performed (common blood count, blood chemistry test, coagulation test, and urinalysis). In Moscow, the central laboratory is a Federal Budgetary Institution of Science "Central Research Institute of Epidemiology" of The Federal Service on Customers' Rights Protection and Human Well-being Surveillance (FBUN TsNII of Epidemiology of Rospotrebnadzor). In Saint Petersburg, the central laboratory is Research Center Eco-safety LLC.
Pharmacokinetic laboratory	Exacte Labs LLC Legal and actual address: 117246, Russia, Moscow, Nauchny proezd, 20, bldg. 2. **Contact person:** Vasily Kazey, PhD, General Director. Email: Tel:
Central Independent Committee for the evaluation of computed tomography data (CIC on CT)	The study plans to organize a Central Independent Committee (CIC) for the evaluation of computed tomography data (CT), which will be responsible for the reference evaluation of the results of computed tomography of patients throughout the entire period of their participation in the study. The decision on how to manage patients based on CT data will be made at the study site where the patient is recruited, taking into account the conclusion of the CIC on CT.
Independent Data Monitoring Committee (IDMC)	The study plans to set up an Independent Data Monitoring Committee (IDMC), which will be responsible for periodically reviewing safety and efficacy data and making medical decisions in complex cases for individual patients (if necessary). The rules of operation of the IDMC (frequency of meetings and cases considered) are regulated by the Charter of the IDMC.
Study Aims	**Study Aim:** • To study the efficacy and safety of TL-FVP-t in patients with coronavirus disease (SARS-CoV-2/COVID-19) of mild to moderate severity compared

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	to the "standard"[1] therapy.
Study objectives	**Main objective:** • To evaluate the effect of TL-FVP-t on the rate of improvement of clinical status[2] in patients compared to the "standard" therapy. • Evaluate the effect of TL-FVP-t on the rate of virus elimination[3] in patients based on the results of qualitative analysis on SARS-CoV-2 compared to the "standard" therapy. **Additional objectives:** • Evaluate the effect of TL-FVP-t on the frequency of improvement of clinical status[4] in patients at fixed time points compared to the "standard" therapy. • Evaluate the effect of TL-FVP-t on the frequency of virus elimination at fixed time points compared to the "standard" therapy. • Evaluate the effect of TL-FVP-t on the duration of the period before temperature normalization[5] compared to the "standard" therapy. • Evaluate the effect of TL-FVP-t on the probability of resolution of radiological changes in the lungs according to CT data on day 14 compared to the "standard" therapy. • Evaluate the safety and tolerability of TL-FVP-t in patients with coronavirus disease (SARS-CoV-2/COVID-19) of mild to moderate severity compared to the standard therapy, when used against the background of recommended concomitant therapy, including the frequency and severity of drug-related AEs and SAEs, the frequency of severe drug-related AEs and SAEs, and the frequency of early discontinuation of treatment due to drug-related AEs and SAEs). **Exploratory issues** • To study the effect of TL-FVP-t on the average clinical status in patients (the average score on the WHO Ordinal Scale for Clinical Improvement) at fixed time points compared to the "standard" therapy. • To study the effect of TL-FVP-t on the duration of

[1] The "standard" therapy refers to recommended etiotropic therapy in accordance with the current version of the Interim guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study, for patients with mild to moderate COVID-19.

[2] Clinical status is measured in points on the WHO Ordinal Scale for Clinical Improvement; improvement in clinical status is defined as a decrease of at least 1 point on the scale compared to the screening level.

[3] Elimination is defined as a "negative" result when conducting 2 consecutive studies by PCR of biological samples obtained from patients (smears from the upper respiratory tract) at intervals of 24 hours at least.

[4] Clinical status is measured in points on the WHO Ordinal Scale for Clinical Improvement; improvement in clinical status is defined as a decrease of at least 1 point on the scale compared to the screening level.

[5] Normalization is considered the reduction the axillary temperature to less than 37 °C without the use of antipyretics for at least 48 hours.

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	individual symptoms (cough, myalgia, weakness, shortness of breath, headache) in patients compared to the "standard" therapy. • To study the effect of TL-FVP-t on the frequency of hospitalization of patients who were under outpatient observation compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy). • To study the effect of TL-FVP-t on the duration of hospitalization of patients compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy). • To study the effect of TL-FVP-t on the frequency of need for artificial lung ventilation (AVL) compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy). • To study the effect of TL-FVP-t on the frequency of transfer of patients to the intensive care unit compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy). • To study the effect of TL-FVP-t on the incidence of death in patients compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy). • To study the pharmacokinetics of favipiravir and its main metabolite M1 and calculate the pharmacokinetic parameters after a single (AUC_{0-12}; C_{max}; T_{max}; $T_{1/2}$; Cl, V_d, and Kel, etc.) and multiple application of TL-FVP-t (AUC_{0-12}; C_{max}; T_{max}; $T_{1/2}$; Cl, V_d, and K_{el} on days 5 and 10, as well as $C_{min\ ss}$, etc.).
Study Design	This study is a multi-center, open-label, randomized, 3-phase study in parallel groups, the purpose of which is to evaluate the efficacy and safety of TL-FVP-t compared with the recommended standard etiotropic therapy in patients with mild to moderate coronavirus disease (SARS-CoV-2/COVID-19). The study will include 168 (randomized) patients; a maximum of 200 will be screened. **IC signing, randomization, and blinding** Before enrollment in the study, patients will be provided with complete information about the clinical study, its goals, and the risks associated with participating in it. After signing the informed consent to participate in the study and screening, patients who meet the inclusion criteria and do not have non-inclusion criteria will be stratified and randomized to one of the study groups. There will be central randomization performed in a 2:1 ratio in the study therapy group and the comparison group, respectively. The study assumes stratification by the following parameters: according to the severity of the disease (mild and moderate), age (from 18 to 44

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	and 45 and older), and the severity of pathology on chest CT scan (CT-0 – CT-1 and CT-2 – CT-3). The study is open-label, so the blinding of the therapy is not expected.
	Study periods In general, the study will include the following periods: 1) **Screening period: 2 days** Includes days -1-0 (before randomization and inclusion in the study). 2) **Therapy period: 10 days** It includes 10-day therapy with the study drug or the "standard" therapy according to the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study, against the background of recommended concomitant therapy, data collection on clinical symptoms, monitoring of the study subject, assessment of vital signs (body temperature, BP, HR, RR, SpO_2), as well as a sampling of biomaterial to determine the elimination of the virus, monitoring of laboratory findings, ECG, and CT of the chest. 3) **Follow-up period**: **14 (±2) days** It includes days 11 to 28 and involves the collection of biomaterial to determine the elimination of the virus, procedures for monitoring the patient's condition, laboratory tests, ECG, and chest CT to monitor the patient's condition.

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	Description of the therapy **The TL-FVP-t group.** Patients in this group will receive oral therapy with TL-FVP-t for 10 days. On the first day of the therapy, patients will receive a loading dose of TL-FVP-t – 1800 mg at 12-hour intervals (i.e. twice daily), then on days 2 to 10 patients will receive 800 mg at intervals of 12 hours (i.e. twice daily). **Comparison group.** Patients in this group will receive the recommended "standard" etiotropic therapy in accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study. These drugs include umifenovir, chloroquine, hydroxychloroquine, mefloquine, lopinavir+ritonavir, hydroxyloroquine in combination with azithromycin, interferons (at the time of writing this Protocol). In the comparison group, patients will receive either umifenovir in combination with interferon-alpha, or chloroquine, or its derivatives (chloroquine/hydroxychloroquine or mefloquine) using standard regimens and dosages according to the Guidelines. **Concomitant therapy.** In addition to the study drug and "standard" etiotropic therapy, patients in both groups may be prescribed concomitant therapy in accordance with the above Guidelines. Concomitant therapy is prescribed at the discretion of the study physician and is determined by the actual condition and needs of a patient. It involves symptomatic therapy, pathogenetic therapy and antibacterial therapy (for complicated forms of infection), recommended according to the current version of the Interim guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study, for patients with mild and moderate disease, as well as corresponding to the standards adopted at the study site. Symptomatic therapy includes: • Relief of fever (antipyretic drugs; the recommended drug is acetaminophen, it is permissible to use NSAIDs, for example, ibuprofen). • Complex therapy of rhinitis and/or rhinopharyngitis (moisturizing/irrigation drugs, nasal decongestants); • Complex therapy of bronchitis (mucoactive drugs, broncholytic drugs, and other). Pathogenetic therapy may include antithrombotic and anti-inflammatory drugs.
	Hospitalization and outpatient monitoring Patients who will be included in the study, depending on the severity of the disease and the condition, may be hospitalized or may be observed at home, in an outpatient setting.

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	Patients who are at home during the screening period and the main period, until the virus is eliminated, will be quarantined at home. They will be monitored using telemedicine technology. If the symptoms of SARS-CoV-2 (COVID-19) coronavirus disease worsen in such patients or become more severe, according to the decision of the investigator, the patients will be admitted to a hospital, where they will continue to be monitored for tracking their status (ICU, AVL, fatal outcome) (if possible). If there is no possibility of further monitoring of hospitalized patients and communication with them, they are excluded from the study. Discharge from the hospital is made in accordance with the local practice of the study site in compliance with the current sanitary and epidemiological regime.
	Examination of patients To assess the efficacy of the therapy in all patients, a regular assessment of the clinical status, assessment of subjective symptoms, sampling of biomaterial (smear) from the upper respiratory tract to determine the content of the SARS-CoV-2 (by PCR), measurement of body temperature, BP, HR, RR, determination of blood oxygen saturation according to pulse oximetry (SpO_2), ECG, chest CT will be performed. Measurement of body temperature, BP, HR, and SpO_2 (in an outpatient setting — independently by the patient, with remote video monitoring by a study physician) will be performed daily for 10 days of therapy (body temperature measurement and pulse oximetry must be performed at least 3 times daily), then – on days 14, 21, and 28. The survey of the patient about the subjective symptoms and the calculation of RR will be carried out by the study physician daily for 10 days of the therapy, then – on days 14, 21, and 28. The patient will also keep The Patient's Diary for the first 14 days, then on days 21 and 28, recording the facts of receiving the study therapy and concomitant therapy drugs, symptoms, results of measurement of body temperature, BP, HR, and SpO_2. The clinical status will be assessed by a study physician during screening and daily for 10 days of the therapy, then – on days 14, 21, and 28. The sampling of biomaterial to determine the content of the SARS-CoV-2 virus will be carried out on days 3, 5, 7, 10, 14, 21, and 28. After receiving a negative test result for the presence of the SARS-CoV-2 virus, a second study to confirm the fact of elimination of the virus will be carried out after a minimum of 24 hours. After confirmation of the elimination of the SARS-CoV-2 virus (2 negative tests), the sampling will be stopped, and the patient can end the quarantine period (if at home) and be removed from the register. Then the patients will

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	be monitored in accordance with the planned schedule of visits in the study. Despite confirmation of virus elimination, the patients should wear a mask, live in a separate room, avoid close contact with family members, eat separately, keep their hands clean, and avoid outdoor activities. CT of the chest and mediastinum and ECG will be performed at the screening, and then on days 5, 14, and 28 (the latter is performed as necessary, at the discretion of the study physician). If necessary, additional CT scans may be performed on other days to monitor the patient's condition. Evaluation of laboratory findings will be performed at the screening, then on days 5, 14, and 28. The following parameters will be evaluated: - Clinical blood test (hemoglobin, erythrocyte count, leukocyte count, neutrophil count, lymphocyte count, platelet count, ESR). - Blood chemistry test (glucose, ALT, AST, LDH, total bilirubin, creatinine, CPK, ferritin, lactate, uric acid); - C-reactive protein; - coagulation test (activated partial thromboplastin time (APTT), prothrombin time, fibrinogen, D-dimer); - urine analysis. Safety will be assessed based on the obtained data on complaints, clinical status, as well as on the results of laboratory tests. On the 28th day of the study, the patient completes participation in the study.
	PK study subgroup (PK-subgroup) A subgroup (15 patients) for pharmacokinetic study will be selected in the study drug group, periodical blood plasma sampling will be performed in this subgroup to study the pharmacokinetics of the drug. Blood samples will be taken as follows: Day 1: at least 5 minutes before the first drug intake, then at points: 20 min; 40 min; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours. Day 2 to Day 10: 5 minutes before the next (morning) drug intake. Days 5 and 10: in addition to the pick-up points prescribed for Day 2 to Day 10, the sampling will be made in 20 min; 40 min; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours after the first (morning) intake on these days. The PK-subgroup will include patients who sign up for additional IC to participate in this study, and only in study sites, available for sampling.
Study population	This study will include patients aged 18 to 60 years with a mild to moderate coronavirus disease (SARS-CoV-2 confirmed by the results of a PCR study of smears from the upper respiratory tract) without respiratory failure.

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Planned sample size	168 randomized (included) patients, up to 200 screened patients (taking into account the possible discontinuation at the screening stage).
Inclusion criteria	1. Informed consent form signed by the patient and the study physician. 2. Males and females aged 18 to 60 years. 3. Diagnosis of a mild to moderate coronavirus disease caused by SARS-CoV-2 (COVID-19) (without respiratory failure). In accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19): - Mild form: specific symptoms in the absence of criteria for moderate and severe form. - Moderate form: fever above 38 °C; RR more than 22/min; shortness of breath during exercise; pneumonia (verified by CT of the lungs); SpO_2 < 95%; serum CRP more than 10 mg/l). 4. Duration of infection symptoms shall be no more than 6 days (preferably no more than 3 days) before randomization. 5. SARS-CoV-2 infection should be verified by the results of PCR test (the screening takes into account the patient's existing results, or the test is performed in a study site out of the Protocol). 6. Ability to follow the requirements of the Protocol and fulfill all the clinical study procedures 7. Willingness of participants and their sexual partners with retained childbearing potential to use reliable contraception methods throughout the study and for 3 months after the treatment completion. This requirement does not apply to participants who have undergone surgical sterilization. Reliable methods of contraception involve the use of the first barrier method in combination with one of the following: spermicides, intrauterine spiral/oral contraceptives in a sexual partner. 8. Willingness not to take alcohol throughout the entire period of the study. **Additional inclusion criteria for the PK-subgroup** 1. Signed informed consent to participate in further study of pharmacokinetics. 2. Body mass index 18.5–30.0 kg/m^2. 3. In the reasonable opinion of the study physician, a patient is able to participate in further study of pharmacokinetics and sampling of the required number of blood samples.
Non-inclusion criteria	1. Age less than 18 or more than 60 years. 2. A patient has been prescribed any etiotropic therapy for

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	SARS-CoV-2 (COVID-19) coronavirus disease before being included in the study. 3. Moderate form with the presence of respiratory failure, severe or extremely severe form of the disease caused by SARS-CoV-2 (COVID-19). 4. Respiratory failure (RR>30/min, $SpO_2 \leq 93\%$) or the need for mechanical ventilation at the screening. 5. Decreased level of consciousness (disorientation in place, time, and self-identity), agitation at the screening. 6. Hemodynamic instability (systolic BP less than 100 mm Hg or diastolic BP less than 60 mm Hg) found at the screening. 7. Subtotal diffuse ground-glass induration of pulmonary tissue and pulmonary consolidation combined with reticular changes; involvement of ≥ 75% of lung parenchyma; hydrothorax (CT findings corresponding to CT-4 and higher according to the guidelines of Department of Health of Moscow). 8. Comorbidities: a) Chronic obstructive pulmonary disease or moderate to severe asthma. b) Severe chronic cardiovascular diseases (rhythm and conduction disorders, artificial heart rhythm driver, myocardial infarction or unstable angina in history, heart failure). c) Immunocompromised individuals (HIV, cancer, autoimmune diseases, immunosuppressive therapy). d) Severe obesity (body mass index [BMI] 40 or higher). e) Diabetes. f) Chronic renal failure. g) Moderate to severe chronic liver diseases. 9. The presence of any of the following deviations in laboratory findings at the screening: AST or ALT levels greater than 2.5 upper normal levels (UNL), platelet count $< 50x10^9/l$. 10. Any medical history that, in the opinion of the investigator, may lead to difficulties in interpreting the results of the study or create an additional risk for the patient as a result of their participation in the study. 11. More than 2 CT diagnostic procedures in the last 6 months prior to randomization into the study (with the exception of chest CT performed no more than 4 days before inclusion in the study). 12. The patient is taking therapy with drugs that significantly inhibit CYP28C, and these drugs cannot be discontinued for the period of the entire study. 13. Malabsorption syndrome or another clinically

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	significant disease of the gastrointestinal tract that may affect the study product absorption (uncontrollable vomiting, diarrhea, ulcerative colitis, etc.). 14. Pregnancy or breastfeeding; women with a probable pregnancy at the screening; women planning to conceive during the entire period of the study. 15. Known (from the medical history) or suspected alcohol or psychotropic drug abuse; drug dependence, illicit drug addiction. 16. Mental illnesses, including the medical history. 17. A condition or disease that, in the opinion of the investigator or medical monitor, may put the patient's safety at risk or affect the safety assessment of the investigational drug.
Total duration of the study	The total expected duration of the study is 6 months: • the period for initiating study sites and recruiting patients is 3 months, • the main study period and follow-up period is 28±2 days (about 1 month), • data collection and statistical processing of results – 2 months. The expected duration of each subject's participation in the study will be a maximum of 30±2 days, including screening periods (2 days), the main study period (a total of 14 days), and the follow-up period (14±2 days).
Efficacy evaluation	**Primary endpoint:** • Time to improve clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category) (median, in days). • Time to reach virus elimination (defined as the absence of SARS-CoV-2 based on the results of 2 consecutive PCR of smears at intervals not less than 12 hours) (median, in days). **Secondary endpoints:** • Percentage of patients (%) with improved clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category[6]) on day 7 (from the beginning of the therapy). • Percentage of patients (%) with established virus elimination on days 5 and 7 (from the beginning of the therapy). • Time to temperature normalization (median, in days). • Percentage of patients (%) with resolution of changes in the lungs according to CT data on day 14 (from the beginning of the therapy). **Exploratory endpoints:**

[6] Ordinal Scale for Clinical Improvement

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	• Average score on the WHO Ordinal Scale for Clinical Improvement on days 7 and 14 of the study. • Percentage of patients (%) with improved clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category[7]) on day 14 (from the beginning of the therapy). • Percentage of patients (%) with established virus elimination on study days 3, 10, 14, 21, and 28 (from the beginning of the therapy). • Time to reversal of individual symptoms (fever, cough, myalgia, weakness, shortness of breath, headache) (median, in days). • Frequency (%) of hospitalization of patients who were under outpatient observation for a period of 28 days (from the beginning of the therapy). • Duration of hospitalization of patients for a period of 28 days (from the beginning of the therapy). • Frequency (%) of ventilator use for a period of 28 days (from the beginning of the therapy). • Frequency (%) of transfer to the intensive care unit for a period of 28 days (from the beginning of the therapy). • Frequency (%) of deaths for a period of 28 days (from the beginning of the therapy). **Efficacy evaluation methods:** The following methods will be used for efficacy evaluation: • Assessment of clinical status by a study physician remotely using telemedicine technologies – at the screening and on days 3, 5, 7, 10, 14, 21, and 28 of the study. • Sampling of biomaterial from the upper respiratory tract to determine SARS-CoV-2 (by PCR) on days 3, 5, 7, 10, 14, 21, and 28. • Measurement of body temperature, BP, HR, RR, blood oxygen saturation according to pulse oximetry (SpO_2) – daily for the first 10 days, then – on days 14, 21, and 28. • Assessment of subjective symptoms – daily when interviewed by a study physician for the first 10 days, then on days 14, 21, and 28. • Chest CT on days 5, 14, and 28. The patient will also keep The Patient's Diary for the first 14 days, then on days 21 and 28, recording the facts of receiving the study therapy and concomitant therapy drugs, symptoms, results of measurement of body temperature, BP, HR, and SpO_2.

[7] Ordinal Scale for Clinical Improvement

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The patient's clinical status will be assessed on the WHO Ordinal Scale for Clinical Improvement):

The patient's status	Appearance	Evaluation
Healthy*	Absence of clinical manifestations and laboratory confirmation of absence of SARS-CoV-2 (COVID-19) infection	0
Outpatient	Activities of daily living are not restricted	1
	Activities of daily living are restricted	2
Hospitalized, moderate	Oxygen therapy is not required	3
	Oxygen therapy through a mask or nasal cannulas is required	4
Hospitalized, severe	Non-invasive ventilation or high-flow oxygenation	5
	Intubation, mechanical ventilation	6
	AVL + treatment of organ failure (vasopressors, extracorporeal membrane oxygenation, renal replacement therapy)	7
	Fatal outcome	8

* In the absence of clinical manifestations and laboratory confirmation of the absence of SARS-CoV-2 infection in hospitalized patients, they are also classified as "0", i.e. "Healthy"
** The catarrhal symptom "cough" is allowed to remain, with no more than 1 point of severity

Safety evaluation

Secondary endpoints:

- The frequency and severity of all drug-related cases of AE and SAE in patients who received at least one dose of the study drug.
- The frequency of drug-related severe AEs (Grade 3-5 according to CTCAE 5.0) in patients who received at least one dose of the study drug.
- The frequency of cases of early discontinuation of the study due to drug-related AEs/SAEs.

The evaluation will be made for the entire period of patient participation in the study.

Safety evaluation methods:

The following will be performed for safety evaluation:

- Collecting complaints, interviewing a patient about subjective symptoms – daily for 10 days of the therapy, then – on days 14, 21, and 28;
- Measurement of body temperature, BP, HR, RR, and SpO_2 – daily for 10 days of the therapy, then – on days 14, 21, and 28.
- Evaluation of laboratory findings will be performed at the screening, then on days 5, 14, and 28:
  - Clinical blood test (hemoglobin, erythrocyte count, leukocyte count, neutrophil count,

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	lymphocyte count, platelet count, ESR). - Blood chemistry test (glucose, ALT, AST, LDH, total bilirubin, creatinine, CPK, ferritin, lactate, uric acid, C-reactive protein). - Coagulation test (activated partial thromboplastin time (APTT), prothrombin time, fibrinogen, D-dimer). - Urine analysis. • ECG will be performed at the screening, then on days 5, 14, and 28. Based on the data received, the AEs and SAEs will be registered.
Pharmacokinetics evaluation:	In the PK-subgroup (in TL-FVP-t treatment arm), the plasma concentrations of favipiravir and its main metabolite M1 (the metabolite will be determined if technically possible) will be determined at discrete time intervals to construct pharmacokinetic concentration-time curves with repeated administration of the study drug. **Exploratory endpoints:** After a single dose of TL-FVP-t, the following drug parameters will be determined: • Maximum plasma concentration (C_{max}). • The area under the pharmacokinetic concentration-time curve for 12 hours ($AUC_{(0-12)}$). • Time to reach the maximum concentration (T_{max}). • Apparent elimination half-life ($T_{1/2}$). • Clearance (Cl). • Elimination constant (K_{el}). After repeated administration of TL-FVP-t, the following drug parameters will be determined: • The above PK parameters on the days of taking the drug are 5 and 10. • The minimum concentration in the blood plasma of patients in the steady state ($C_{min\ ss}$). Assay of favipiravir and its main metabolite M1 (the metabolite will be determined if technically possible) in blood plasma will be carried out using a highly sensitive and selective method of high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS).
Ethical and regulatory aspects	The study will be conducted in full compliance with this Protocol, ICH GCP requirements, rules of Good Clinical Practice of the Eurasian Economic Union, Order of the Ministry of Health of the Russian Federation No. 200n dated April 1, 2016 "On Approval of Rules of Good Clinical Practice", GOST R52379-2005 "Good Clinical Practice", ethical principles of the Declaration of Helsinki in the latest revision, and the Rules of compulsory insurance of life and health of a patient involved in clinical studies of the medicinal product, as well as with applicable laws and regulatory

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	requirements of The Russian Federation and the Eurasian Economic Union.
Statistical methodology	**Calculating the sample size** There are planned 2 primary endpoints in the study: • Time to improve clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category) (median, in days). • Time to reach virus elimination (defined as the absence of SARS-CoV-2 based on the results of 2 consecutive PCR of smears at intervals not less than 12 hours) (median, in days). The sample was calculated for both endpoints. The calculation given below shows the maximum size: for the primary endpoint, the time to improve clinical status. Information about the rate of improvement of the clinical status, resolution of clinical manifestations, and virus elimination in patients with non-severe COVID-19 is limited. The possibility of direct use of the literature data is also limited by the fact that the data are provided for observation of patients in real clinical practice, in which patients receive a variety of symptomatic and etiotropic therapy. Thus, according to Li et al. (2020) in patients with mild to moderate form when using the "standard" etiotropic therapy, including lopinavir/ritonavir, umifenovir, and other drugs, the median time to virus elimination was 9.0–9.3 days, provided that patients were included in the study for an average of 3-6 days after the development of symptoms. According to the data, the average time from virus elimination to the resolution of symptoms is 2.5 days (1.25–4.5), therefore, it can be assumed that clinical improvement with the use of the "standard" therapy can occur no earlier than 11.5–13.5 days. According to Cai et al. (2020), the median time to virus elimination in a comparative clinical study of favipiravir versus lopinavir/ritonavir was 4 (2.5–9) and 11 (8–13) days, respectively, provided that patients were included no later than 7 days after the development of symptoms. Considering that patients should be included in this study no later than day 6 (on average, day 3) after the development of symptoms, as well as the plans to use a mix of patients with mild and moderate form, it can be assumed that in the experimental group, the improvement of the clinical status will occur on day 7, and in the comparison group – on day 13. Based on these assumptions, sampling was calculated. The sample size was determined by the time-to-event method using the gsDesign package (version 3.0-1) of the statistical programming language R (version 3.5.3), based on the following assumptions: 1) Type I error (α) = 0.025 (due to the fact that a one-sided hypothesis of superiority is being tested, and a two-sided

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	95% confidence interval will be calculated). 2) Type II error (β) = 0,1 (respectively, the power is 90%). 3) The minimum detectable hazard ratio between the control group and the TL-FVP-t treatment group is 1.857. 4) Distribution into groups will be made in the ratio 2:1 (TL-FVP-t : "standard" therapy). 5) An interim analysis at the onset of a minimum number of events, which allows identifying the presence of differences in the groups, is also planned in the study. This analysis will be carried out after the occurrence of 54 events after 14 days of participation in the study. For the interim analysis, about 69 patients will be included in the study. According to calculations using the above conditions, an event should occur in 129 patients (improvement in clinical status). Taking into account the probability of early withdrawal from the study, as well as the probability of no event occurring by the end of the study, the sample size is planned to increase by 30% and include 168 patients: 112 patients in the TL-FVP-t treatment group and 56 patients in the comparison group. Considering the probability of withdrawal at the screening, the study is planned to screen no more than 200 patients.
	Selecting populations for analysis **Population for safety analysis** The safety analysis will be performed in a population of patients who received at least one dose of the test product (study drug or comparison drug). **Population for efficacy analysis** The efficacy analysis will be performed in the ITT-population (intent-to-treat) of all patients included in the study and in the PP-population (per protocol): • **Complete population analysis (intent-to-treat).** Efficacy evaluation of the main population is defined as the complete population analysis and includes all randomized patients. • **The "per protocol" population.** The "per protocol" population includes all patients from the complete population analysis without significant deviations from the Protocol who have taken at least one dose of the study therapy and in whom the efficacy can be evaluated. • **Population for pharmacokinetics analysis.** The population will include all patients from whom blood samples have been taken to study the pharmacokinetics of the drug and for whom the pharmacokinetic profile can be adequately described.
	Methods of statistical analysis

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	Statistical analysis will be conducted under the guidance of a responsible biostatistician, in accordance with ICH requirements, as well as other applicable requirements and laws. This multicenter study will be conducted in several study sites. Before starting the analysis, data from all study sites will be combined. Pre-analysis will be conducted aimed to study whether the relevant data belongs to a single General population, as well as the to research the issue of the legitimacy of combining data from different study sites, along with the method of aggregation problem. Statistical processing of data obtained during the research will be performed using the statistical data processing programming language R (version 3. x), or other appropriate software.
	Preparation of reports After the end of 14 days of participation and the onset of 54 events, an interim data analysis will be performed and an interim report will be prepared. After completion of the study by all included patients, the main report on the study will be prepared. An additional report will be prepared after obtaining full pharmacokinetic data in the study.

1. RATIONALE OF THE STUDY

1.1. Introduction

1.1.1. Review of data on pathogenesis, epidemiology, and current treatment options for the disease

1.1.1.1. Epidemiology and significance of the disease

Coronavirus disease is an acute viral disease with a predominant lesion of the upper respiratory tract caused by an RNA-genomic virus of the genus Betacoronavirus of the family Coronaviridae. On February 11, 2020, the international Committee on virus taxonomy assigned an official name to the infectious agent – SARS-CoV-2. Coronaviruses (lat. Coronaviridae) – a family that includes 40 species of RNA-containing complex viruses with a supercapsid as of January 2020. They are grouped into two subfamilies that affect humans and animals. The name is related to the structure of the virus: large club-shaped spines that resemble a crown protrude from the supercapsid.

Until 2002, coronaviruses were considered as agents that cause mild upper respiratory diseases (with extremely rare fatal outcomes). At the end of 2002, a coronavirus (SARS-CoV), the pathogen of atypical pneumonia that caused SARS, a severe acute respiratory syndrome in humans, appeared. In total, more than 8 thousand cases were registered in 37 countries during the epidemic, including 774 fatal cases. Since 2004, no new cases of SARS-CoV-induced atypical pneumonia have been reported. In 2012, the world encountered a new coronavirus (MERS-CoV), a Middle East respiratory syndrome pathogen belonging to the genus Betacoronavirus. Since 2012, there have been 2,519 cases of coronavirus disease caused by the MERS-CoV, of which 866 have been fatal. All cases are geographically associated with the Arabian Peninsula (82% of cases are reported in Saudi Arabia). MERS-CoV continues to circulate and cause new cases of the disease.

The new coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus-2) is a single-stranded RNA-containing virus belonging to the family Coronaviridae, to the lineage B Beta-CoV. Currently, the main source of infection is an infected person, including those who are at the end of the incubation, prodromal period (the beginning of virus release from target cells), and during clinical manifestations. The mechanism of transmission is aspiration. Transmission: airborne (virus release when coughing, sneezing, talking) in close contact. The household contact transmission is implemented through the next factors: water, food, and objects (door handles, smartphone screens) contaminated with the pathogen. The risk of transmission of the virus from the hands to the mucous membranes of the eyes, nose, and mouth and the development of the disease is proven. Susceptibility to the pathogen is high in all population groups. The risk groups for severe disease and the risk of death include people over 60 years of age, patients with chronic diseases (diseases of the respiratory system, cardiovascular system, cancer).

The outbreak occurred in late 2019 in Wuhan, the people's Republic of China (PRC). The original source of infection has not been identified. The first cases of the disease may have been related to visiting a seafood market where poultry, snakes, bats, and other animals were sold. Since the end of January 2020 in many

countries around the world, cases of COVID-19 have been reported in most related to trips to China. At the end of February 2020, the epidemiological situation for COVID-19 in South Korea, Iran and Italy was sharply complicated, which subsequently led to a significant increase in the number of cases in other countries of the world associated with travel to these countries. WHO announced the beginning of the COVID-19 pandemic on March 11, 2020. SARS-CoV-2 is included in the list of diseases that pose a danger to others (Decree of the Government of the Russian Federation No. 66 dated January 31, 2020).

1.1.1.2. Existing treatment options

In the case of the new coronavirus disease (SARS-CoV-2/COVID-19), unfortunately, there are currently no etiotropic drugs that have proven their efficacy in controlled clinical studies. The analysis of literature data on the clinical experience of managing patients with SARS-CoV and MERS-CoV associated with coronaviruses today allows us to identify several etiotropic drugs, which, however, do not have a clear evidence base confirming their efficacy against SARS-CoV-2/COVID-19. These include chloroquine, hydroxychloroquine, lopinavir+ritonavir, azithromycin (in combination with hydroxyloroquine), interferons, and umifenovir. These drugs are recommended for use in COVID-19 in the Russian Federation in accordance with the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), approved by E.G. Kamkin, version 6 dated April 28, 2020.

It is important to note that on May 1, 2020, the new drug remdesivir received an emergency use permit (EUA) from the FDA, based on preliminary data that demonstrated a shorter time for convalescence in hospitalized patients with severe form (NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19. National Institute of Allergy and Infectious Diseases (NIAID). April 29, 2020), however, at the time of preparation of this Investigator's Brochure, this drug is not included in the Interim recommendations of the MoH of Russia.

Today, numerous antiviral drugs continue to be studied and developed as potential treatments for COVID-19: several hundred clinical studies are being conducted worldwide. Recently, a number of reviews on etiotropic pharmacotherapy of COVID-19 have been published.

According to published data, these medicinal products can also be used today in the treatment of patients with COVID-19. However, the information available today on the results of therapy with these drugs does not allow us to make a clear conclusion about their efficacy or inefficacy, so their use is permissible by the decision of the medical commission in the appropriate manner if the potential benefit to the patient outweighs the risk of their use.

Among the drugs that are promising for the treatment of COVID-19, a group of antimalarial agents should be noted: chloroquine, hydroxychloroquine, mefloquine. These drugs are used for the treatment of malaria and some other protozoal infections. In addition, due to its anti-inflammatory and immunosuppressive effects, chloroquine and hydroxychloroquine have been used in the treatment of patients with systemic connective tissue diseases such as rheumatoid arthritis and lupus erythematosus. Mechanism of action of antimalarial

drugs against some viral infections have not been fully studied, and published data indicate several variants of their effects on COVID-19, which prevent the virus from entering the cell and replicating. In small clinical studies, it was shown that the combination of azithromycin with hydroxychloroquine increases the antiviral effect of the latter, but the available data on the efficacy of this group is extremely contradictory.

The combined drug lopinavir+ritonavir is an HIV protease inhibitor. Previously conducted studies have shown that it is also able to inhibit the activity of the coronavirus protease. The proposed antiviral mechanism of action for the new coronavirus based on computer simulations is related to the effect on the main SARS-CoV-2 protease (endopeptidase C30, non-structural protein Nsp5). This drug has been used in the treatment of MERS-CoV infection, and today can be used for the treatment of infection caused by the new SARS-CoV-2 coronavirus. The conducted randomized controlled study demonstrated that lopinavir+ritonavir monotherapy for SARS-CoV-2-induced diseases did not reduce the duration of hospitalization and did not demonstrate greater efficacy than standard symptomatic therapy (in a randomized study of lopinavir and ritonavir (LPV/RTV) in China in hospitalized adult patients with severe COVID-19 compared LPV/RTV in combination with the standard therapy versus the standard therapy alone. In the ITT-population, there was no difference in the time to clinical improvement, which was 16 days in both groups[8]). In this regard, the use of the drug in monotherapy can be recommended only if there are contraindications to the treatment with chloroquine, hydroxychloroquine, mefloquine.

Interferon beta-1b (IFN-β1b) has antiproliferative, antiviral, and immunomodulatory activity. In current clinical studies of MERS-CoV infection, IFN-β1b is used in combination with lopinavir+ritonavir. Previous *in vitro* studies have determined that it shows maximum activity in comparison with other interferons (IFN-α1a, IFN-α1b, and IFN-B1a). Due to the ability to stimulate the synthesis of anti-inflammatory cytokines, treatment with IFN-β1b can have a positive effect.

Umifenovir is a broad-spectrum antiviral drug with *in vitro* activity against different viruses, including coronaviruses. A randomized, single-center study (NCT0425885) was conducted in China to evaluate the efficacy of umifenovir in combination with the standard therapy, LPV/RTV in combination with the standard treatment versus the standard treatment without antiviral drugs in 86 hospitalized patients with mild to moderate COVID-19. The average elimination time of SARS-CoV-2 was 9.0 days in the LPV/RTV group, 9.1 in the Arbidol group, and 9.3 in the control group, with no statistical difference between them ($p = 0.981$). The frequency of cough resolution and CT improvement on days 7 and 14 did not show any statistical difference between the three groups ($P > 0.05$).

Depending on the severity of the disease, different types of therapy are of leading importance. Thus, in the case of a mild SARS-CoV-2 infection, the main directions of therapy are etiotropic and symptomatic. According to the Interim Guidelines of the MoH of Russia (IG) for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of

[8] Cao B., Wang Y., Wen D. et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020; (PubMed 32187464) (DOI 10.1056/NEJMoa2001282)

the study, recommended etiotropic therapy for mild form are chloroquine derivatives or a combination of umifenovir with an intranasal form of recombinant interferon-alpha. In moderate forms, pathogenetic therapy drugs are added to the treatment, so the detection of pneumonia according to the IG is an indication for anticoagulant therapy, low-molecular-weight heparins in preventive doses are indicated to all hospitalized patients. Also, in patients with moderate form and risk factors, the use of chloroquine derivatives in combination with azithromycin or lopinavir-ritonavir in combination with interferon beta-1b is recommended as etiotropic therapy. In severe forms of the disease in the pathogenesis of acute respiratory distress syndrome (ARDS) due to COVID-19, the main role is played by an excessive response of the immune system with a rapidly developing severe life-threatening cytokine release syndrome. In these conditions, it is extremely important to start preemptive therapy, the main drugs of which are IL-6 blockers. These include tocilizumab and sarilumab, which are well known as drugs for the treatment of rheumatoid arthritis. Drugs of preemptive anti-inflammatory therapy are used in combination with etiotropic therapy with chloroquine derivatives with azithromycin or lopinavir-ritonavir in combination with interferon beta-1b.

1.1.1.3. Introductory information on the treatment to be studied

Favipiravir was developed by Toyama Chemical Co., Ltd. as a new antiviral drug against the flu. The therapeutic effect of favipiravir is based on the effect on the replication process of various RNA viruses. When ingested, favipiravir is metabolized inside cells to the active metabolite of favipiravir ribosyl triphosphate (RTP), which binds to the RNA-dependent RNA polymerase of the influenza virus leading to its inhibition, which cause a termination of replication. In the case of other RNA viruses, the therapeutic effect can also be caused by a chain break during replication and the induction of lethal mutagenesis by embedding favipiravir RTP in the RNA of the next generation of the virus. Favipiravir has almost no effect on human DNA polymerases. IC50 inhibition of human RNA polymerase is three orders of magnitude higher compared to viral. In preclinical studies, no effect of favipiravir on the cardiovascular and respiratory systems was found. The sedative effect on the nervous system was detected only at exposures 6.6 times higher than those observed in clinical studies.

In vitro and *in vivo* studies have shown the antiviral activity of favipiravir against influenza virus and SARS-CoV-2 coronavirus.

After oral administration, favipiravir is rapidly and completely absorbed. The maximum concentration in blood plasma is achieved on average during [miss a period of time] in both healthy volunteers and in patients with a viral infection of the flu. Absolute bioavailability in preclinical studies reached 97.6% in rats. The effect of food intake on the pharmacokinetics of favipiravir is expressed in a slowdown in absorption, an increase in tmax and a decrease in C_{max}, while the AUC does not change significantly. Favipiravir is metabolised to the inactive metabolite of favipiravir hydroxide (M1) in the liver, primarily by aldehyde oxidase. Favipiravir is excreted primarily as a metabolite (M1) by the kidneys (>80% in various animals and >90% in humans), with bile excreted a small amount of an orally administered dose (<20%). The toxicity of the M1 metabolite was investigated and was found in all studies to be lower than that of favipiravir itself.

No genotoxicity or immunotoxicity of favipiravir was found in studies. In studies of phototoxicity, a certain effect of favipiravir was found, which was no higher than in the case of ciprofloxacin and completely resolved after discontinuation of the drug.

In December 2019, a new pneumonia caused by a previously unknown pathogen appeared in Wuhan, a city of 11 million people in Central China. The initial cases were related to a seafood market in Wuhan. The pathogen was soon identified as a new coronavirus (2019-nCoV, currently – SARS-CoV-2), which is closely related to the severe acute respiratory syndrome CoV (SARS-CoV) virus genetically. Currently, there is no special treatment for the new virus, so it is urgent to find effective antiviral drugs to fight the disease.

An effective approach to drug discovery is to test the efficacy of existing antiviral drugs in treating associated viral infections. SARS-CoV-2 belongs to the beta-coronavirus family, which also includes pathogens of severe acute respiratory syndrome SARS-CoV and Middle East respiratory syndrome MERS-CoV. Some drugs, such as ribavirin, interferon, lopinavir-ritonavir, and corticosteroids have been used in patients with SARS-CoV and MERS-CoV infections, but data on their efficacy is ambiguous. Antiviral activity against the SARS-CoV-2 clinical isolate was evaluated *in vitro* in the study by Wang M. et al. *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30:269-71* for ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, and two broad-spectrum antiviral drugs – remdesivir (GS-5734) and favipiravir (T-705). Standard analyses were performed to measure the effects of these compounds on cytotoxicity, virus yield, and infection rates. Favipiravir has been shown to effectively inhibit SARS-CoV-2 infection in Vero E6 cells (ATCC-1586) (half-maximal effective concentration (EC_{50}) = 61.88 mmol/l, half-maximal cytotoxic concentration (CC_{50})> 400 mmol/l, selectivity index (SI)> 6.46).

Data on the efficacy of favipiravir are currently obtained in 2 clinical studies. An open-label, prospective, randomized, multicenter study was conducted in 236 adults with COVID-19 pneumonia in China (ChiCTR2000030254): favipiravir (1600 mg orally twice daily on the first day, then 600 mg twice daily for 7–10 days) was associated with a higher rate of clinical recovery after 7 days compared to a control group receiving umifenovir (Arbidol®; 200 mg 3 times daily for 7–10 days) (61% vs. 52%). After stratification by disease severity, the rate of clinical recovery on day 7 in patients with moderate severity of COVID-19 pneumonia was 71% in the favipiravir group and 56% in the umifenovir group; the rate of clinical recovery in patients with severe COVID-19 pneumonia was 6% vs. 0%, respectively. In an open-label non-randomized study of patients with non-severe COVID19 in China (ChiCTR2000029600), the favipiravir group (1600 mg orally twice daily on day 1, then 600 mg orally twice daily on days 2–14) (n = 35) showed a reduction in the average period to virus elimination (4 vs. 11 days) and a higher level of improvement in chest CT results on day 14 (91 vs. 62%) compared to the control group of lopinavir/ritonavir therapy (n = 45); both groups also received the aerosol Interferon α-1B.

1.2. Names and descriptions of the study products

The study products include the study drug and the comparison drug.

Study drug:

Internal code: TL-FVP-t.
Trade name: FAVIPIRAVIR-TL.
INN: Favipiravir
Finished dosage form: film-coated tablets.
Dosage: 200 mg.
Manufacturer: R-Pharm JSC, Moscow, Russia.
MA Holder and Developer: Drugs Technology LLC, Russia.

The comparison drug:

Recommended "standard" etiotropic therapy in accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study.

Favipiravir is a broad-spectrum antiviral drug that blocks RNA replication of Riboviria viruses. The effect of favipiravir has been studied in the treatment of influenza and Ebola virus infections and has been shown to be effective in these diseases. The toxicity profile of favipiravir has been well studied. Favipiravir is a relatively low-toxicity drug. It is known to use favipiravir in doses up to 6000 mg per day with no serious dose-limiting toxic effects. The main adverse events are effects on the gastrointestinal tract, a decrease in neutrophils in the blood, an increase in liver enzymes, as well as an increase in uric acid in the blood, which are moderate and do not cause discontinuation of therapy, or a reduction in the dose

Currently, data on the efficacy of favipiravir in the new COVID 19 coronavirus disease are presented by two preclinical studies, which confirmed the potential of this drug for COVID19 therapy. However, these studies are not sufficient to evaluate the efficacy of this drug for this indication.

1.3. Summary of potential clinically relevant results obtained in preclinical studies, as well as results of clinical studies significant to this study

This section provides literature data on preclinical and clinical studies of favipiravir.

1.3.1. Preclinical study

1.3.1.1. Preclinical pharmacodynamics

1.3.1.1.1. Mechanism of action

Favipiravir is a chemical compound related to nucleoside analogues. When favipiravir penetrates into a cell, it is converted by intracellular enzymes to the active metabolite favipiravir ribosyl triphosphate

(RTP). Favipiravir RTP acts as a more effective substrate for influenza A virus as related to RNA polymerase compared to ATP and GTP, exceeding their activity by 30 and 19 times, respectively (Jin et al., 2013). *In vitro*, the inhibitory activity of favipiravir on influenza virus was studied on MDCK cells with the addition of purine and pyrimidine bases and their metabolites. It was found that when an excess of adenine, guaninine, adenosine, and guanosine was added to the cell culture, the antiviral activity of favipiravir was significantly reduced, while the addition of cytosine, thymine, and uracil had almost no effect on antiviral activity. Thus, favipiravir RTP is able to inhibit the enzymatic activity of the RNA-dependent RNA polymerase of the influenza type A virus (Furata et al., 2004), which leads to a violation of virus replication. However, the mechanism of a broad spectrum of antiviral activity of favipiravir against other types of RNA viruses is currently not studied enough. This can be the inhibition of RNA polymerase due to stronger binding to conservative domains of the enzyme, chain breakage during replication, as well as lethal mutagenesis due to improper embedding of favipiravir in the virus genome. It has been shown that favipiravir RTP is embedded in the growing RNA chain by viral RNA-dependent RNA polymerase, which in the future can lead to both RNA chain breakage and replication stop (Sangawa H. et al, 2013). An alternative mechanism is also shown in which embedding during replication leads to mutations in the next generation of viral particles that are incompatible with further reproduction of viruses of the next generations (lethal mutagenesis).

1.3.1.1.2. Primary pharmacodynamics

The antiviral activity of favipiravir against various types of viruses was studied *in vitro* using MDCK cells. Favipiravir has been shown to be active against all studied virus types (A-H1N1, H2N2, and H3N2; B and C) with an EC50 of 0.02 to 0.55 μg/ml. Activity on various clinical isolates was also studied. The activity of favipiravir against all studied types of viruses, including strains of pandemic avian (H5N1) and swine (H1N1) influenza, was shown.

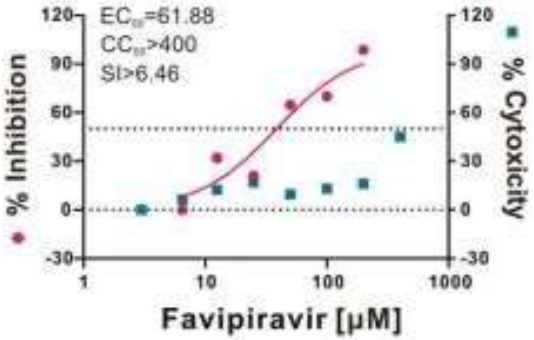
Favipiravir reduced viral activity against viral strains resistant to amantadine, oseltamivir, and zanamivir.

In Phase III clinical study, clinical isolates of various types of influenza were isolated and the antiviral activity of favipiravir against these strains was determined.

Table 1.1. Antiviral activity of favipiravir against clinical isolates of various types of influenza virus.

Type	Number of strains	EC_{50} (μg/ml)	
		Interval	Average
A (H1N1)a)	254	0.045–3.8	0.98
A (H3N2)	40	0.058–0.86	0.23
B	38	0.086–2.3	0.77

Figure 1.1. Antiviral activity *in vitro* on Vero E6 cells against the SARS-CoV-2 virus.



Of all the isolates studied, only two had EC50 greater than 3 μg/ml. In one case, the virus was not detected in the patient on the second day of taking favipiravir, and in another case – on the third day after the beginning of taking favipiravir.

Antiviral activity against the *Coronaviridae* family (SARS-CoV-2 virus) was studied *in vitro* on Vero E6 cells. The inhibitory concentration of favipiravir was from 60 to 100 μg/ml.

1.3.1.1.3. Preclinical pharmacodynamics *in vivo*

The therapeutic efficacy of favipiravir was studied in a mouse model after infection with various strains of influenza A(H3N2), A(H5N1) virus at a lethal dose. Favipiravir significantly increased the survival rate of mice after infection. When administered 100 mg/kg/day, the survival rate for almost all studied viral strains was 100%. At the same time, the survival rate in oseltamivir groups (20 mg/kg/day) was from 20 to 50%.

Moreover, the therapeutic effect was also demonstrated in a model of immunodeficient mice of the SCID line. After infection with the flu virus and taking the drug, the survival rate of mice was significantly higher in the favipiravir groups compared to oseltamivir.

1.3.1.1.4. Secondary pharmacodynamics

The effect of favipiravir on human DNA and RNA polymerases was studied in comparison with ribavirin. Favipiravir practically does not affect the activity of alpha, beta and gamma DNA polymerases. The inhibitory concentration IC_{50} of favipiravir for human RNA polymerase II is more than 1,000 times higher than IC_{50} for influenza virus RNA polymerase.

1.3.1.1.5. Pharmacological safety

Effects on the nervous system

In a study on mice, there was no effect on the central nervous system in the intended doses.

Effects on the cardiovascular system

Studies have been conducted to determine the effect of favipiravir on hERG K+ channels. Blocking of hERG channels by favipiravir was insignificant and observed

only at the highest studied concentrations. No effect of M1 on hERG was found in the entire studied concentration range.

Effects on the respiratory system

In a study on rats, no effects associated with the administration of favipiravir were observed.

1.3.1.1.6. Pharmacodynamic drug interactions

Based on the results of preclinical studies, the possibility of using favipiravir in combination with oseltamivir for the treatment of influenza has been substantiated. Thus, it has been shown that the combination of favipiravir with oseltamivir increases the antiviral activity of both drugs.

1.3.1.2. Preclinical pharmacokinetics

Absorption

The bioavailability of favipiravir was studied with a single administration on 2 types of rodents (mice, rats), with multiple administration – on rodents (mice, rats), dogs, and monkeys.

With a single intravenous and oral administration to mice, the concentrations of favipiravir and favipiravir hydroxide (M1) in blood plasma changed over time in a similar way, the bioavailability was 97.6%.

After a single oral administration to mice and rats, pharmacokinetic linearity was confirmed in these animal species.

In studies with multiple oral administration to dogs and monkeys, pharmacokinetic nonlinearity was demonstrated.

Distribution

After a single oral administration of ^{14}C-marked favipiravir at a dose of 20 mg/kg to male rats, the maximum levels of radioactivity were reached in 0.5–1 hours after administration, after a single oral administration of ^{14}C-marked favipiravir at a dose of 20 mg/kg to male monkeys, the maximum levels of radioactivity were reached in 0.5 hours after taking the drug.

In vitro protein binding of ^{14}C-marked favipiravir in mouse, rat, rabbit, dog, and human serum samples was almost constant in the study concentration range (0.3–30 μg/ml), and ranged from 8.3% to 10.9% in mouse serum, from 53.7% to 57.9% in rat serum, from 56.4% to 59.8% in rabbit serum, from 23.9% to 31.5% in dog serum, and from 53.4% to 54.4% in human serum.

Metabolism

Metabolites of favipiravir were studied in the plasma, urine, bile, feces, and tissues of rats and monkeys receiving a single oral dose of ^{14}C-marked favipiravir, as well as in the lungs of mice receiving a single oral dose of favipiravir.

To study the main metabolites, rats were given a single oral dose of 20 mg/kg of ^{14}C-marked favipiravir. In 0.5, 4 and 8 hours after taking the drug, favipiravir was detected mainly in plasma, brain and skeletal muscles (accounting for 84.36–93.53% of the received radioactivity), and favipiravir and M1 were mainly detected in the lungs, liver, kidneys, and testes. In the urine, feces, and bile 0–24 hours after taking the drug, M1 was mainly detected. In the urine, in addition to M1, M2 and favipiravir were detected, and in the bile, in addition to M1, favipiravir was detected.

Excretion

After a single oral administration of ^{14}C-marked favipiravir to rats and monkeys under fasting conditions, the cumulative elimination of radioactivity occurred mainly in the urine (83.06–91.14%), to a lesser extent in the feces. Excretion in the feces occurs mainly through the bile.

After a single oral administration of ^{14}C-marked favipiravir to rats during lactation, the maximum level of milk radioactivity was reached 4 hours after taking the drug, and then decreased over time.

1.3.1.3. Toxicological study

1.3.1.3.1. Single dose toxicity

Single dose toxicity has been studied in oral and intravenous administration in mice, as well as in oral administration studies in rats and dogs. Acute toxicity in monkeys was evaluated in a dose selection study

The approximate lethal dose was determined as >2000 mg/kg administered orally and intravenously in studies in mice, >2000 mg/kg administered orally in studies in rats, and >1000 mg/kg in dogs and monkeys.

1.3.1.3.2. Repeated dose toxicity

Repeated dose toxicity was evaluated in rats and dogs (administration within 1 month) and monkeys (administration within 2 weeks). The studies showed the following effects: effect on hematopoietic tissue (decrease in findings associated with erythrocytes and reduction in myelopoiesis), liver effects (increased alkaline phosphatase (AP), alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin, increased liver weight, and vacuolation in hepatocytes), and a toxic effect on the testicles. The effect on hematopoietic tissues was evaluated in repeated oral dose toxicity studies (within 3 days, 7 days, 2 weeks, 1 month, and 3 months) in rats.

To study the effect on hematopoietic tissues, 3-day, 7-day, and 2-week repeated oral dose toxicity studies were conducted in Sprague Dawley rats. There was detected a decrease in reticulocyte count, myeloid hypoplasia, a decrease in the myeloid-erythroid ratio (M/E), a decrease in erythrocyte count and hemoglobin concentration.

1.3.1.3.3. Genotoxicity

To assess genotoxicity, a reverse mutation test was performed on bacteria and an unscheduled DNA synthesis test was performed to repair damage in rat hepatocytes after oral administration (up to 2000 mg/kg/day). Both analyses showed negative results.

Favipiravir induced chromosomal aberrations in tests with cultured mammalian cells (Chinese hamster lung cells [CHL/IU]) and in a mouse lymphoma thymidine kinase test. Favipiravir-induced chromosomal aberrations were not caused by direct DNA damage, but by an unbalanced intracellular pool of nucleic acids

According to the results of a micronucleus test of myeloid tissue in rats, the risk of genotoxicity of favipiravir was considered low.

1.3.1.3.4. Carcinogenicity

Since favipiravir is intended to be used for a short period in clinical settings, no carcinogenicity studies have been conducted. In repeated dose toxicity studies, no precancerous lesions were observed; no accumulation or persistence of favipiravir in any specific tissue was detected; and in repeated dose toxicity studies, no local reactions associated with the prolonged presence of favipiravir or its metabolites in tissues were found.

1.3.1.3.5. Reproductive and ontogenetic toxicity

To assess reproductive and ontogenetic toxicity, studies of fertility and early embryonic development before implantation in rats, studies of embryonic development in mice, rats, and rabbits, as well as studies of prenatal and postnatal development in rats, including maternal function, and studies of embryonic development in monkeys were conducted.

In the study of fertility in rats, there was an effect on testes and sperm, as well as a decrease in fertility in males, and in females, anestrus was observed at a high dose. In studies of intrauterine development of the embryo, results indicating teratogenicity in mice, rats, rabbits, and monkeys were noted, as well as a decrease in the body weight of fetuses and the number of live fetuses.

1.3.1.3.6. Immunotoxicity

To study immunotoxicity, studies were conducted on the effect of favipiravir on the production of T-cell-dependent antibodies in rats and on the production of cytokines by mononuclear cells of human peripheral blood.

In the study in rats, no effect on the immune system was found.

The effect of favipiravir and hydroxypavipiravir (M1) on the production of LPS-induced cytokines (IL-1β, IL-6, IL-8, TNF-α) was also not detected.

1.3.1.3.7. Toxicity of metabolites

Since hydroxyphavipiravir M1 is the main systemic metabolite of favipiravir, M1 toxicity has also been studied in various studies, including genotoxicity studies, repeated oral dose toxicity studies in rabbits, and reproductive and ontogenetic toxicity studies in rats.

Tests of reverse mutations on bacteria, an *in vitro* test, and a study of micronuclei in mammalian cells (CHL/IU) showed the absence of genotoxicity of the M1 metabolite.

When studying toxicity of M1, rabbits were found to have yellowing fur, increased triglycerides, bile duct hyperplasia, and inflammatory cell infiltration in the portal region of the liver.

No effect of M1 on either maternal animals or embryo and fetal development was observed, NOAEL was defined as 100 mg/kg/day for both total toxicity for maternal animals and embryo and fetal development

1.3.1.3.8. Phototoxicity

To assess the phototoxicity of favipiravir, studies were conducted on mice and Guinea pigs. The results showed that favipiravir has phototoxicity. Therefore, for the clinical use of favipiravir, precautions are necessary to exclude exposure to sunlight.

1.3.1.3.9. Toxic effect on testes

To assess the toxic effect of favipiravir on the testes, 2-week repeated oral dose studies were conducted in mice, rats, and rabbits. According to research results, rodents (especially rats) were more sensitive to the toxic effect of favipiravir on the testes, compared with rabbits and monkeys. In monkeys treated with favipiravir at a dose of 150 mg/kg/day for a period corresponding to the period of sperm formation (6 weeks), no effect on the testes was found. In rats, the toxic effect of favipiravir on the testes developed at doses of ≥100 mg/kg/day (2-week treatment) and ≥60 mg/kg/day (6-week treatment), while both the severity and development of the toxic effect depended on the treatment period. The toxic effect of favipiravir on the testes of rats was reversible.

1.3.1.3.10. Juvenile toxicity

To assess the possibility of using favipiravir in children, 1-month repeated oral dose studies were conducted in juvenile dogs and rats. In a one-month repeated dose study, the dose of the drug at which death occurred in young dogs was lower than in adult dogs, there were also signs of toxicity typical for young animals, such as degeneration and necrosis of hepatocytes, degeneration and necrosis of the papillary heart muscle, atrophy and degeneration of skeletal muscle fibers, and gait disorders. Therefore, the use of favipiravir for children is not recommended.

1.3.2. Clinical study

No clinical studies of FAVIPIRAVIR-TL (TL-FVP-t) (Drugs Technology LLC, Russia) were conducted. Since TL-FVP-t developed by Drugs Technology LLC is a generic drug of favipiravir, it is expected that its properties will be identical to those of the original drug Avigan®, film-coated tablets (Toyama Chemical, Japan), to which TL-FVP-t fully corresponds in the qualitative and quantitative composition of active and inactive ingredients, as well as in the dosage form and dosage. In this regard, the following data on the effects of favipiravir in humans, obtained in studies on Avigan®.

1.3.2.1. Clinical pharmacology

1.3.2.1.1. Pharmacokinetics

The pharmacokinetics of favipiravir have been studied in healthy volunteers and in patients. Analyses of favipiravir and M1 metabolite were performed mainly by HPLC-MC.

Studies in healthy volunteers were conducted in the male population. The average age in studies in healthy volunteers was usually between 26 and 60 years. A repeated dose study was also conducted in the elderly. Most of the volunteers included in the study were Japanese. However, studies have also been conducted on the American population. Several pharmacokinetic studies have been performed in patients infected with various types of influenza virus.

Table 1.2. PK-parameters after a single dose of favipiravir in healthy volunteers.

Study	Dose, mg (after meals/under fasting conditions)	Dosage form:	n	C_{max} (µg/ml) (CV%)	T_{max} (h) min-max	$AUC_{(0-\infty)}$ (µg*h/ml) (CV%)	$T_{½}$ (h)
JP101 under fasting conditions	30 mg	Capsules	6	1.39 (17.9)	0.5 (0.25, 0.5)	2.58, (20.2)	1.3 ± 0.1
	90 mg	Capsules	6	4.06 (17.4)	0.5 (0.25, 0.75)	9.23 (12.6)	1.5 ± 0.1
	200 mg	Capsules	6	8.39 (11.1)	0.5 (0.5, 0.5)	19.67 (18.2)	1.5 ± 0.2
	400 mg	Capsules	6	16.59 (6.0)	0.5 (0.25, 0.75)	39.41 (16.0)	1.6 ± 0.2
	800 mg	Capsules	6	33.35 (22.6)	0.9 (0.5, 1)	113.15 (2.,6)	2.2 ± 0.3
	1600 mg	Capsules	6	78.61 (26.5)	0.6 (0.5, 0.75)	538.42 (9.7)	3.9 ± 0.3
JP102	400 (under fasting conditions)	Capsules	6	15.58 (26.5)	0.5 (0.5, 1)	42.11 (36.7%)	-
	400 (after meals)	Capsules	6	7.18 (21.1%)-	2.0 (1.5, 4)	36.64 (31.3%)	-
JP114	1200 (under fasting conditions)	Tablets	6	44.24 (23.7)	1 (0.5-3.0)	280.95 (59.3)	-
	1200 (after meals)	Tablets	6	40.29 (17.1)	2 (1.0–3.0)	271.58 (53.3)	-
JP110	400 (after meals)	Capsules		15.98 (14.3)	-	46.67 (26.4%)	-
	400 (after meals)	Tablets		16.22 (19.5)	-	46.39 (24.7%)	-
JP104 (Elderly)	400 (under fasting conditions)	Capsules		22.14 (20.9)	0.5 (0.5, 1)	58.63 (25.5)	
	800 (under fasting conditions)	Capsules		47.29 (12.4)	0.5 (0.5, 0.5)	149.93 (23.4)	
Note: ND – no data; n – number of subjects.							

The pharmacokinetic parameters for repeated administration in the intended therapeutic regimen of 1600/600 mg twice daily are shown in Figure 1.2

Figure 1.2. PK-curves after repeated administration of favipiravir in healthy volunteers.

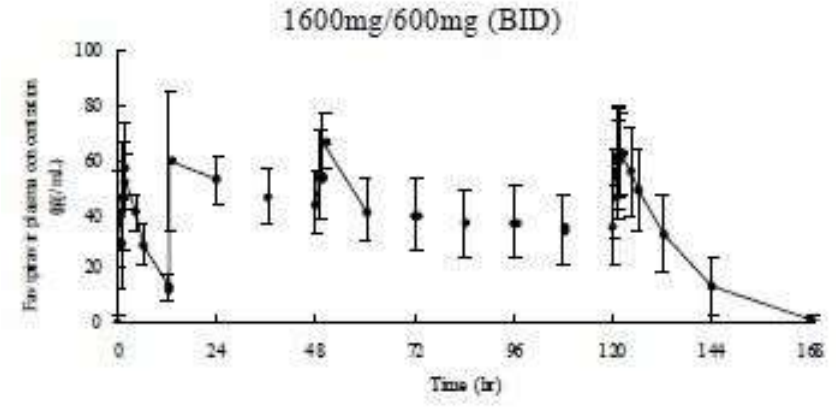


Table 1.3. PK-parameters after repeated administration of favipiravir in healthy volunteers (Japanese).

Strength		C_{max} (µg/ml)	AUC (µg*h/ml)	T_{max} (h)	$T_{1/2}$ (h)
1600 mg/600 mg twice daily	Day 1	64.56	446.09	1.5	4.8
	Day 6	64.69	553.98	1.5	5.6

Absorption

Favipiravir is well absorbed after oral administration. The maximum concentration in blood plasma is reached in less than an hour after taking under fasting conditions. Food intake slightly slows down absorption, the maximum concentration is reached within two hours after administration. At the same time, food intake practically does not affect the AUC. The JP102 study showed a decrease in C_{max} by approximately 50% when taken after meals. However, data from calculations of the absorption constant and simulation of the regime with repeated doses showed that the effect of reducing C_{max} with food is decreased with repeated doses. Nevertheless, it is recommended to take favipiravir no earlier than 30 minutes after meals. In the JP101 study, it was determined that more than 90% of the administered dose of favipiravir is excreted through the kidneys. Thus, bioavailability in healthy volunteers can be considered more than 90%.

After absorption, favipiravir binds to blood proteins, mainly blood plasma, 55% of binding to plasma proteins (albumin and alpha-1 acid glycoprotein), and 28–37% of binding to plasma proteins for the main M1 metabolite.

Distribution and metabolism

Favipiravir is a drug with complex nonlinear pharmacokinetics. The pharmacokinetic profile of favipiravir has been studied in dose escalation studies in healthy Japanese volunteers. After a single dose, the maximum plasma concentration was reached within 2 hours. Plasma concentrations decreased rapidly due to intensive metabolism. The half-life was from 1.5 to 4 hours. After repeated doses, the time to reach the maximum plasma concentration and the half-life increased. American volunteers had a lower plasma concentration of about 50% compared to Japanese volunteers (Madelain et al., 2016). The main enzyme involved in the elimination of favipiravir is aldehyde oxidase, which converts favipiravir to the inactive M1 metabolite.

Favipiravir is metabolized primarily in the liver with the participation of the enzyme aldehyde oxidase (AO), and to a lesser extent xanthine oxidase to hydroxyphavipiravir M1. In cells, favipiravir is metabolized to ribosyl favipiravir and favipiravir ribosyl triphosphate, which is an active metabolite. In an *in vitro* study of the metabolite profile of ^{14}C-marked favipiravir (30, 300 mmol/l) in frozen human hepatocytes (1×10^6 cells/ml), unchanged favipiravir was the main marked substance detected, followed by favipiravir hydroxide (M1). In the blood plasma, favipiravir and M1 are mainly determined.

Excretion

Pharmacokinetics analysis based on data from patients who received a single dose of favipiravir showed that the average half-life is about 1.5–2 hours. Favipiravir is excreted primarily as an M1 metabolite in the urine (>90%).

Pharmacokinetics in special populations Patients with renal impairment

Since favipiravir is mainly excreted through the kidneys, the pharmacokinetic parameters of patients with moderate renal impairment were evaluated. It was found that C_{max} and AUC in patients with renal impairment increased by 3 and 2 times, respectively, due to reduced clearance of M1 through the kidneys. At the same time, no adverse events were found in these patients, except for a moderate increase in the blood uric acid.

Patients with hepatic impairment

Since the metabolism of favipiravir results in irreversible inhibition of aldehyde oxidase, the effect of hepatic impairment on the pharmacokinetics and metabolism of favipiravir has been studied.

When oral administration of favipiravir to patients with mild to moderate hepatic impairment (Child-Pugh classification A and B, 6 people in each) of 1200 mg twice daily for 1 day followed by administration of 800 mg twice daily for 4 days, compared with healthy adult volunteers, C_{max} and AUC on day 5 were higher by about 1.6 times and 1.7 times, respectively, in patients with a mild hepatic impairment and 1.4 times and 1.8 times – with moderate. When oral administration of favipiravir to patients with severe hepatic impairment (Child-Pugh classification C, 4 subjects) at a dose of 800 mg twice daily for 1 day followed by 400 mg twice daily for 2 days, C_{max} and AUC were approximately 2.1 times and 6.3 times higher on day 3, respectively, compared to healthy adult volunteers.

Sex

The safety analysis in the subgroups did not reveal any clinically significant differences between the sexes.

Race and weight

Comparison of pharmacokinetics data for single administration in populations of healthy Japanese and American volunteers revealed a decrease in C_{max} and AUC in the American population. This difference was attributed to a difference in the weight of the volunteers who participated in the study. However, when normalizing the pharmacokinetic parameters for body weight (60 kg), the differences in pharmacokinetic parameters did not differ significantly.

A comparison of studies with repeated administration showed that on day 1, C_{max} and AUC in Japanese volunteers were higher than in American, while CL/F in Japanese volunteers was lower than in American. When normalized to a body weight of 60

kg, these differences decreased. On day 7 or 5 (final dose), C_{max} and AUC in Japanese volunteers were higher than in American, while CL/F and Vd/F in Japanese volunteers were lower than in American, as on day 1. Normalization of body weight to 60 kg reduced these differences, but AUC remained higher, CL/F was lower, and Vd/F was slightly lower in Japanese volunteers, compared to American. The ratio of AUC values for M1 and favipiravir was lower in Japanese volunteers. The decrease in this ratio after administration of the final dose was also greater in Japanese volunteers.

Elderly patients

When elderly volunteers took favipiravir, an increase in C_{max} and AUC was observed compared to a group of young volunteers. The difference increased with repeated doses, reaching 30% and 50%, respectively. At the same time, in elderly patients, clearance decreased and the half-life increased.

1.3.2.1.2. Pharmacodynamics

Secondary pharmacodynamics

Since QT prolongation was detected in preclinical studies in dogs, this parameter was evaluated when taking favipiravir in healthy volunteers. In a 4-time, 4-period, cross-sectional study of the effect of favipiravir on heart rate, 56 volunteers took a single 1200 mg or 2400 mg of favipiravir, placebo, or 400 mg of moxifloxacin (positive control). In the favipiravir groups, there was no change in QTcF (QT corrected interval) from the average (ΔQTcF) compared to placebo, while in the moxifloxacin group, the values were 5–15 ms higher. The difference in ΔQTcF between volunteers taking the drug and volunteers taking placebo (ΔΔQTcF) peaked after 3 hours after taking favipiravir at a dose of 1200 mg (0.83 [-1.33; 3.00] ms), 6 hours after taking favipiravir at a dose of 2400 mg (0.50 [-1.88; 2.88] ms), with a maximum value below 4 ms any time. Thus, there was no significant effect of favipiravir on the heart rate.

1.3.2.1.3. Drug interaction

Drug interactions were studied in combinations of favipiravir with theophylline and oseltamivir, as well as with raloxifen and hydralazine. Pharmacokinetic studies have not revealed the effect of both favipiravir on the pharmacokinetics of theophylline, and the effect of theophylline on the pharmacokinetics of favipiravir when taken repeatedly. There was also no cross-effect on pharmacokinetics between favipiravir and oseltamivir. In all cases, the ratio of C_{max} and AUC when used in monotherapy and in combination for all the studied drugs was in the range of 0.8–1.2.

In a study on healthy volunteers using acetaminophen and favipiravir together, favipiravir increased the AUC of acetaminophen and acetaminophen glucoronide by 20% and 23–34%, respectively. At the same time, the AUC of acetaminophen sulfate decreased by 29–35%, and the excretion of acetaminophen and acetaminophen glucoronide through the kidneys increased.

Also, according to the data on the metabolism of favipiravir, there is a risk of drug interaction with the following drugs.

Table 1.4[9]. Drug interactions of favipiravir.

Drug	Symptoms and signs	Mechanism and risk factors
Pyrazinamide	Increased uric acid levels in the blood. When taking 1.5 g of pyrazinamide with favipiravir according to the regimen 1200/400 mg twice daily, the uric acid level was 11.6 mg/dl with pyrazinamide monotherapy and 13.9 mg/dl in combination with favipiravir	Reabsorption of uric acid in the renal tubules has an additive effect
Repaglinide	The concentration of repaglinide in the blood may increase, which may lead to repaglinide-related side effects	Favipiravir weakly inhibits CYP2C8, which can lead to an increased repaglinide level in the blood
Famciclovir Sulindak	The efficacy of these drugs may be reduced	Inhibition of aldehyde oxidase by favipiravir may reduce the level of active forms of these drugs

1.3.2.2. Clinical efficacy and safety

1.3.2.2.1. The efficacy in registration studies

The clinical development program for favipiravir for the treatment of influenza virus consisted of a major Phase II study, JP205, and two Phase III studies, JP312 and JP313.

JP205 study

To study the efficacy and safety of favipiravir in Japanese patients with seasonal influenza virus infection, a double-blind parallel group active-controlled study was conducted. Patients were randomized into three groups: two favipiravir groups with different dosage regimens and the oseltamivir phosphate group. All patients in the favipiravir groups took the drug no earlier than 30 minutes after meals.

The median (95% CI) duration of pyrexia (primary efficacy endpoint) was 40.2 hours (31.5; 42.8) in the high-dose group, 42.2 hours (37.3; 62.1) in the low-dose group, and 28.8 hours (19.8; 41.5) in the oseltamivir phosphate group.

JP312 study

To study the efficacy and safety of favipiravir in patients with influenza virus infection, a double-blind parallel group active-controlled study was conducted. Favipiravir was taken orally for 5 days in accordance with the following dosage regimen: at a dose of 1200 mg (first dose) and at a dose of 400 mg (second dose) on day 1, and then at a dose of 400 mg twice daily from day 2 to day 5. In

[9] Zhao Y. *et al.* Favipiravir inhibits acetaminophen sulfate formation but minimally affects systemic pharmacokinetics of acetaminophen. Br. J. Clin. Pharmacol. 80, 1076–1085 *(*2015*).*

the oseltamivir phosphate group, drug was administered orally at a dose of 75 mg twice daily for 5 days.

The median time to relief of major flu symptoms (95% CI) was the primary endpoint in the efficacy analysis and was 55.4 (50.4, 62.5) hours in the favipiravir group and 47.8 (44.4, 55.8) hours in the oseltamivir phosphate group.

US205 study

In a placebo-controlled, randomized, double-blind parallel study of patients in the United States, 134 patients took favipiravir at a dose of 1000 mg twice daily on the first day and 400 mg twice daily on days 2–5 (the low-dose group), 195 patients took favipiravir at a dose of 1200 mg twice daily on the first day and 800 mg twice daily on days 2–5 (the high-dose group), and 201 patients took placebo.

The average time for relief of flu symptoms (the primary efficacy criterion) was 100.4 (82.4, 119.8) hours in the low-dose group, 86.5 (79.2, 102.1) hours in the high-dose group, and 91.9 (70.3, 105.4) hours in the placebo group. A pairwise comparison of the placebo groups of low and high doses did not reveal a statistically significant difference ($p > 0.05$, Gehan-Wilcoxon criterion).

US213 study

In a placebo-controlled, randomized, double-blind, parallel, comparative study of patients in the United States, 184 patients took favipiravir at 1800 mg twice daily on day 1 and 800 mg twice daily on days 2–5, 182 patients took favipiravir at 2400 mg + 600 mg twice daily on day 1 and 600 mg three times daily on day 2–5 (high-dose group), and 201 patients took placebo. The pharmacokinetics and safety of these regimens were also studied.

The time to stop flu symptoms was 82.3 hours in the twice-daily group and 97.3 hours in the placebo group. Pairwise comparison showed a statistically significant difference between the twice-daily and placebo groups ($P = 0.010$, Gehan-Wilcoxon test). However, there was no statistically significant difference between the three-times-daily and placebo groups.

A comparison of the pharmacokinetics of the American and Japanese patient populations showed that the expected effective dose may be higher in the American population than in the Japanese population.

Study of the use of favipiravir in combination with oseltamivir for the treatment of complicated influenza virus infection in patients in critical condition

This study involved patients with a confirmed RT-PCR diagnosis of influenza virus infection, respiratory failure ($PaO_2/FiO_2 \leq 300$ mm Hg), or mechanical ventilation, who had no more than 10 days since the onset of symptoms.

Patients in the favipiravir group (40 patients) received oseltamivir at a dose of 75 mg twice daily and favipiravir at a dose of 1600 mg twice daily the first day and 600 mg 2–10 days. One patient received 1,800 mg twice daily on the first day and 800 mg twice daily on the following days. Patients in the oseltamivir monotherapy group (128 patients) received oseltamivir at a dose of 75 mg twice daily.

The combination of favipiravir with oseltamivir significantly improved the course of severe cases of viral influenza infection

Table 1.5. Efficacy indicators of the combination of favipiravir with oseltamivir in severe cases of viral influenza infection.

Outcome	Favipiravir+ oseltamivir (N = 40)	Oseltamivir (N = 128)	p value
In-hospital mortality	7 (17.5)	36 (28.1)	0.1789
Mortality on day 28	7 (17.5)	34 (26.6)	0.2441
Clinical improvement			
Days from the beginning of the therapy to clinical improvement	12.0 (9.5, 15.0)	12.0 (8.0, 19.0)	0.0477
Nosocomial pneumonia	9 (22.5)	65 (50.8)	<0.001
ICU length of stay	12.0 (7.0, 20.5)	10.5 (5.7, 19.4)	0.1811
Hospital length of stay	15.5 (12.0, 21.0)	16.0 (10.0, 24.5)	0.8844
Days from hospitalization to discharge	17.0 (12.0, 21.0)	17.5 (11.5, 26.0)	0.7408
Days from hospitalization to death	13.0 (11.0, 17.0)	12.0 (9.5, 22.5)	0.6799
Scale category on day 7	5.0 (4.0, 5.5)	5.0 (4.0, 6.0)	0.2225

1.3.2.2.2. Efficacy of the treatment of the novel COVID-19 coronavirus disease

Efficacy of favipiravir in the treatment of the novel COVID-19 coronavirus disease has been studied in two clinical studies:

1) in comparison with the umifenovir (n = 236) (C. Chen et al., 2020) and

2) in combination therapy with alpha-interferon compared to the combination of lopinavir/ritonavir + interferon alpha (n = 80) (Cai Q. et al., 2020).

A clinical study of favipiravir versus the combination of lopinavir/ritonavir + interferon alpha (n = 80) (Cai Q. et al., 2020)

An open-label non-randomized comparative study of favipiravir versus lopinavir/ritonavir (LPV/RTV) in patients with COVID-19 coronavirus disease involved 80 people with a laboratory-confirmed diagnosis of COVID-19. In the study group, patients received favipiravir orally according to the following regimen (day 1: 1600 mg twice daily; days 2–14: 600 mg twice daily with additional inhalation of the aerosol interferon (5 million units twice daily). Patients in the control group were screened after receiving previously prescribed LPV/RTV therapy. Patients in the control group received LPV/RTV for 14 days at a dose of 400 mg/100 mg twice daily with additional inhalation of the aerosol interferon (5 million units twice daily). The used endpoints were changes on

computed tomography scan of the lungs (CT), virus C elimination, and safety assessment.

The following criteria were used for inclusion in the study: age 16–75 years, a positive test (PCR) for SARS-CoV-2, the period from the onset of symptoms to the beginning of therapy no more than 7 days, and no problems with swallowing tablets. Patients in a serious condition with one of the following manifestations were not included: resting respiratory rate greater than 30 per minute, oxygen saturation less than 93%, and an oxygenation index (OI) < 300 mm Hg (1 mm Hg = 133.3 Pa), respiratory failure, shock, a condition requiring the involvement of the intensive care unit.

The favipiravir group included 35 patients, and the LPV/RTV group included 45. The patient statuses are shown in Figure 4.5 below. The comparison groups were generally balanced by the initial characteristics of the patients. The average age of patients in the favipiravir group was 43 (35.5–59) years, in the LPV/RTV group — 49 (36–61). In the favipiravir group, 14 (40.0%) were men, in the group – 21 (46.7%). The median points on the CT assessment scale were: 12 for the favipiravir group 12 (4.0–14.0), 10 in the LPV/RTV group (4.5–13.5). Among the symptoms, the majority of patients had fever – in 22 (62.9%) and 37 (82.2%) patients from the favipiravir group, respectively; less often – cough in 12 (34.3%) and 10 (22.2%), headache/myalgia in 3 (8.6%) and 5 (11.1%), and rarely chills, diarrhea and nasal congestion/sore throat.

The number of patients who remained positive for SARS-CoV-2 decreased significantly faster in the favipiravir group. The median time to virus elimination in the favipiravir group was 4 days (MCD: 2.5–9) versus 11 days (MCD: 8-13) in the LPV/RTV group (P < 0.001).

Lung CT scans also showed a faster improvement in the favipiravir group compared to lopinavir at all stages of evaluation. On day 14 of therapy, improvement was observed in 91.43% of patients in the favipiravir group versus 62.22% in the lopinavir group. To assess changes in CT scans, a multiple logistic regression analysis was performed to identify independent factors that affect their changes. The authors selected changes on chest CT (0 = no changes or worsening, 1 = improvement) as the dependent variable, and the following independent variables: age, underlying disease, and severity of the disease at baseline. The result showed that there were two statistically significant factors in the model: antiviral therapy (odds ratio (OR) = 3.190, CI 95% (CI) = 1.041–9.78) and fever (OR = 3.622, CI 95% = 1.054– 12.442). This means that antiviral therapy and fever were independent factors that affected CT scans. Patients who received favipiravir had objectively greater pronounced improvement on chest CT compared to the LPV/RTV group (see Table 1.6.).

Lung CT scans also showed a faster improvement in the favipiravir group compared to lopinavir at all stages of evaluation. On day 14 of therapy, improvement was observed in 91.43% of patients in the favipiravir group versus 62.22% in the LPV/RTV group. The overall tolerability of therapy in the favipiravir group was higher than 11% of adverse drug reactions versus 55% in the lopinavir group.

Figure 1.3. The Kaplan-Meyer curve of the time to virus elimination for each group.

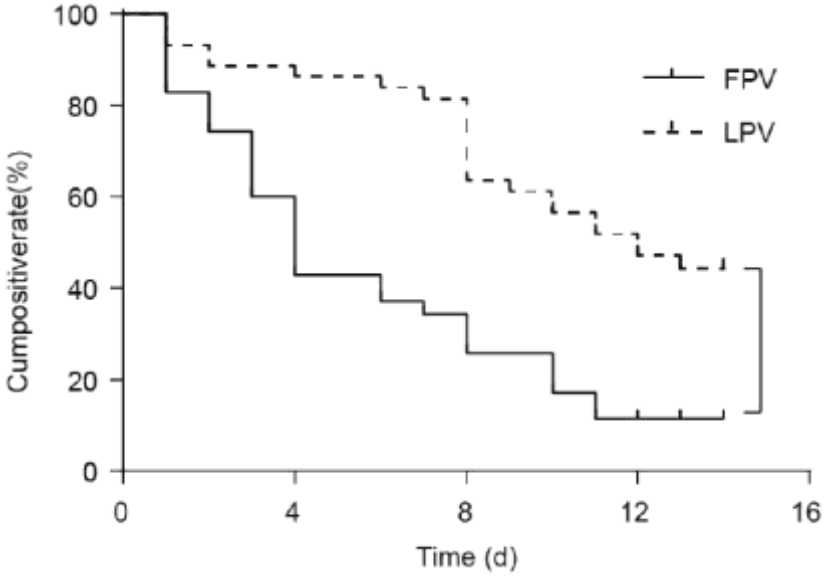


Table 1.6. Dynamics of CT changes in patients with COVID-19 in the favipiravir and LPV/RTV groups.

CT changes	Patients with COVID-19 (n = 80)		p value
	Favipiravir (n = 35)	LPV/RTV (n = 45)	
Day 4 after the beginning of the therapy			
Improvement	8 (22.8%)	8 (17.78%)	0.42
Worsening	9 (25.71%)	15 (33.33%)	
No changes	18 (51.43%)	22 (48.89%)	
Day 9 after the beginning of the therapy			
Improvement	18 (56.25%)	16 (35.55%)	0.11
Worsening	8 (25.00%)	116 (35.55%)	
No changes	6 (18.75%)	13 (28.90%)	
Day 14 after the beginning of the therapy			
Improvement	32 (91.43%)	28 (62.22%)	0.004
Worsening	1 (3.23%)	9 (20.00%)	
No changes	2 (6.45%)	8 (17.78%)	

Overall tolerability of therapy in the favipiravir group was better: 11% of adverse drug reactions versus 55% in the LPV/RTV group.

A clinical study of favipiravir versus umifenovir (n = 236) (Chen C. et al., 2020)

A prospective open-label multicenter randomized study of the efficacy of favipiravir compared with umifenovir for the treatment of the novel coronovirus infection involved 236 patients with COVID-19: 116 patients (98 with moderate form and 18 with severe) in the favipiravir group and 120 in the umifenovir group (111 with moderate form and 9 with severe).

The study included patients older than 18 years with a clinical picture of COVID-19, who had symptoms less than 12 days before the start of therapy. A positive test for viral RNA was not a criterion for inclusion in the study, due to the low accuracy of determining in the available tests. Only 54 (46.55%) patients in the favipiravir group and 46 (38.33%) in the umifenovir group who had a characteristic clinical picture for the novel COVID-19 coronovirus infection tested positive for SARS-CoV-2. Chest CT was performed for 116 patients in the favipiravir group and 119 in the umifenovir group, COVID-19-related pneumonia was diagnosed in 112 (96.55%) and 114 (95.80%) patients according to diagnostic criteria (p = 0.7635). Patients in severe condition with a life expectancy of less than 48 hours were excluded.

In the favipiravir group, 59 (50.86%) were male and 57 (49.14%) were female, 87 (75.00%) were <65 years old and 29 (25.00%) were ≥65 years old, 36 (31.03%) patients had hypertension, and 14 (12.07%) had diabetes mellitus. In the umifenovir group, 51 (42.50%) were male, and 69 (57.50%) were female, 79 (65.83%) were <65 years old and 41 (34.17%) were ≥65 years old, 30 (25.00%) had hypertension, and 13 (10.83%) had diabetes. In general, there were no significant differences in the main characteristics of patients between the two groups. However, a slightly higher number of patients with severe and critical condition were in the favipiravir group (16 with severe form + 2 in critical condition) compared to the umifenovir group (8 + 1, respectively) (p = 0.0658).

Patients received favipiravir orally according to the following regimen (day 1: 1600 mg twice daily; days 2–10: 600 mg twice daily). In the control group, patients received umifenovir 200 mg three times daily for 7–10 days.

The primary endpoint was an improvement in the clinical picture, expressed in the following criteria: temperature ≤36.6 °C; respiratory rate ≤24/min; oxygen saturation ≥98% without the use of an oxygen mask; slight cough or lack of it. Secondary endpoints: time from randomization to temperature reduction, time from randomization to cough relief, frequency of oxygen therapy, mortality, frequency of respiratory failure (SpO_2≤90% or PaO_2/FiO_2 < 300 mm Hg without oxygen inhalation). Also on day 3 and 7, blood chemistry test, coagulation test, SARS-CoV-2 test, and computed tomography were performed.

Improvement of the clinical picture on day 7 was observed in 51.67% (62/120) in the umifenovir group and 61.21% (71/116) in the favipiravir group; for patients with moderate form – in 55.86% (62/111) in the umifenovir group versus 71.43% (70/98) in the favipiravir group; for patients with severe form – 0% (0/9) in the umifenovir group and 5.56% (1/18) in the favipiravir group; for patients with hypertension and/or diabetes – 51.43% (18/35) in the umifenovir group and 54.76% (23/42) in the favipiravir group.

Thus, improvement was observed mainly in groups of patients with moderate form.

Table 1.7. Comparison of indicators of clinical improvement on day 7.

Variables	Favipiravir	Umifenovir	Frequency difference (95% CI)	p value
All patients	N = 116	N = 120	-	-
Clinical improvement, n (%)	71 (61.21)	62 (51.67)	0.0954 (-0.0305, 0.2213)	0.1396

Variables	Favipiravir	Umifenovir	Frequency difference (95% CI)	p value
Patients with moderate form	N = 98	N = 111	-	-
Clinical improvement, n (%)	70 (71.43)	62 (55.87)	0.1557 (0.0271, 0.2843)	0.0199
Patients with severe form	N = 98	N = 111	-	-
Clinical improvement, n (%)	1 (5.56)	0 (0,00)	0.0556 (-0.0503, 0.1614)	0.4712
Patients with hypertension or diabetes	N = 42	N = 35	-	-
Clinical improvement, n (%)	23 (54.76)	18 (51.43)	0.0333 (-0.1904, 0.2571)	0.7704

At the screening in the favipiravir group, 71/116 (61.2%) patients had hyperthermia and 78/116 (67.2%) – cough; and in the umifenovir group, 74/120 (61.7%) patients had hyperthermia and 73/120 (60.8%) – cough. Although the incidence of hyperthermia and cough did not differ between the two groups at the screening. The study showed that the time to control hyperthermia and reduce cough in the favipiravir group was significantly shorter than in the umifenovir group (p <0.0001) (Fig. 4.7). The frequency of supplemental oxygen therapy (SOT) used *de novo* or non-invasive ventilation (NIV) was 27/120 (22.50%) in the umifenovir group and 21/116 (18.10%) in the favipiravir group (P = 0.4015) (DRR: -4.40%, CI 95%:

-14.64% ~ 5.85%). For all cases included in this study, all-cause mortality was 0. The number of cases of respiratory failure was 4 in the umifenovir group and 1 in the favipiravir group (p = 0.3700). At the screening, there were 15/120 (12.5%) patients with dyspnea in the umifenovir group and 13/116 (11.2%) in the favipiravir group (p = 0.7588). Further analysis showed that new cases of dyspnea during the course of treatment were observed in 4/116 (3.45%) patients in the favipiravir group and in 14/120 (11.67%) patients in the umifenovir group (p = 0.0174). Therefore, it can be concluded that when considering secondary endpoints, favipiravir significantly reduced the time to relieve coughing and hyperthermia. Favipiravir was not associated with a decrease in the frequency of SOT or NIV, shortness of breath, overall frequency of respiratory failure, ICU hospitalization, or all-cause mortality.

Table 1.8. Comparison of other secondary clinical endpoints in the study groups.

Variables	Favipiravir	Umifenovir	Frequency difference (95% CI)	p value
All patients	N = 116	N = 120	-	-
SOT or NIV, n (%)	21 (18.10)	27 (22.50)	- 0.0440 (-0.1464, -0.0585)	0.4015
Patients with hypertension or diabetes	N = 42	N = 35	-	-

Variables	Favipiravir	Umifenovir	Frequency difference (95% CI)	p value
SOT or NIV, n (%)	9 (21.43)	10 (28.57)	- 0.0714 (- 0.2658, -0.1230)	0.4691
All-cause mortality, n (%)	0 (0,00)	0 (0,00)	-	-
Shortness of breath after the beginning of the therapy, n (%)	4 (3.45)	14 (11.67)	-	0.0174
Respiratory failure, n (%)	1 (0.86)	4 (3.33)	-	0.3700

1.3.2.2.3. The safety of favipiravir as part of the registration studies and post-marketing use

Safety assessment of favipiravir in patients with the flu

Safety assessment was performed in a population of 501 patients who received favipiravir in Phase II (JP205), Phase III (JP312), and pharmacokinetics studies in patients with viral infection (JP313). The results of the analysis are presented in table 4.10 below.

Relatively common adverse events (AEs) in the proposed group of doses of favipiravir were diarrhea (6.3%, 25 of 394 patients) and increased uric acid levels in the blood (5.6%, 22 of 394 patients). As for adverse drug reactions (ADR), the causal relationship of which with the study drug is not excluded, relatively frequent reactions in the proposed group of doses were elevated uric acid in the blood (5.6%, 22 of 394 patients) and diarrhea (4.1%, 16 of 394 patients). The frequency of increased blood uric acid levels in the suggested favipiravir dose group was higher than in the low-and high-dose favipiravir groups (JP205), and it elevated with the increasing favipiravir dose. The incidence of diarrhea was comparable to that in the oseltamivir group (6.7%, 29 of 433 patients). The incidence of nausea and vomiting, relatively common adverse events in the oseltamivir group, was 3.0% (13 of 433 volunteers) and 2.3% (10 of 433 volunteers), respectively, while in the group of the suggested dose of favipiravir, it was 0.8% (3 of 394 volunteers) and 0.5% (2 of 394 volunteers), respectively, which was lower than in the oseltamivir group.

No deaths were reported. Serious AEs (SAEs) included pneumonia in 1 patient in the low-dose favipiravir group, hematochezia in 1 patient in the high-dose favipiravir group, cellulite in 1 patient in the suggested-dose favipiravir group, and spontaneous abortion in 1 patient in the control group. With the exception of hematochezia, the cause-and-effect relationship of these AEs with the study drug was excluded, and the outcome of all AEs was resolved. AEs leading to discontinuation of the treatment included dizziness in 1 patient in the high-dose favipiravir group, infectious enteritis and eczema in 1 patient in the suggested favipiravir dose group, as well as gastroenteritis in 2 patients, and herpes simplex, vomiting, corono, eczema, itching and rash in 1 patient (some AEs occurred in the same patient) in the control group. The causal relationship of all AEs, except for infectious enteritis in the proposed group of doses of favipiravir and herpes simplex in the control group, with the study drug was not excluded, but all AEs were resolved. The most frequent AE was an increase in the level of uric acid in the blood, which occurred more often than in the control group. The frequency of this AE tended to

elevate with increasing doses. Although diarrhea was common in the favipiravir group, its frequency was comparable to that in the oseltamivir group.

Table 1.9. Adverse events and adverse drug reactions reported in ≥2% of patients with the influenza virus infection (data from the combined analysis of Phase II and III clinical studies (JP205, JP312, and JP313) in adults.

	Adverse event				**Adverse drug reaction**			
Total dose (mg)	**Favipiravir**			**Oseltamivir**	**Favipiravir**			**Oseltamivir**
	Low dose	**High dose**	**Suggested dose**		**Low dose**	**High dose**	**Suggested dose**	
	2800	**3600**	**4800**		**2800**	**3600**	**4800**	
Patients (n)	52	55	394	433	52	55	394	433
AE	20 (38.5%)	22 (40.0)	124 (31.5)	119 (27.5)	20 (38.5)	22 (40.0)	124 (31.5)	119 (27.5)
AEs for which the relationship could not be established	8 (15.4%)	14 (25.5)	78 (19.8)	70 (16.2)	8 (15.4)	14 (25.5)	78 (19.8)	70 (16.2)
AEs by organ system class								
Violations by the gastrointestinal tract								
diarrhea	4 (7.7)	8 (14.5)	25 (6.3)	29 (6.7)	3 (5.8)	5 (9.1)	16 (4.1)	24 (5.5)
nausea	-	1 (1.8)	3 (0.8)	13 (3.0)	-	-	3 (0.8)	11 (2.5)
vomiting	2 (3.8)	1 (1.8)	2 (0.5)	10 (2.3)	1 (1.9)	1 (1.8)	1 (0.3)	7 (1.6)
Deviations in laboratory findings								
Increased urea levels	-	1 (1.8)	22 (5.6)	1 (0.2)	-	1 (1.8)	22 (5.6)	1 (0.2)
Note: Oseltamivir phosphate was taken at a dose of 75 mg/day, twice daily for 5 days.								

Increased uric acid levels

According to preclinical data, favipiravir and its M1 metabolite inhibit OAT1 and OAT3 transporters, which leads to a decrease in renal uric acid secretion. M1 also increases uric acid reabsorption through the URAT1 transporter, resulting in reduced uric acid secretion.

The AEs associated with uric acid levels in the blood and urine after taking favipiravir are listed in the table below. The incidence of increased uric acid levels in the blood (hyperuricemia) was 9.9% in healthy adult Japanese volunteers (24 out of 242, 26 AEs) and 4.8% in patients with influenza virus infection (24 out of 501, 24 AEs), and was previously observed in 5.8% (23 out of 394, 23 AEs) of patients receiving the suggested dose of favipiravir. There were no cases of increased uric acid levels in the blood of healthy adult volunteers in the United States. AE of decrease in uric acid levels in the urine was observed in 1.7% of healthy Japanese volunteers (4 out of 242, 4 AEs), and an increase in blood uric acid levels was also observed in all 4 volunteers. Neither subjective symptoms associated with changes in uric acid levels in the blood, nor an attack of gout were reported in any patient, including those who had these AEs.

Changes in the level of uric acid in the blood compared to the baseline level in patients with influenza virus infection over time during the study are shown in the figure below. Changes in blood uric acid levels in patients receiving favipiravir tended to increase slightly on day 3 in both males and females receiving any dosage regimen, and this

change tended to resolve 1 day after the end of the treatment. Females had changes in uric acid levels in the blood more often than males. The number of male and female patients with large changes in uric acid levels in the blood increased with increasing the total dose. In patients receiving oseltamivir, uric acid levels in the blood remained almost unchanged in both males and females.

Effect on testes

Since favipiravir has shown testicular toxicity in preclinical studies, favipiravir was evaluated for testicular toxicity in clinical studies in healthy volunteers in the United States. 116 volunteers received favipiravir at a dose of 1200 mg on the first day twice daily and 800 mg from the second to the fifth day.

In terms of pharmacokinetics, the average C_{max} and $AUC_{0–24}$ were 35.9 μg/ml and 346 μg·h/ml on the first day, and 57.6 μg/ml and 957 μg·h/ml on the fifth day. Thus, both parameters increased with increasing duration of administration. No changes were detected in the T_{max}. The concentration of favipiravir in semen 29 days after discontinuation of the treatment for all volunteers were below the limit of quantitation (0.0200 μg/ml), while M1 was detected in 31 volunteers at a concentration of 6 mg/ml 29 days after the treatment, and in 6 volunteers 60 days after the treatment, however, 90 days after the treatment, levels were below the limit of quantitation (0.0500 μg/ml)

Moreover, 60 and 90 days after the end of administration, there was no effect of favipiravir on the parameters of seminal fluid (volume, sperm concentration, mobility, vitality, number of spermatozoa, the proportion of normal-form spermatozoa, the proportion of mobile spermatozoa). No trends were found in the deterioration of these parameters compared to the placebo group. Thus, favipiravir did not have any long-term, irreversible effect on the testes.

The development of neuropsychiatric symptoms

Patients who received favipiravir in accordance with the proposed dosage regimen did not experience any neuropsychiatric symptoms (impaired consciousness, abnormal behavior, delirium, convulsions). Adverse manifestations of psychiatric disorders in clinical studies included anxiety and insomnia in the group of suggested doses of favipiravir (1 patient out of 394) and nightmares in the control group (1 patient out of 433). Disorders of the nervous system included headache, head tension, and cervicobrachial syndrome in the low-dose group (1 AE in 1 patient out of 52), headache, dysgeusia, and intercostal neuralgia (1 AE in 1 patient) in the group of suggested doses, headache and dizziness (1 AE in 3 patients), head discomfort and cervicobrachial syndrome (1 AE in 1 patient) in the control group. Out of them, AEs, for which it was impossible to exclude a causal relationship with the study drug, were dysgeusia in the group of suggested doses of favipiravir, headache and dizziness (in 2 patients) and a nightmare (in 1 patient) in the control group.

Prolongation of the QT/QTc interval

Changes in QTcF and AQTcF from baseline up to 4 hours after taking the study drug, including t_{max}, were investigated by the level of the first dose (<200, 400, 600, 800, 1200, 1600, 2000, and 2400 mg) in healthy Japanese adults. Furthermore, changes in QTcF and AQTcF were studied by dose level (<200, 400, 600, 800, and 1200 mg) in healthy American adults. As a result, neither QTcF nor AQTcF demonstrated

a dose dependence in healthy Japanese or American adults. The relative contribution of AQTcF to plasma concentrations of favipiravir was 0.0032 in healthy Japanese adults and 0.0095 in healthy American adults; no correlation was found for both populations, and AQTc did not increase as a function of favipiravir concentrations. The relative contribution of maximum AQTcF to the cumulative AUC of favipiravir was 0.0123 in healthy Japanese adults and 0.0338 in healthy American adults; no correlation was found for both populations, and the AQTc did not increase with increasing AUC of favipiravir. Even in patients with influenza virus infection, there was no tendency to prolong the QT/QTc interval, and AQTc >60 me was observed in 5 patients with influenza virus infection but the QTc value was small; thus, the AE was not of clinical significance. AEs associated with heart disease occurred in 6 patients, in the form of increased BP, decreased BP, and supraventricular extrasystoles, but all of these AEs were mild and resolved. The above data showed that favipiravir does not prolong the QT/QTc interval.

Safety of favipiravir in the treatment of coronavirus disease

Safety assessment in patients with COVID-19 was performed in populations of patients from 2 clinical studies of favipiravir:

1) in comparison with the umifenovir (n = 236) (C. Chen et al., 2020) and
2) in combination therapy with alpha-interferon compared to the combination of lopinavir/ritonavir + interferon alpha (n = 80) (Cai Q. et al., 2020).

A clinical study of favipiravir versus the combination of lopinavir/ritonavir + interferon alpha (n = 80) (Cai Q. et al., 2020).

In the study group, patients received favipiravir orally according to the following regimen (day 1: 1600 mg twice daily; days 2-14: 600 mg twice daily with additional inhalation of the aerosol interferon (5 million units twice daily) (n = 35). Patients in the control group received LPV/RTV for 14 days at a dose of 400 mg/100 mg twice daily with additional inhalation of the aerosol interferon (5 million units twice daily) (n = 45).

Adverse drug reactions were found in 4 patients (11.43%) in the favipiravir group, which is significantly less than in the control group of lopinavir/ritonavir – 25 (55.56%). Two of the 4 patients had diarrhea, one had an effect on the liver, and one had a loss of appetite. Thus, all the detected AEs were not significant.

Table 1.10. Adverse events identified in a clinical study of favipiravir for the treatment of COVID-19 compared with lopinavir/ritonavir.

Parameter	Favipiravir (n = 35)	LPV/RTV (n = 45)	p value
Total AEs	4 (11.43%)	25 (55.56%)	<0.001
Diarrhea	2 (5.71%)	5 (11.11%)	0.46
Vomiting	0 (0%)	5 (11.11%)	0.06
Nausea	0 (0%)	6 (13.33%)	0.03
Rash	0 (0%)	4 (8.89%)	0.13
Effects on the liver and kidneys	1 (2.86%)	3 (6.67%)	0.63
Other	1 (2.86%)	2 (4.44%)	1.00

A clinical study of favipiravir versus umifenovir (n = 236) (Chen C. et al., 2020)

In the study comparing with umifenovir, patients received favipiravir orally according to the following regimen (day 1: 1600 mg twice daily; days 2–10: 600 mg twice daily) (n = 116). In the control group, patients received umifenovir 200 mg three times daily for 7–10 days (n = 120).

In the experimental group, 59 males and 57 females, 87 (75.00%) younger than 65 years and 29 (25.00%) from 65 years and older, 36 (31.03%) had a history of hypertension and 14 (12.07%) diabetes mellitus. The control group included 51 males and 69 females, 79 (65.83%) younger than 65 years and 41 (34.17%) from 65 years and older, 30 (25.00%) had a history of hypertension and 13 (10.83%) diabetes mellitus. There was no significant difference in the main characteristics of patients between the two groups.

The most frequent AEs were changes in the blood chemistry values of liver samples, neuropsychiatric symptoms, gastrointestinal effects, and increased serum uric acid levels (3 [2.50 %] in the umifenovir group versus 16 [13.79%] in the favipiravir group, $p < 0.0001$).

There were 37 cases of AEs in the favipiravir group and 28 cases in the umifenovir group. The most frequent AEs were elevated serum uric acid levels (3 [2.50 %] vs. 16 [13.79%], $p = 0.0014$), which were more common in patients of the favipiravir group than in patients of the umifenovir group. No statistically significant differences were observed for elevated ALT and/or AST (12 [10.00%] in the umifenovir group vs. 9 [7.76%] in the favipiravir group, $p = 0.5455$), neuropsychiatric symptoms (1 [0.83%] vs. 2 [1.72%]; $p = 0.6171$), and gastrointestinal effects (nausea, reflux, flatulence) (14 [11.67%] vs. 16 [13.79%]; $p = 0.6239$). These AEs were resolved when most of the patients were discharged from the hospital.

Table 1.11. Adverse events identified in a clinical study of favipiravir in the treatment of COVID-19 compared with umifenovir.

Parameter	Favipiravir (n = 116)	Umifenovir (n = 120)	p value
Total AEs	37 (31.90%)	28 (23.33%)	0.1410
↑ hepatic enzyme levels	9 (7.76%)	12 (10.00%)	0.5455
↑ uric acid level	16 (13.79%)	3 (2.50%)	0.0014
Neuropsychiatric symptoms	2 (1.72%)	1 (0.83%)	0.6171
Violations by the gastrointestinal tract	16 (13.79%)	14 (11.67%)	0.6239

Safety assessment of favipiravir in Ebola patients

In a study of the efficacy of favipiravir for the treatment of Ebola virus infection in 126 patients, favipiravir was used in higher doses: on day 1, a total of 6000 mg (2400/2400/1200 mg three times daily) and 2400 mg (1200 mg twice daily) on days 2–9. Favipiravir was generally very well tolerated. In this case, the deterioration of blood chemistry values was observed only in deceased patients and was associated with the development of the disease, and not taking the drug. AEs of 3–4 degrees of severity, which could be

associated with the drug, was not identified. All fatalities were associated with uncontrolled EBOV viremia and disease progression.

All patients who survived the study, including those who had very poor blood chemistry values at the beginning of the study, did not need to stop taking the drug, and the blood chemistry values against the background of taking the drug improved. Therefore, the results of this study showed that favipiravir can be used at doses 1.5–2 times higher than recommended for the treatment of influenza virus infection (Sissoko et al., 2016).

1.3.3. Conclusion and justification of the study

Currently, a large amount of data on the safety of favipiravir has been collected, both in clinical studies and in postmarketing surveillance. Favipiravir is an antiviral drug that specifically affects the RNA-dependent RNA polymerase of various RNA viruses and leads to a violation of their replication. A number of clinical studies have shown reliable efficacy of favipiravir in the treatment of viral diseases caused by the influenza virus, including strains resistant to other antiviral drugs, in addition, there are data from both preclinical studies of efficacy and clinical experience in the treatment of infections caused by the Ebola virus and SARS-CoV-2.

As part of an extensive program of preclinical studies that preceded the introduction of the drug into clinical practice, the pharmacodynamic effects of the drug *in vitro*, *in vivo*, pharmacological safety, pharmacokinetics and toxicity of favipiravir were studied. Favipiravir was not found to be genotoxic or carcinogenic, but the drug can have embryotoxic and teratogenic effects.

Currently in Japan and China, favipiravir is authorized for the treatment of a novel and pandemic influenza virus infections when alternative drugs are ineffective or their efficacy is insufficient. The efficacy of the drug in the treatment of influenza virus infection was established in the US213 clinical study, which demonstrated faster relief of the flu infection symptoms compared to placebo.

The use of the drug as indicated for the treatment of the novel COVID-19 coronavirus disease is represented by data from two pilot clinical studies, during which preliminary encouraging results were obtained related to the efficacy of the use of favipiravir compared with alternative experimental treatment regimens. Thus, despite the potential of favipiravir for the treatment of COVID-19, the clinical efficacy of favipiravir has not yet been studied enough and further studies are needed to confirm the drug efficacy.

The side effects are well-studied. Favipiravir is a relatively low-toxicity drug. It is known that favipiravir was used in doses up to 6000 mg daily with no serious dose-limiting toxicity effects. The main adverse events are effects on the gastrointestinal tract, a decrease in neutrophils in the blood, an increase in liver enzymes, as well as an increase in uric acid in the blood, which are moderate and do not cause discontinuation of therapy, or a reduction in the dose.

Favipiravir-TL (internal code-TL-FVP-t), film-coated tablets (Drugs Technology LLC, Russia), is

a generic drug of favipiravir related to Avigan® (Toyama Chemical, Japan). It completely corresponds to the qualitative composition of the active ingredient, dosage (200 mg), and dosage form (film-coated tablets) of Avigan, and, therefore, will have a similar safety profile, and can be recommended for clinical studies in patients with the novel COVID-19 coronavirus disease in order to obtain data on the drug efficacy in this indication.

1.4. Summary of known and potential risks and benefits for study subjects (risk-benefit ratio)

1.4.1. Evaluation of benefits

Currently, no drugs have been authorized for the treatment of the novel coronavirus disease, and clinical studies of drugs that potentially have antiviral activity against the SARS-CoV-2 virus are actively being conducted.The use of drugs that are considered to have an etiotropic effect in SARS-CoV-2 infection is expected to not only reduce the duration of elimination of the virus, but also to reduce the severity of clinical manifestations, accelerate recovery, and reduce the frequency of severe and critical forms of the disease.

Open-label non-randomized comparative study of favipiravir versus lopinavir+ritonavir (LPV/RTV) in patients with the novel COVID-19 coronavirus disease involved 80 patients with a laboratory-confirmed diagnosis of COVID-19. Patients received favipiravir orally according to the following regimen (day 1: 1600 mg twice daily; days 2–14: 600 mg twice daily with additional inhalation of the aerosol interferon (5 million units twice daily). Patients in the control group received LPV/RTV for 14 days at a dose of 400 mg/100 mg twice daily with additional inhalation of the aerosol interferon (5 million units twice daily). Changes on lung CT scans, virus elimination, and safety assessment were used as control points. The number of patients with positive test results for the novel coronavirus disease decreased faster in the favipiravir group. The median for favipiravir was 4 days versus 11 in the LPV/RTV group.

A prospective open-label multicenter randomized study of the efficacy of favipiravir compared with umifenovir for the treatment of the novel coronovirus infection involved 116 patients (98 with a moderate form and 18 with severe) in the favipiravir group and 120 (111 with moderate form and 9 with severe) in the umifenovir group. Patients received favipiravir orally according to the following regimen (day 1: 1600 mg twice daily; days 2–10: 600 mg twice daily). In the control group, patients received umifenovir 200 mg three times daily for 7–10 days.

Improvement of the clinical picture on day 7 was observed in 51.67% (62/120) in the umifenovir group and 61.21% (71/116) in the favipiravir group. For patients with moderate form 55.86% (62/111) in the umifenovir group versus 71.43% (70/98) in the favipiravir group; for patients with severe form 0 (0/9) in the umifenovir group and 5.56% (1/18) in the favipiravir group; for patients with hypertension and/or diabetes, 51.43% (18/35) in the umifenovir group and 54.76% (23/42) in the favipiravir group. There was also an acceleration of improvement in the clinical picture in the favipiravir group compared to the umifenovir group. Thus, when using favipiravir, the effect occurred

faster compared to umifenovir, although the main improvement was observed mainly in groups of patients with moderate disease.

The study of the efficacy and safety of favipiravir is currently ongoing in numerous clinical studies registered in clinical trial registries of the USA (NCT04310228, NCT04319900, NCT04303299, NCT04333589, NCT04336904, NCT04345419, NCT04351295, NCT0434924, NCT04356495, NCT04359615, NCT04373733), China (ChiCTR2000029544, ChiCTR2000030113, ChiCTR2000029548, ChiCTR2000030894, ChiCTR2000030987, ChiCTR2000029996), and Japan (JapicCTI-205238, JPRN-jRCTs031190226, JPRN - jRCTs041190120).[10]

Thus, the benefit that patients can get from their participation in the study is the possibility of receiving therapy that will potentially reduce the duration and severity of symptoms of the disease, reduce the period of elimination of the virus, reduce the risk of developing life-threatening manifestations of the disease.

1.4.2. Risks assessment

The risk of using the drug TL-FVP-t is associated primarily with reactions registered in clinical studies of the original drug of favipiravir.

In post-marketing studies, including efficacy studies for the novel coronavirus disease, favipiravir was mainly used in the recommended regimen of 1600/600 mg twice daily. However, for Ebola virus infection, favipiravir was also used at significantly higher doses (a total of 6000 mg (2400/2400/1200 mg three times daily) on the first day and 2400 mg (1200 mg twice daily) on subsequent days) with no evidence of dose-limiting toxicity. Thus, if necessary, it is possible to use favipiravir in higher doses without significantly increasing the safety risks.

According to the results of pharmacokinetic studies, the parameters of C_{max} and AUC were different in the American population compared to the Japanese. The optimal regimen for the Asian patient population was determined as 1600/600 mg twice daily, while for the European population, as for the American population, comparable pharmacokinetic findings are expected when using 1800/800 mg twice daily.

In this study, favipiravir will be used in the form of 200 mg film-coated tablets at a loading dose of 1800 mg twice daily on the first day, followed by 800 mg twice daily for the next 10 days. The chosen dosage regimen of TL-FVP-t in the study is based on favipiravir doses, which showed optimal efficacy in the treatment of influenza in patients in the United States and the duration of therapy of 10 days, according to the literature data, evaluated when using favipiravir for the treatment of SARS-CoV-2 infection.

Currently, studies with the following treatment regimens have been registered on ClinicalTrials.gov:

- Protocol NCT04336904, treatment of moderate forms of COVID-19 at a dose of favipiravir 1800 mg twice daily on day 1, then 600 mg three times daily for up to 14 days.

[10] Assessment of Evidence for COVID-19-Related Treatments: Updated 5/8/2020 https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx

- Protocol NCT04346628, treatment of mild forms of COVID-19 at a dose of favipiravir 1800 mg twice daily on day 1, then 800 mg twice daily on days 2–10.
- Protocol NCT0434924, treatment of non-severe forms of COVID-19 at a dose of favipiravir 1600 mg every 12 hours on day 1, then 600 mg every 12 hours on days 2–10.
- Protocol NCT04358549, treatment of COVID-19, favipiravir dosage of 1800 mg twice daily on day 1, then 1000 mg twice daily on days 2–14.

The safety profile is expected to match that of the original drug of favipiravir in clinical studies. The risk of using Favipiravir-TL, according to previous studies, is associated primarily with the reactions listed in the Table below (information is collected based on clinical studies of favipiravir).

Table 1.12. Adverse drug reactions according to the data presented in the main information on Avigan, revision of November 2017[11]

Organ system class	Frequency		
	>1%	**0.5-<1%**	**<0.5%**
Blood and lymphatic system events	Decrease in neutrophil count, lymphocyte count		Increase in the lymphocyte count, monocyte count Decrease in reticulocyte count
Immune system events		Rash	Eczema, itching
Metabolism and nutrition events	Increased blood uric acid levels, increased triglyceride levels	Glucose in urine	Decreased blood potassium levels
Nervous system events			dizziness
Ocular events			blurred vision, ophthalmalgia
Respiratory system events and those related to chest and mediastinal organs			Asthma, Sore throat, rhinitis, nasopharyngitis
Gastrointestinal events	Diarrhea	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, hematochezia, gastritis
Hepatic and biliary tract events	AST increased ALT increased γ-GTR increased		Increased alkaline phosphatase and bilirubin in the blood

[11] Taisho Toyama Pharmaceutical Co., Ltd. Avigan® (favipiravir) tablets prescribing information [English translation]. Tokyo, Japan; 2017 Nov. Accessed 2020 Apr 14. Available at: https:// www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstwzvw

Organ system class	Frequency		
	>1%	0.5-<1%	<0.5%
Other			Increased creatine kinase, blood in urine, and urine pigmentation

The most common side effects when using favipiravir in patients in studies were diarrhea, signs of hepatic impairment, including increased activity of liver enzymes, decreased neutrophil count, and increased blood uric acid levels. All adverse drug events were moderate and did not lead to premature dechallenge of the drug administration, and quickly stopped after the end of the therapy.

In addition to registration studies in patients with the flu virus, data on the safety of favipiravir were obtained in studies in patients with the Ebola virus and the novel coronavirus disease.

In a study of the use of favipiravir (a regimen of 1600 mg twice daily on the first day and 600 mg on days 2–14) for coronavirus disease (35 patients), adverse drug reactions were found in 4 patients (11.43%), which is less than in the control group of lopinavir – 25 (55.56%). Two patients had diarrhea, one had a hepatic effect, and one had a loss of appetite. Thus, the side effects of the drug were not significant. (Q. Cai, 2020)

In a comparative study on Arbidol, elevated blood uric acid levels were observed in the favipiravir group, more often than in the Arbidol group. In addition, there were cases of increased liver enzymes, mental disorders, and gastrointestinal disorders, without statistical significance in frequency in the favipiravir and Arbidol groups. All abnormalities were resolved after the end of the therapy by the time the patients were discharged from the hospital (Chang Chen, 2020).

In a study of the efficacy of favipiravir for the treatment of Ebola virus infection in 126 patients, favipiravir was used in higher doses: on the first day, a total of 6000 mg (2400/2400/1200 mg three times daily) and 2400 mg (1200 mg twice daily) on days 2–9. At the same time, favipiravir was generally very well tolerated. The deterioration of blood chemistry values was observed only in deceased patients and was associated with the development of the disease, and not taking the drug. All patients who survived the study, including those who had very poor blood chemistry values at the beginning of the study, did not need to stop taking the drug, and the blood chemistry values against the background of taking the drug improved. Thus, the results of this study showed that favipiravir can be used in doses 1.5–2 times higher than recommended for the treatment of influenza virus infection (Sissoko, (2016). Thus, according to completed clinical studies on favipiravir, the following adverse drug reactions may develop: diarrhea, nausea, vomiting, dysgeusia, itching, rash, increased transaminase levels (increased ALT, increased AST, increased ALP, increased GGT), increased C-reactive protein, increased blood triglycerides, itching, increased blood uric acid, hyperuricemia, increased APTT, neutrophil count changes, decreased uric acid in urine.

Potential risks of using favipiravir, according to preclinical studies, are: increased total bilirubin levels, increased albumin levels,

increased blood sodium levels, decreased potassium levels, increased fibrinogen levels, phototoxicity, hair color change, nail color change.

In this study, patients will receive favipiravir in doses no higher than in previous studies (regimen 1800/800 mg twice daily). Thus, the most likely adverse drug reactions in this study are those previously observed in registration clinical studies, as well as in post-marketing use for the treatment of influenza, the novel coronavirus disease, and Ebola virus infection. Thus, it is assumed that adverse events will correspond to the safety profile of favipiravir and are characterized primarily by a mild or moderate form.

Concerning the known drug interactions of favipiravir, the most significant for this study is the effect on the pharmacokinetics of acetaminophen, which changes the profile of acetaminophen metabolites in the blood. However, according to the literature data, this effect did not have any clinical effect that affects the overall safety of the therapy, affecting the recommendations for the co-use of these drugs. Care should be exercised in the co-use of the product with the following drugs: pyrazinamide, repaglinide, sulindac, and famciclovir.

Due to these arguments, the risk of serious adverse events for patients is minimal.

1.4.3. Conclusion

Currently, favipiravir is registered in Japan and China for the treatment of complicated, as well as novel and pandemic influenza virus infection, if alternative drugs are ineffective or their efficacy is not sufficient. A series of registration clinical studies were conducted at various doses of favipiravir.

The most common adverse drug reactions that occur when using favipiravir for the treatment of influenza are moderate diarrhea, a certain decrease in neutrophils, and an increase in uric acid in the blood, which passes without symptoms.

Currently, the clinical data for the use of favipiravir in the novel COVID 19 coronavirus disease is limited to two clinical studies. In two studies of treatment of patients with the novel COVID 19 coronavirus disease in the favipiravir groups, improvement in the clinical condition of patients, as well as a decrease in the viral load below a detection limit, was observed faster in the favipiravir groups compared to the comparison drug groups (combinations of lopinavir/ritonavir and Arbidol). At the same time, the greatest effect was found in patients in the early and moderate stages of the disease.

Similar data were obtained for the treatment of complicated influenza infection and Ebola virus infection. The use of favipiravir had the best effect in groups with a lower initial viral load (Ebola), or in patients with moderate respiratory failure without the use of invasive methods of oxygen therapy (complicated influenza). Thus, the most effective is the use of favipiravir in groups of patients with mild to moderate disease, to reduce the risk of progression to more severe forms.

No serious side effects when using favipiravir in patients with the novel coronavirus disease, in addition to those previously identified in clinical studies in healthy volunteers and patients with influenza infection,

was detected.

1.5. Description and justification of the mode of administration, dosage, dosage regimen, and course of treatment

1.5.1. Description and justification of the design

This clinical study has the design of a multi-center open-label comparative randomized parallel-group study.

Currently, there are no specific recommendations from Russian or foreign regulatory agencies for the clinical study of drugs for the treatment of patients with the novel SARS-CoV-2 coronavirus disease. The design of the study was developed taking into account WHO guidelines for planning clinical studies of drugs for the treatment of the novel coronavirus disease, Synopsis of the Study of the Treatment for the Novel Coronavirus Disease,[12] as well as the guidelines of the US Food and Drug Administration (FDA) on a study of clinical efficacy and safety of medicines for the treatment of influenza[13].

Based on the existing results of pilot studies of the efficacy of favipiravir in the treatment of SARS-CoV-2 infection, this study is planned to provide reliable evidence of the efficacy and safety of favipiravir therapy (TL-FVP-t) in patients with mild to moderate coronavirus disease (SARS-CoV-2/COVID-19) compared to the control group of recommended "standard" etiotropic therapy. Considering the selected patient population, the combined primary endpoint was selected based on data on the clinical course of mild and moderate forms of SARS-CoV-2 infection, as well as literature data on the results of previous studies. The conclusion about the efficacy of the drug will be made on the basis of virological and clinical evaluation of the results of the study therapy.

The study therapy will be evaluated by comparing the control group of recommended "standard" etiotropic therapy. Taking into account the updated recommendations for the treatment of COVID-19, various etiotropic drugs can be prescribed according to the decision of the study physician, approved by the Principal Investigator and the study sponsor, if necessary, approved at the meeting of the Independent Data Monitoring Committee (IDMC), which can potentially improve the prognosis of patients. In this regard, the use of placebo control is not ethical and is not planned in this study, patients in the comparison group will receive standard therapy as part of routine clinical practice in accordance with current clinical recommendations for the period of the study.

[12] WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

[13] Guidance for Industry. Influenza: Developing Drugs for Treatment and/or Prophylaxis. US Food and Drug Administration, 2011.

1.5.2. Description and justification of the mode of administration, dosage, dosage regimen, and course of the treatment

Comparison of pharmacokinetics data for single administration in populations of healthy Japanese and American volunteers revealed a decrease in C_{max} and AUC in the American population. This difference was attributed to a difference in the weight of the volunteers who participated in the study. However, when normalizing the pharmacokinetic parameters for body weight (60 kg), the differences in pharmacokinetic parameters did not differ significantly.

A comparison of studies with repeated administration showed that on day 1, C_{max} and AUC in Japanese volunteers were higher than in American, while CL/F in Japanese volunteers was lower than in American. When normalized to a body weight of 60 kg, these differences decreased. On day 7 or 5 (final dose), C_{max} and AUC in Japanese volunteers were higher than in American, while CL/F and Vd/F in Japanese volunteers were lower than in American, as on day 1. Normalization of body weight to 60 kg reduced these differences, but AUC remained higher, CL/F was lower, and Vd/F was slightly lower in Japanese volunteers, compared to American. The ratio of AUC values for M1 and favipiravir was lower in Japanese volunteers. The decrease in this ratio after administration of the final dose was also greater in Japanese volunteers. In a placebo-controlled, randomized, double-blind, parallel comparative study in patients with the flu in the United States, taking favipiravir at a dose of 1800 mg twice daily on the first day and 800 mg twice daily on days 2–5 demonstrated advantages over placebo. A comparison of the pharmacokinetics of the American and Japanese patient populations showed that the expected effective dose may be higher in the American population than in the Japanese population.

The planned multicenter study will be conducted in the territory of the European part of the Russian Federation, thus, when planning the regimen of administration of favipiravir need to keep these studies of pharmacokinetics and efficacy of favipiravir obtained in a population of volunteers and patients in the U.S., and their differences from data obtained in Asian (Japanese) population. The established differences in pharmacokinetics, and as a result, the recommended dosage regimen, are presumably associated with differences in the average body weight of patients in these populations. The planned study is expected to include a predominantly Caucasian patient population, which suggests that pharmacokinetic features of the drug will be similar to those obtained in studies of favipiravir in the United States. Therefore, the chosen dosage regimen of TL-FVP-t in the study is based on favipiravir doses, which showed optimal efficacy in the treatment of influenza in patients in the United States and the duration of therapy of 10 days, according to the literature data, evaluated when using favipiravir for the treatment of SARS-CoV-2 infection.

In an open-label non-randomized comparative study of favipiravir versus lopinavir+ritonavir (LPV/RTV) in patients with the novel COVID-19 coronavirus disease, patients received favipiravir orally as follows (day 1: 1,600 mg twice daily; day 2–14: 600 mg twice daily with additional inhalation of aerosol interferon (5 million units twice daily). The number of patients with a positive test for the novel coronavirus disease decreased faster in the favipiravir group, the median for favipiravir was 4 days (2.5, 9 days) versus 11 days in the LPV/RTV group.

In a prospective open-label multicenter randomized study of the efficacy of favipiravir compared with umifenovir for the treatment of the novel coronavirus infection, patients received favipiravir orally according to the following regimen (day 1: 1600 mg twice daily; days 2–10: 600 mg twice daily). In the control group, patients received umifenovir 200 mg three times daily for 7 to 10 days.

Taking into account the median elimination time of the virus of 4 days, with an interquartile range of 2.5–9 days, the duration of the drug use of 10 days in patients with mild to moderate SARS-CoV-2 infection is sufficient. Currently, studies with the following treatment regimens have been registered on ClinicalTrials.gov:

- Protocol NCT04336904, treatment of moderate forms of COVID-19 at a dose of favipiravir 1800 mg twice daily on day 1, then 600 mg three times daily for up to 14 days.
- Protocol NCT04346628, treatment of mild forms of COVID-19 at a dose of favipiravir 1800 mg twice daily on day 1, then 800 mg twice daily on days 2–10.
- Protocol NCT0434924, treatment of non-severe forms of COVID-19 at a dose of favipiravir 1600 mg every 12 hours on day 1, then 600 mg every 12 hours on days 2–10.
- Protocol NCT04358549, treatment of COVID-19, favipiravir dosage of 1800 mg twice daily on day 1, then 1000 mg twice daily on days 2–14.

Patients in this study will receive TL-FVP-t according to the following regimen: on day 1, 1800 mg twice daily at intervals of 12 hours, then 800 mg twice daily at intervals of 12 hours on days 2–10.

In order to ensure maximum safety of the use of favipiravir, this study will take into account the contraindications to favipiravir administration.

1.5.3. The rationale for the selection of the comparison drug

Currently, data on the clinical course and progression of SARS-CoV-2 infection are limited, and the probability of rapid development of the severe and critical diseases cannot be excluded, regardless of the clinical picture of initial manifestations. Therefore, the use of a placebo in a clinical study is unreasonable, including in patients with mild and asymptomatic disease at the time of inclusion in the clinical study. According to the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19)[14],

valid at the time of the study, various etiotropic drugs can be used for the treatment of SARS-CoV-2 infection, which can potentially improve the prognosis of patients. In this regard, patients in the comparison group will receive

“standard” therapy as part of routine clinical practice in accordance with current clinical guidelines.

[14] Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19) https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/122/original/28042020_%D0%9CR_COVID-19_v6.pdf

1.6. Compliance of the clinical study with the requirements of standard regulatory documentation

The study will be conducted in full compliance with this Protocol, ICH GCP requirements, principles of GCP, the EAEU requirements, Order of Ministry of Health of the Russian Federation No. 200n dated April 1, 2016 "On Approval of the Principles of Good Clinical Practice", GOST R52379-2005 "Good Clinical Practice", ethical principles of the Declaration of Helsinki in the latest revision, and the Rules of compulsory insurance of life and health of a patient involved in clinical studies of the medicinal product, as well as with the applicable laws and regulatory requirements of the Russian Federation and the Eurasian Economic Union.

1.7. Description of the study population

This study will include patients aged 18 to 60 years with a mild to moderate coronavirus disease (confirmed by the results of the PCR test of SARS-CoV-2) (without respiratory failure).

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2. STUDY AIMS AND OBJECTIVES

2.1. Study Aims

- To study the efficacy and safety of TL-FVP-t in patients with a mild to moderate coronavirus disease (SARS-CoV-2/COVID-19) compared to the "standard" therapy.

2.2. Study objectives

Main objective:

- To evaluate the effect of TL-FVP-t on the rate of improvement of clinical status[15] in patients compared to the "standard" therapy.
- Evaluate the effect of TL-FVP-t on the rate of virus elimination[16] in patients based on the results of qualitative analysis of SARS-CoV-2 compared to the "standard" therapy.

Additional objectives:

- Evaluate the effect of TL-FVP-t on the frequency of improvement of clinical status[17] in patients at fixed time points compared to the "standard" therapy.
- Evaluate the effect of TL-FVP-t on the frequency of virus elimination at fixed time points compared to the "standard" therapy.
- Evaluate the effect of TL-FVP-t on the duration of the period before temperature normalization[18] compared to the "standard" therapy.
- Evaluate the effect of TL-FVP-t on the probability of resolution of radiological changes in the lungs according to CT data on day 14 compared to the "standard" therapy.
- To evaluate the safety and tolerability of TL-FVP-t in patients with a mild to moderate coronavirus disease (SARS-CoV-2/COVID-19) compared to the "standard" therapy when co-used with recommended concomitant therapy, including the frequency and severity of drug-related AEs and SAEs, the frequency of severe drug-related AEs and SAEs, the frequency of early discontinuation of the therapy due to drug-related AEs and SAEs.

Exploratory issues

- To study the effect of TL-FVP-t on the average clinical status in patients (the average score on the WHO Ordinal Scale for Clinical Improvement) at fixed time points compared to the "standard" therapy.
- To study the effect of TL-FVP-t on the duration of individual symptoms (cough, myalgia, weakness, shortness of breath, headache) in patients compared to the "standard" therapy.
- To study the effect of TL-FVP-t on the frequency of hospitalization of patients who were in the outpatient setting compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy).
- To study the effect of TL-FVP-t on the duration of hospitalization of patients compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy).

[15] Clinical status is measured in points on the WHO Ordinal Scale for Clinical Improvement; improvement in clinical status is defined as a decrease of at least 1 point on the scale compared to the screening level.

[16] Elimination is defined as a "negative" result when conducting 2 consecutive studies by PCR of biological samples obtained from patients (smears from the upper respiratory tract) at intervals of 24 hours at least.

[17] Clinical status is measured in points on the WHO Ordinal Scale for Clinical Improvement; improvement in clinical status is defined as a decrease of at least 1 point on the scale compared to the screening level.

[18] Normalization is considered the reduction the axillary temperature to less than 37 °C without the use of antipyretics for at least 48 hours.

- To study the effect of TL-FVP-t on the frequency of need for artificial lung ventilation (AVL) compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy).
- To study the effect of TL-FVP-t on the frequency of transfer of patients to the intensive care unit compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy).
- To study the effect of TL-FVP-t on the incidence of death in patients compared to the "standard" therapy for a period of 28 days (from the beginning of the therapy).
- To study the pharmacokinetics of favipiravir and its main metabolite M1 and calculate the pharmacokinetic parameters after a single (AUC_{0-12}; C_{max}; T_{max}; $T_{1/2}$; Cl, Vd, and K_{el}) and multiple (AUC_{0-12}; C_{max}; T_{max}; $T_{1/2}$; Cl, V_d, and K_{el} on days 5 and 10, as well as $C_{min\ ss}$) use of TL-FVP-t.

3. STUDY HYPOTHESIS

This clinical study is based on the following hypothesis: the efficacy of TL-FVP-t in relation to the rate of virus elimination and resolution of clinical symptoms of SARS-CoV-2 infection exceeds the efficacy of the "standard" therapy.

4. STUDY DESIGN

4.1. Main and additional parameters to be evaluated during the study

4.1.1. Primary and secondary endpoints

Primary endpoint:

- Time to improve clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category) (median, in days).
- Time to reach virus elimination (defined as the absence of SARS-CoV-2 based on the results of 2 consecutive PCR tests of smears at intervals of 24 hours at least) (median, in days).

Secondary endpoints:

- The percentage of patients (%) with improved clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category[19]) on day 7 (from the beginning of the therapy).
- Percentage of patients (%) with established virus elimination on days 5 and 7 (from the beginning of the therapy).
- Time to temperature normalization (median, in days).
- Percentage of patients (%) with resolution of changes in the lungs according to CT data on day 14 (from the beginning of the therapy).

4.1.2. Additional (exploratory) endpoints

Exploratory endpoints:

[19] Ordinal Scale for Clinical Improvement

- Average score on the WHO Ordinal Scale for Clinical Improvement on days 7 and 14 of the study.
- Percentage of patients (%) with improved clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category[20]) on day 14 (from the beginning of the therapy).
- Percentage of patients (%) with established virus elimination on study days 3, 10, 14, 21, and 28 (from the beginning of the therapy).
- Time to stop individual symptoms (cough, myalgia, weakness, shortness of breath, headache) (median, in days).
- Frequency (%) of hospitalization of patients who were under outpatient observation for a period of 28 days (from the beginning of the therapy).
- Duration of hospitalization of patients for a period of 28 days (from the beginning of the therapy).
- Frequency (%) of ventilator use for a period of 28 days (from the beginning of the therapy).
- Frequency (%) of transfer to the intensive care unit for a period of 28 days (from the beginning of the therapy).
- Frequency (%) of deaths for a period of 28 days (from the beginning of the therapy).

4.1.2.2. Endpoints for safety assessment

- The frequency and severity of all AEs and SAEs.
- The frequency of Grade 3–4 AEs according to CTCAE 5.0.
- All cases of early withdrawal from the study related to AEs/SAEs.

4.2. Description of the study type/design, graphic diagram, procedures, and stages of the study

Study Design

This study is a multi-center, blind, randomized, 3-phase parallel study, the purpose of which is to evaluate the efficacy and safety of TL-FVP-t in patients with a mild to moderate coronavirus disease (SARS-CoV-2/COVID-19) compared to the "standard" therapy.

In total, the study is planned to include (randomize) 168 patients; no more than 200 patients will be screened. Randomization will be performed in a ratio of 2:1 (study drug group: comparison group).

During the study, patients will receive either treatment with the study drug for 10 days, or the "standard" etiotropic therapy according to the current version of the IG "Prevention, diagnosis and treatment of coronavirus disease (COVID-19)" and the routine practice at the study site, prescribed by the study physician. Both the study drug and the "standard" etiotropic therapy will be co-used with the concomitant therapy recommended according to the IG.

A pharmacokinetics subgroup will be selected from the cohort of hospitalized patients in the study therapy group. In patients of this subgroup, in addition to evaluating the efficacy and safety of the therapy, blood samples will be taken to study the pharmacokinetics of TL-FVP-t and its main metabolite M1 (the metabolite will be determined if technically possible).

[20] Ordinal Scale for Clinical Improvement

After the end of 14 days of participation and the onset of 54 events, an interim data analysis will be performed and an interim report will be prepared. After completion of the study by all included patients, the main (final) report on the study will be prepared. An additional report will be prepared after obtaining full pharmacokinetic data in the study.

IC signing, randomization, and blinding

Before enrollment in the study, patients will be provided with complete information about the clinical study, its goals, and the risks associated with participating in it. After signing the informed consent to participate in the study and screening, patients who meet the inclusion criteria and do not have the exclusion criteria (as confirmed by the screening form) will be stratified and randomized to one of the study groups. Central randomization will be performed in a ratio of 2:1 (112 and 56 patients) in the study drug group and the comparison group, respectively.

The study assumes stratification by the following parameters:

- age (<45; ≥ 45 years)
- severity of COVID-19 (mild/moderate)
- pathology severity on chest CT (CT-0 – CT-1 / CT-2 – CT-3).

Description of the therapy

The TL-FVP-t group. Patients in this group will receive oral therapy with TL-FVP-t for 10 days. On the first day of therapy, patients will receive a loading dose of TL-FVP-t-1800 mg at intervals of 12 hours (i.e. twice daily), then on days 2–10, patients will receive 800 mg at intervals of 12 hours (i.e. twice daily).

Comparison group. Patients in this group will receive the recommended "standard" etiotropic therapy in accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study. Such drugs (at the time of writing of this Protocol) include umifenovir, chloroquine, hydroxychloroquine, mefloquine, lopinavir+ritonavir, hydroxyloroquine in combination with azithromycin, interferons. In the comparison group, patients will receive either umifenovir in combination with interferon-alpha, or chloroquine, or its derivatives (chloroquine/hydroxychloroquine or mefloquine) using standard regimens and dosages according to the Guidelines.

Concomitant therapy. Furthermore, in patients in both groups, besides the study drug and the "standard" etiotropic therapy, may be prescribed concomitant therapy in accordance with the above guidelines. Concomitant therapy is prescribed at the discretion of the study physician and is determined by the actual condition and needs of a patient. It involves symptomatic therapy, pathogenetic therapy and antibacterial therapy (for complicated forms of infection), recommended according to the current version of the Interim guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study, for patients with mild and moderate disease, as well as corresponding to the standards adopted at the study site.

Symptomatic therapy includes:

- Relief of fever (antipyretic drugs; the recommended drug is acetaminophen, it is permissible to use NSAIDs, for example, ibuprofen).
- Complex therapy of rhinitis and/or rhinopharyngitis (moisturizing/irrigation drugs, nasal decongestants);
- Complex therapy of bronchitis (mucoactive drugs, broncholytic drugs, and other).

Pathogenetic therapy may include antithrombotic and anti-inflammatory drugs.

Study periods

In general, the study will include the following periods:

1) Screening period: 2 days

Includes days -1-0 (before randomization and inclusion in the study;

2) Therapy period: 10 days

It includes days 1–10 of the treatment with the study drug/"standard" therapy against the background of recommended concomitant therapy, data collection on clinical symptoms, observation of study participants, assessment of vital signs (measurements of body temperature, BP, HR, RR, and SpO_2), as well as a sampling of biomaterial to determine virus elimination, monitoring of laboratory findings, ECG, and chest CT. In the PK subgroup, a sampling of biomaterial will also be done to evaluate PK of favipiravir and its main metabolite M1 (the metabolite will be determined if technically possible).

3) Follow-up period:

It includes days 11–28 and involves biomaterial sampling to determine the elimination of the virus, procedures for monitoring of the patient's condition, laboratory tests, ECG, and chest CT.

A graphical diagram of the study is shown in Figure 4.1.

Hospitalization and outpatient monitoring

Patients who will be included in the study, depending on the severity of the disease and the condition, may be hospitalized or may be observed at home, in an outpatient setting.

Patients who are at home during the screening period and the main period, until the virus is eliminated, will be quarantined at home. They will be monitored using telemedicine technology. If the symptoms of SARS-CoV-2 (COVID-19) coronavirus disease worsen in such patients or become more severe, according to the decision of the investigator, the patients will be admitted to a hospital, where they will continue to be monitored for tracking their status (ICU, AVL, fatal outcome) (if possible). If there is no possibility of further monitoring of hospitalized patients and communication with them, they are excluded from the study. Discharge from the hospital is made in accordance with the local practice of the study site in compliance with hospital hygiene and infection control.

For outpatients, CT and ECG are provided in medical facilities that have been converted to receive coronavirus patients, in special areas equipped for working with them. Patients will be transported to the medical center by special transport in compliance with hygienic requirements. Biomaterial sampling for clinical blood test can be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

For hospitalized patients, the period of hospitalization should not be less than 10 days. When hospitalized patients are discharged from the hospital, follow-up will be carried out by the study site. If necessary, routing similar to the routing of outpatients can be used for CT, ECG, and laboratory test selection.

The study provides a total of the following visits: screening and 10 visits (daily) in the therapy period and 3 visits in the follow-up period (on days 14, 21, and 28).

Food and water intake

In this study, there are no restrictions on food and water intake. TL-FVP-t is taken at least 30 minutes after a meal.

Blood sampling

From the study drug group, a PK subgroup will be selected, in which blood will be sampled for the study of the pharmacokinetics of the drug. Blood samples will be taken on Day 1 before the first administration of the drug, then at the following points: 20 min; 40 min; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours. Day 2 to Day 10: 5 minutes before the next (morning) drug intake.

Days 5 and 10: in addition to the sampling points indicated for Days 2–10, the sampling will be carried out at points 20 min; 40 min; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours after the first (morning) administration on these days.

The PK subgroup will include patients who have signed up an additional IC to participate in this study, and only in study sites that have the possibility of sampling.

The PK subgroup will include 15 patients.

In total, 690 bio-samples will be collected from 15 patients.

Analytical method

Assay of favipiravir and its metabolite in blood plasma will be performed using a highly sensitive and selective method of high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS) using an internal standard. The extraction of the analyte from the matrix will be carried out by a protein precipitation method or extraction (liquid, solid-phase).

Examination of patients

To assess the efficacy and safety of the therapy in all patients, the clinical status, subjective symptoms, biomaterial sampling (smear) from the upper respiratory tract will be performed regularly to determine the content of the SARS-CoV-2 virus (by PCR), as well as measurement of body temperature, BP, HR, RR, determination of blood oxygen saturation using pulse oximetry (SpO_2), and chest CT.

Measurement of body temperature, BP, HR and SpO_2 (outpatients should do it on their own, with remote video monitoring by the study physician) will be performed daily for 10 days of the therapy (body temperature and pulse oximetry should be performed at least 3 times daily), then – on days 14, 21, and 28.

Reviewing of patients about the subjective symptoms and RR measurement will be carried out by the study physician daily for 10 days of the therapy, then – on days 14, 21, and 28. The patient will also keep the Patient's Diary for the first 14 days (every day) and then on days 21 and 28, recording the facts of taking the study therapy and

concomitant drugs, symptoms, results of measurements of body temperature, BP, HR, and SpO_2.

The clinical status will be assessed by a study physician during screening and daily for 10 days of the therapy, then – on days 14, 21, and 28.

The sampling of biomaterial to determine the content of the SARS-CoV-2 virus will be carried out on days 3, 5, 7, 10, 14, 21, and 28. After receiving a negative test result for the presence of the SARS-CoV-2 virus, a second study to confirm the fact of elimination of the virus will be carried out after a minimum of 24 hours. After confirmation of the elimination of the SARS-CoV-2 virus (2 negative tests), the sampling will be stopped, and the patient can end the quarantine period (if at home) and be removed from the register. Then the patients will be monitored in accordance with the planned schedule of visits in the study. Despite confirmation of virus elimination, the patients should wear a mask, live in a separate room, avoid close contact with family members, eat separately, keep their hands clean, and avoid outdoor activities.

CT of the chest and mediastinum and ECG will be performed at the screening, then on days 5, 14, and 28 (the latter is performed as necessary, at the discretion of the study physician).

Evaluation of laboratory findings will be performed at the screening, then on days 5, 14, and 28. The following parameters will be evaluated:

- Clinical blood test (hemoglobin, erythrocyte count, leukocyte count, neutrophil count, lymphocyte count, platelet count, ESR).
- Blood chemistry test (glucose, ALT, AST, LDH, total bilirubin, creatinine, CPK, ferritin, lactate, uric acid).
- C-reactive protein;
- coagulation test (activated partial thromboplastin time (APTT), prothrombin time, fibrinogen, D-dimer);
- urine analysis.

If necessary, to monitor the patient's condition, an additional CT scan and other examinations may be performed on other days, according to the decision of the investigator.

Safety will be assessed based on the obtained data on complaints, clinical status, as well as on the results of laboratory tests. On the 28th day of the study, the patient completes participation in the study.

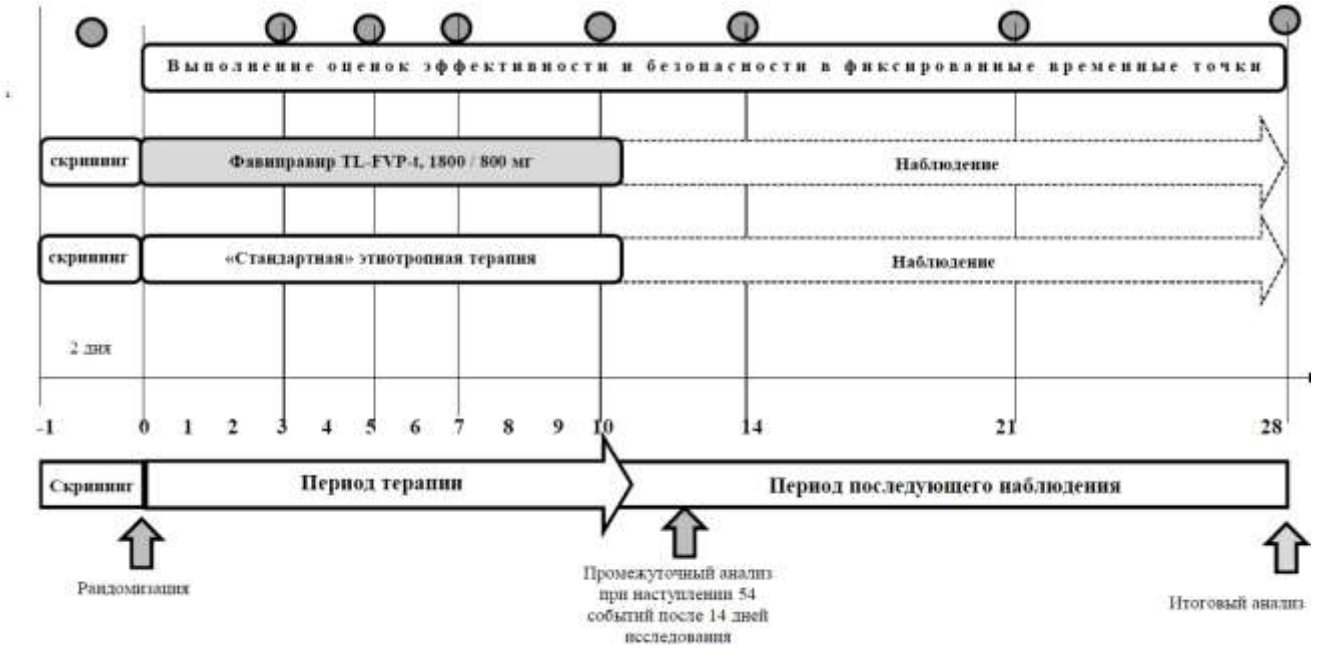
Duration of the study and participation

The total expected duration of the study is 6 months:

- the period of initiation of the study site and recruitment of patients is 3 months,
- the main study period and follow-up period is 28±2 days (about 1 month),
- data collection and statistical processing of results – 2 months.

The expected duration of each subject's participation in the study will be a maximum of 30±2 days, including screening periods (2 days), the main study period (a total of 14 days), and the follow-up period (14±2 days).

Figure 4.1. Study Diagram.



	Performing efficacy and safety assessments at fixed time points
	screening
	Favipiravir TL-FVP-t 1800/800 mg
	Follow-up
	The “standard” etiotropic therapy
	Period of therapy
	Follow-up period
	Randomization
	Interim analysis when 54 events occur after 14 days of research
	The final analysis

4.3. Description of activities aimed at minimizing/excluding subjectivity

4.3.1. Distribution of patients to study sites

Recruitment in the sites will be conducted on a competitive basis. When 168 participants will be included (randomized), patient enrollment in the study will be stopped. The hospital cohort is planned to recruit no more than 50% of patients, so after the inclusion of 84 hospitalized participants in the study, recruitment of patients who need hospitalization will be discontinued.

4.3.2. Procedure for assigning study codes

Randomization, stratification, and assignment of study numbers is carried out according to the internal instructions of Drugs Technology LLC.

Each study site will be assigned a two-digit identification number. For example, the first site is 01, the second is 02, the third is 03, and so on.

After a patient signs the Informed Consent Form, they are assigned a four-digit screening number consisting of a two-digit study site number, and a two-digit patient number (patient numbering is continuous, in the order that patients were included in the screening at this study site), which is noted in the primary documentation and in the patient screening log. For example, at site 02, the first patient to sign informed consent will receive the screening number 02-01.

After all screening procedures have been performed and the investigator has decided that the patient meets the inclusion criteria and does not have any exclusion criteria, the investigator fills out a special screening form and emails it to the project manager of the clinical study of Drugs Technology LLC. If Drugs Technology LLC confirms the inclusion of the patient in the study, the patient is randomized using an electronic system that distributes it to the appropriate group and it is assigned a three-digit randomization code, based on which the patient's identification number (subject ID) is formed. The investigator receives the subject ID during randomization. The investigator records the subject ID and the drug group in the primary documentation and CRF and emails it to the clinical study manager on the same day.

The subject ID consists of 5 digits – 2 digits are the code of the study site, 3 digits are the sequence number of the patient in the study, corresponding to the randomization code. For example, the subject identifier “01-112”:

- “01” is a code of the study site,
- “112” is the sequential number of the patient in the study.

The subject ID consists of 5 digits – 2 digits are the code of the study site, 3 digits are the sequence number of the patient in the study, corresponding to the randomization code. For example, the subject identifier “01-112”:

- “01” is a code of the study site,
- “112” is the sequential number of the patient in the study.

4.3.3. Stratification procedure

Before randomization, patients are stratified to ensure maximum equivalence of groups. Stratification is based on the following criteria:

- age (< 45; ≥ 45 years);
- severity (mild/moderate). According to the current version of the IG, mild form: body temperature below 38 °C, cough, weakness, sore throat, lack of criteria for a moderate and severe form; moderate form: fever above 38 °C; RR more than 22/min; shortness of breath during exercise; pneumonia (confirmed by the lung CT); SpO_2 < 95%; serum CRP more than 10 mg/l);
- pathology severity on chest CT (CT-0 – CT-1 / CT-2 – CT-3).

Thus, as a result of stratification, patients in the groups will be equal in disease severity, CT results, and age.

4.3.4. Randomization procedure

If, after all the procedures planned as part of the screening, the investigator decides that patients can participate in the study, they are randomized and stratified. Randomization (a method of distribution according to probability theory) is necessary to minimize subjectivity in the distribution of patients into therapy groups.

Randomization of patients in the study will be central and will be performed using an electronic system. Patients will be randomized into 2 groups in a ratio of 2:1. The randomization number of the patient will be assigned to the study subject in order of accessing the system.

Randomization code (number) is generated using special software with the function of a random number generation taking into account stratification (below is a brief description of the algorithm).

Before randomization, in order to ensure maximum equivalence of groups, patients are stratified in accordance with the above criteria. Block randomization will be used, i.e. patients included in the study are adaptively distributed to therapy groups in a ratio of 2:1 within each block (see Figure 4.2). Therefore, as a result of stratification, all groups will be equal in the number of patients with particular disease severity and age group.

The essence of the block randomization method is as follows. Random infinite sequences of 6 digits (1,2,3,4,5,6) are created using a random number generator program. Each of the 6 digits (from 1 to 6) corresponds to one of the 6 possible unique blocks (see Table 4.1). Since the study does not determine in advance how many patients will be inside each of the 2 strata (see Figure 4.2), in order to maintain a uniform distribution, randomization is performed inside each stratum, respectively, each stratum contains its own sequence of blocks (and, respectively, the symbols “1” and “2” corresponding to the 2:1 distribution).

Figure 4.2. Scheme for randomization with stratification.

	INCLUSION
	Severity
	Mild
	Mild Moderate
	<45 years
	≥ 45 years
	CT 0-1
	Stratum A
	Stratum B
	Stratum C
	Stratum D

Uniform distribution within each of the 2 study groups

Table 4.1. Examples of blocks for performing block randomization.

No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
1	1	2	1	1	2
2	1	1	1	2	1
1	2	1	2	1	1

These 2-digit blocks consist of symbols: “1” and “2”, each of them corresponds to the study groups: for example, “1” implies group No. 1, “2” – group No. 2, in the ratio 2:1.

As a result, the following table, consisting of a random sequence of blocks with 2 digits in each, is formed. Each stratum is assigned an infinite random sequence of blocks (see Table 4.2 for example).

Table 4.2. Example of assigning a sequence of blocks to strata.

Stratum	Sequence of blocks
Stratum A (mild, < 45 years, CT 0-1)	No. 1
	No. 6
	No. 5
	No. 2
	…
Stratum B (mild, ≥ 45 years; CT 2-3)	No. 4
	No. 3
	No. 5

Stratum	Sequence of blocks
	No. 1
	…

Before starting the study, investigators will be trained in the rules of working with the system, as well as receive unique access codes to the system and instructions for working with the randomization system.

When accessing the system, the investigator will be asked to enter unique access codes. If authorization is successful, the investigator will need to enter patient identification data that does not contain personal information, including information about stratification criteria, before performing the randomization procedure.

The electronic randomization system allocates the patient to the appropriate stratum, assigns him the first available group number in the block and a three-digit randomization number encoding this group (corresponds to the sequence number of the patient in the study). For example, the first patient from study site “02” falls into the “B” stratum, in this case, he is assigned the first available number of the first block (the first block in this stratum is No. 4) — “2”, which determines the distribution of the patient to the group No. 2. The patient is then assigned a corresponding three-digit randomization number (the sequence number of the patient in the study), under which the treatment group is encoded, “001”.

The result of accessing the system will be a randomization confirmation that contains:

– date and time of accessing the system;
– data about the investigator who performed the patient randomization procedure;
– patient identification data that does not contain personal information;
– five-digit subject ID;
– the therapy group that the patient will receive during the study.

Confirmation of randomization will be available for printing. Notification of randomization will be sent to the email addresses of the project team members.

The randomization code of each patient must be registered in the primary documentation and the patient's CRF.

If patients complete the study early (being excluded from the study for any reason), their randomization code will not be reused.

Drugs Technology LLC should keep lists of screening numbers, randomization numbers, and subject IDs with indication of the group of randomization of all included patients and batch numbers and series of drugs administered to patients.

At the randomization stage, a representative of Drug Technology LLC tracks the total number of patients included. Patient recruitment is stopped after the inclusion of the 168th randomized patient.

4.3.5. Blinding

This study is open to the patient, investigator, pharmacokinetics laboratory specialists, and biomedical statisticians, so blinding is not applicable.

4.4. Description of the treatment used in the study, dosage and application regimen of the study products. Description of the dosage form, packaging and labeling of the study products

4.4.1. Description of the treatment used in the study, dosage and application regimen of the study products

Description of the therapy

The TL-FVP-t group. Patients in this group will receive oral therapy with TL-FVP-t for 10 days. On the first day of the therapy, patients will receive a loading dose of TL-FVP-t 1800 mg (9 tablets of 200 mg) at intervals of 12 hours (i.e. twice daily), then on days 2–10, patients will receive 800 mg (4 tablets of 200 mg) at intervals of 12 hours (i.e. twice daily).

Comparison group. Patients in this group will receive the recommended "standard" etiotropic therapy in accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study. These drugs include umifenovir, chloroquine, hydroxychloroquine, mefloquine, lopinavir+ritonavir, hydroxyloroquine in combination with azithromycin, interferons (at the time of writing this Protocol). In the comparison group, patients will receive either umifenovir in combination with interferon-alpha, or chloroquine, or its derivatives (chloroquine/hydroxychloroquine or mefloquine) using standard regimens and dosages according to the Guidelines.

Concomitant therapy. In addition to the study drug and "standard" etiotropic therapy, patients in both groups may be prescribed concomitant therapy in accordance with the above Guidelines. Concomitant therapy is prescribed at the discretion of the study physician and is determined by the actual condition and needs of a patient. It involves symptomatic therapy, pathogenetic therapy and antibacterial therapy (for complicated forms of infection), recommended according to the current version of the Interim guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study, for patients with mild and moderate disease, as well as corresponding to the standards adopted at the study site.

Symptomatic therapy includes:

- Relief of fever (antipyretic drugs; the recommended drug is acetaminophen, it is permissible to use NSAIDs, for example, ibuprofen).
- Complex therapy of rhinitis and/or rhinopharyngitis (moisturizing/irrigation drugs, nasal decongestants);
- Complex therapy of bronchitis (mucoactive drugs, broncholytic drugs, and other).

Pathogenetic therapy may include antithrombotic and anti-inflammatory drugs. Detailed symptomatic therapy is described in section 6 of this Protocol.

Tactics for managing patients at the end of the 10-day period of the therapy

Patients in both groups may continue concomitant therapy as indicated.

4.4.2. Description of the dosage form, packaging and labeling of the study products

4.4.2.1. Study drug

Trade name: FAVIPIRAVIR-TL
The internal code of the drug: TL-FVP-t.
International nonproprietary name: favipiravir.
Dosage form: film-coated tablets.
Dosage: 200 mg.
Formulation:

For dosage:	**200 mg**
Active ingredient:	
Favipiravir	200.00 mg
Excipients:	
Uncoated tablet weight:	
Film-coated tablet weight:	

Description: round, biconvex, brownish-yellow film-coated tablets. In the cross section, the tablet core is from white to light yellow.
MA Holder and Developer: Drugs Technology LLC, Russia
Manufacturer: R-Pharm JSC, Moscow, Russia.
Shelf life:
years
Storage and transportation conditions:
Protect from light. Do not store above 25 ºC
Dispensing and packaging:
200 mg film-coated tablets 200 mg tablets in polymer bottles, 50 pcs. A label made of label paper is stuck on the bottle. 1 bottle is placed in a cardboard package.
Mode of administration and dosage regimen:

The drug will be taken orally, on the first day, in a loading dose of 1800 mg at intervals of 12 hours (i.e. twice daily), then on days 2–10, patients will receive 800 mg at intervals of 12 hours (i.e. twice daily).

Labeling

The drug will be labeled in accordance with article 46 of Federal Law No. 61

"On drug circulation" dated April 12, 2010 (latest version) and Annex No. 13 to the Order of the Ministry of Industry and Trade (Minpromtorg) of Russia No. 916 "On approval of the Principles of Good Manufacturing Practice" dated June 14, 2013 (latest version).

In accordance with article 46 of Federal Law No. 61-FZ "On drug circulation" dated April 12, 2010, Order of Minpromtorg of Russia No. 916 dated June 14, 2013 "On approval of the Principles of Good Manufacturing Practice", the Principles of GMP of the EAEU, as well as other regulatory requirements of the participating countries, on the primary packaging of the study drug using a readable font in the language of the participating country will be listed:

- drug name and dosage,
- batch number,
- manufacturing date,
- shelf life,
- protocol number.

On the secondary packaging, the following information will be clearly legible in the language of the participating country:

- drug name and dosage,
- name of the manufacturer of the medicinal product,
- batch number,
- manufacturing date,
- shelf life,
- mode of administration,
- dosage form,
- prescription status,
- storage conditions,
- cautionary warning.

The primary and secondary packaging of the study drug will additionally be marked: "For clinical study only."

On the primary packaging, additional space will be provided for information that will be entered by the study physician about:

- study site number,
- full name of the Principal Investigator, and
- subject ID.

The label will contain the following text: "For clinical study only."

The study drug will be packaged individually for each subject and for each study period directly in the study site.

4.4.2.2. Comparator drug

Patients in this group will receive the recommended "standard" etiotropic therapy in accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study. These drugs include umifenovir, chloroquine, hydroxychloroquine, mefloquine,

lopinavir+ritonavir, hydroxychloroquine in combination with azithromycin, interferons (at the time of writing of this Protocol). In the comparison group, patients will receive either umifenovir in combination with interferon-alpha, or chloroquine, or its derivatives (chloroquine/hydroxychloroquine or mefloquine) using standard regimens and dosages according to the Guidelines.

4.5. Expected duration of the study and participation

The total expected duration of the study is 6 months:

- the period for initiating study sites and recruiting patients is 3 months,
- the main study period and follow-up period is 28±2 days (about 1 month),
- data collection and statistical processing of results – 2 months.

The expected duration of each subject's participation in the study will be a maximum of 30±2 days, including screening periods (2 days), the main study period (a total of 14 days), and the follow-up period (14±2 days).

4.6. Description of the sequence and duration of all study periods

4.6.1. Schedule of visits and procedures

The study, in total, will include the following periods:

1) Screening period: 2 days

Includes days -1-0 (before randomization and inclusion in the study;

1) Therapy period: 10 days

It includes days 1–10 of treatment with the study drug/"standard" therapy in co-use of the recommended concomitant therapy, data collection on clinical symptoms, subject observation, as well as biomaterial sampling to determine virus elimination, monitoring of laboratory findings, assessment of vital signs (measurements of body temperature, BP, HR, RR, SpO_2), ECG and chest CT. In the PK subgroup, a sampling of biomaterial will also be done to evaluate PK of favipiravir and its main metabolite M1 (the metabolite will be determined if technically possible).

3) Follow-up period:

It includes days 11–28 and involves biomaterial sampling to determine the elimination of the virus, procedures for monitoring of the patient's condition, laboratory tests, ECG, and chest CT.

Table 4.1 lists the visit schedule with the flow chart of all study procedures established by this Protocol.

Screening/initial evaluation should be performed within 2 days before the estimated date of the first administration of the drug. For a number of tests or studies scheduled at the screening, it is allowed to use previously obtained results (see section 4.7 for details). Screening procedures should end with an assessment of the inclusion/exclusion criteria and a decision on patient inclusion and randomization. Randomization is performed on the first dosing day of the study drug (day 1) or the day before (day 0).

It is not allowed to deviate from the planned date of the "Days 1-10" and "Day 14" visits, and it is allowed to postpone the "Day 21" and "Day 28" visits for up to 2 days.

Table 4.3. Diagram of procedures and visits in the study.

Procedures	Screening	Period of therapy											Observation Period	
		Day 1 Visit	Day 2 Visit	Day 3 Visit	Day 4 Visit	Day 5 Visit	Day 6 Visit	Day 7 Visit	Day 8 Visit	Day 9 Visit	Day 10 Visit	Day 14 Visit	Day 21 Visit	Day 28 Visit
Days	-1… 0	1	2	3	4	5	6	7	8	9	10	14	21	28
IC process	♦													
Eligibility check	♦													
Randomization	♦													
Delivery of the study drug/comparison therapy		♦												
Taking a medical history	♦													
Interviewing a patient about subjective symptoms[3]	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Concomitant therapy data collection	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Taking the study drug / comparison therapy[2]		♦	♦	♦	♦	♦	♦	♦	♦	♦	♦			
Body temperature measurement[4]	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
BP and HR measurement[4]	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Pulse oximetry (SpO2) and RR measurement[4]	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
SARS-CoV-2 test (PCR)				♦		♦		♦			♦	♦	♦	♦
Assessment of clinical status (WHO scale)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Control of keeping the Patient's Diary		♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Registration of adverse events	♦[5]	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
ECG	♦					♦						♦		♦
Chest CT scanning	♦					♦						♦		♦
Clinical blood test[1]	♦					♦						♦		♦

Procedures	Screening	Period of therapy											Observation Period	
		Day 1 Visit	Day 2 Visit	Day 3 Visit	Day 4 Visit	Day 5 Visit	Day 6 Visit	Day 7 Visit	Day 8 Visit	Day 9 Visit	Day 10 Visit	Day 14 Visit	Day 21 Visit	Day 28 Visit
Days	-1… 0	1	2	3	4	5	6	7	8	9	10	14	21	28
Blood chemistry test and CRP[1]	♦					♦						♦		♦
Coagulation test [1]	♦					♦						♦		♦
Urine analysis[1]	♦					♦						♦		♦
Pregnancy test[6]	♦											♦		
Blood sampling for PK study[7]		♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦		

[1] For outpatients is made during transportation to the medical center / or during a home visit by medical personnel, in compliance with safety rules.
[2]TL-FVP is taken for 10 days according to the regimen 1800 mg every 12 hours (twice daily), then on days 2–10 – 800 mg every 12 hours (twice daily).
[3] Interviewing of a patient about the subjective symptoms is carried out by the study physician daily for 10 days, and then – on days 14, 21, and 28. Based on the results of the interview, a symptom status questionnaire is filled in.
4 Measurement of temperature, BP, HR, and SpO_2 is carried out for 10 days daily (measurement of temperature and SpO_2 at least 3 times daily), and then – on days 14, 21, and 28 (once a day); in the outpatient setting, subjects do it on their own. RR is measuring by the study physician.
[5] From the moment the informed consent is signed until the first dose of the study products is administered, only SAEs are registered.
[6] For patients with preserved reproductive potential.
[7] Blood samples will be taken before administration of the first drug dose, then at the following points: 20 min; 40 min; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours. On days 2–10, blood samples will be taken 5 minutes before the next (morning) intake of the drug. On days 5 and 10, additional blood samples will be taken in 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours after the first administration of the drug on this day.

4.6.2. Individual visit procedures

4.6.2.1. Screening visit

The screening period in the study begins from the moment of signing the informed consent and lasts no more than 2 days (from -1 to 0 days) until the patient is included in the study (randomization).

- Informed consent process (for outpatients, after signing the ICF, they send it to the investigator in the electronic form).
- Collecting a medical history and complaints.
- Data collection on concomitant therapy (including drugs used during the previous month before the date of inclusion in the study).
- Data collection on height and body weight.
- Assessment of vital signs: measurement of BP, HR, body temperature, pulse oximetry (SpO_2), and RR.
- Clinical blood test (3 ml).
- Blood chemistry test (6 ml).
- Coagulation test (6 ml).
- Urine analysis.
- Chest CT*.
- ECG.
- Assessment of clinical status according to the WHO 8-category scale.
- Assessment of the severity of symptoms (in points).
- Pregnancy test.
- Verification of compliance with the inclusion/exclusion criteria.
- Registration of SAEs.
- Decision on inclusion and randomization.

The total volume of blood taken during the visit: 15 ml

* it is allowed to use the results of the study for up to 4 days.

At the screening stage, patients will be invited to participate in the study, and they will be given 2 copies of the patient's information sheet with the informed consent form to review and make a decision about participating in the study. The signed informed consent of a patient to participate in the study must be obtained before performing any of the provided study procedures, including the screening procedures themselves.

Due to restrictions caused by the epidemiological situation, the second copy cannot be delivered to the study site from outpatients at the time of signing the ICF (it will be delivered to the patient by courier service in a contactless manner). After signing the ICF, which will be supervised by the investigator using telemedicine technologies, the patient sends to the investigator a photo of all the pages of the informed consent that was just signed. The original IC can be delivered to the study site only after a time period that ensures the complete elimination of virus particles from paper.

Along with a copy of the patient's information sheet with the informed consent form, a pregnancy test is provided to female patients to review and make a decision on participation in the study. All-female patients must have a negative pregnancy test result, which must be confirmed by a photograph and sent to the investigator.

After signing two copies of the informed consent, all patients are examined, including clinical blood tests and blood chemistry tests, coagulation tests, ECG, CT, pulse oximetry, BP, body temperature, and urine analysis. The study physician collects information about the patient's history, previous and current therapy, and evaluates the patient's clinical status and the severity of symptoms. Anthropometric parameters (height, weight) are recorded from the patient's words. The initial values of vital signs are measured (BP, HR, and body temperature), pulse oximetry (SpO_2), and RR measurement (before the first drug intake).

If there are no results of chest CT performed no more than 4 days before inclusion in the study, the CT procedure is performed during the screening period (the study will be conducted in medical facilities that have been converted to receive patients with a coronavirus disease). The patient will be transported to the CT location by special transport.

For hospitalized patients, all examinations are performed according to the standard regimen in the study site.

Using results of the examination, the doctor makes a conclusion on compliance with the inclusion/exclusion criteria on the basis of which the patient is allowed or not allowed to further participate in the study, and the severity of the disease, on the basis of the classification in the IG of MoH of Russia “Prevention, diagnosis and treatment coronavirus disease (COVID-19)”:

Mild form:

- Body temperature below 38 °C, cough, weakness, sore throat.
- No criteria for moderate and severe form.
- Low severity of the main symptoms or their absence, erased clinical picture of the disease.

Moderate form:

- Fever above 38 °C.
- RR more than 22/min.
- Shortness of breath during exercise.
- Pneumonia (confirmed by lung CT scan).
- $SpO_2 < 95\%$.
- Serum CRP more than 10 mg/l.

The study physician enters the obtained data into the screening form and sends it to the Sponsor's representative.

If the patient does not meet the inclusion criteria or if the conditions and/or diseases described in the exclusion criteria are detected, the patient is excluded from the study. If the patient meets the inclusion criteria and does not meet the exclusion criteria, randomization is performed and Visit 1 is scheduled for the next day (acceptable deviation + 1 day).

4.6.2.2. Treatment period visits

For outpatients, all contacts with the study physician will be carried out in the format of telemedicine technologies. In addition to interviewing the patient, measuring RR, and assessing the severity of symptoms, the study physician will remotely monitor the patient's vital signs measurement procedures and keeping the Patient's Diary, and on the days of smear sampling for PCR diagnostics – the smear sampling technique. The Patient's Diary is kept on days 1–10 daily, and the results of body temperature measurement and pulse oximetry are recorded at least 3 times daily.

Day 1 Visit

- Concomitant therapy data collection.
- Outpatients will be given the Study Participant Kit for outpatients, including:
  1) Packages with the study drug/comparator drug,
  2) Thermometer (1 pc.),
  3) Electronic tonometer (1 pc.),
  4) Portable pulse oximeter (1 pc.),
  5) Set for biomaterial sampling (7 pcs.),
  6) Container for collecting urine (2 pcs.),
  7) Patient's Diary (1 pc.),
  8) Pregnancy test (for women only),
  9) A set of personal protective equipment for transportation to the medical center for CT and tests,
  10) Technical guide for the patient in the study.

  For outpatients, delivery will be carried out with the involvement of a transport company and transferred to a patient by a courier in a contactless way.
- Inpatients will be given a reduced Study Participant Kit for inpatients, including:
  1) Packages with the study drug/comparator drug,
  2) Thermometer (1 pc.),
  3) Electronic tonometer (1 pc.),
  4) Portable pulse oximeter (1 pc.),
  5) Patient's Diary (1 pc.),
- Delivery of the study drug/comparison treatment.
- Interviewing of the patient on the severity of symptoms (result in points) (for outpatients, using telemedicine technologies).
- Assessment of vital signs: measurement of BP, HR and body temperature, pulse oximetry (SpO_2) (in the outpatient setting, patients do it on their own), and RR measurement (in the outpatient setting, performed by the study physician using video monitoring). Body temperature and pulse oximetry should be measured at least 3 times daily.

- Taking the study treatment/comparison treatment.
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary.

PK-subgroup:

- Sampling for PK-study at the following time points: 5 minutes before taking the study drug, then after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours.
- Installation/removal of a venous catheter.

The total volume of blood taken during the visit: 65 ml (5 ml per 1 point).

Day 2, Day 4, Day 6, Day 8, and Day 9 Visits

- Concomitant therapy data collection.
- Interviewing the patient about the severity of symptoms (result in points).
- Assessment of vital signs: measurement of BP, HR and body temperature, pulse oximetry (SpO_2) (in the outpatient setting, patients do it on their own), and RR measurement (in the outpatient setting, performed by the study physician using video monitoring). Body temperature and pulse oximetry should be measured at least 3 times daily.
- Taking the study treatment/comparison treatment.
- Assessment of clinical status (WHO scale).
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary.

PK-subgroup:

- Sampling for PK-study at the following time points: on Days 2, 4, 6, 8, 9 of the study 5 minutes before the next (morning) intake of TL-FVP-t.

The total volume of blood taken at each visit: 5 ml (5 ml per 1 point).

Day 3 Visit

- Concomitant therapy data collection.
- Taking the study treatment/comparison treatment.
- Interviewing the patient about the severity of symptoms (result in points).
- Assessment of vital signs: measurement of BP, HR and body temperature, pulse oximetry (SpO_2) (in the outpatient setting, patients do it on their own), and RR measurement (in the outpatient setting, performed by the study physician using video monitoring). Body temperature and pulse oximetry should be measured at least 3 times daily.
- Taking the study treatment/comparison treatment.
- SARS-CoV-2 test (PCR) (for outpatients, non-contact sampling of biomaterial is performed by the CL*).
- Assessment of clinical status (WHO scale).
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary.

* Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

PK-subgroup:

- Sampling for PK-study at the following time points: 5 minutes before the next (morning) intake of TL-FVP-t.

The total volume of blood taken during the visit: 5 ml (5 ml per 1 point).

Day 5 Visit

- Concomitant therapy data collection.
- Interviewing the patient about the severity of symptoms (result in points).
- For outpatients, performed by the study physician. Administration of the study treatment/comparison treatment
- SARS-CoV-2 test (PCR)*.
- Assessment of clinical status (WHO scale).
- Chest CT*.
- ECG*.
- Clinical blood test (3 ml)*.
- Blood chemistry test and CRP (6 ml)*.
- Coagulation test (6 ml)*.
- Urine analysis*.
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary.

* In the outpatient setting, investigations and biomaterial sampling is carried out in a medical center that has been converted and equipped to work with coronavirus patients where they are transported by specialized transport.

The total volume of blood taken during the visit: 15 ml.

PK-subgroup:

- Sampling for PK-research at the following time points: 5 minutes before the morning intake of the study drug, then after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours.
- Installation/removal of a venous catheter.

The total volume of blood taken during the session: 80 ml (65 ml (5 ml per 1 point) + 15 ml for laboratory investigations).

Day 7 Visit

- Concomitant therapy data collection.
- Taking the study treatment/comparison treatment.
- Interviewing the patient about the severity of symptoms (result in points).
- Assessment of vital signs: measurement of BP, HR and body temperature, pulse oximetry (SpO_2) (in the outpatient setting, patients do it on their own), and RR measurement (in the outpatient setting, performed by the study physician using video monitoring). Body temperature and pulse oximetry should be measured at least 3 times daily.
- Taking the study treatment/comparison treatment.
- SARS-CoV-2 test (PCR)*.

- Assessment of clinical status (WHO scale).
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary.

* Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

PK-subgroup:

- Sampling for PK-study at the following time points: 5 minutes before the next (morning) intake of TL-FVP-t.

The total volume of blood taken during the visit: 5 ml (5 ml per 1 point).

Day 10 Visit

- Concomitant therapy data collection.
- Interviewing the patient about the severity of symptoms (result in points).
- Assessment of vital signs: measurement of BP, HR and body temperature, pulse oximetry (SpO_2) (in the outpatient setting, patients do it on their own), and RR measurement (in the outpatient setting, performed by the study physician using video monitoring). Body temperature and pulse oximetry should be measured at least 3 times daily.
- Taking the study treatment/comparison treatment.
- SARS-CoV-2 test (PCR)*.
- Assessment of clinical status (WHO scale).
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary

* Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

PK-subgroup:

- Sampling for PK-research at the following time points: 5 minutes before the morning intake of the study drug, then after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours.
- Installation/removal of a venous catheter.

The total volume of blood taken during the visit: 65 ml (5 ml per 1 point).

4.6.2.3. Follow-up visits

For outpatients, all contacts with the study physician will be carried out in the format of telemedicine technologies. In addition to interviewing the patient, measuring RR, and assessing the severity of symptoms, the study physician will remotely monitor the patient's vital signs measurement procedures and keeping the Patient's Diary, and on the days of smear sampling for PCR diagnostics – the smear sampling technique. During days 11–14, the patient continues to fix information about vital signs in the diary daily, then on day 21 and 28.

In case of discharge of patients who were under inpatient observation during this period, they continue to be monitored in study sites, or routing is applied to them in the same way as routing of outpatients.

Day 14 Visit

- Concomitant therapy data collection.
- Interviewing the patient about the severity of symptoms (result in points).
- Assessment of vital signs: measurement of BP, HR and body temperature, pulse oximetry (SpO_2) (in the outpatient setting, patients do it on their own), and RR measurement (in the outpatient setting, performed by the study physician using video monitoring).
- SARS-CoV-2 test (PCR)*.
- Assessment of clinical status (WHO scale).
- Chest CT*.
- ECG*.
- Clinical blood test (3 ml)*.
- Blood chemistry test and CRP (6 ml)*.
- Coagulation test (6 ml)*.
- Urine analysis*.
- Pregnancy test (for women only).
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary

* In the outpatient setting, investigations and biomaterial sampling is carried out in a medical center that has been converted and equipped to work with coronavirus patients where they are transported by specialized transport.

The total volume of blood taken during the visit: 15 ml.

Day 21 Visit

- Concomitant therapy data collection.
- Interviewing the patient about the severity of symptoms (result in points).
- Assessment of vital signs: measurement of BP, HR and body temperature, pulse oximetry (SpO_2) (in the outpatient setting, patients do it on their own), and RR measurement (in the outpatient setting, performed by the study physician using video monitoring).
- SARS-CoV-2 test (PCR)*.
- Assessment of clinical status (WHO scale).
- Registration of AEs/SAEs.
- Control of keeping the Patient's Diary.

* Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

Day 28 Visit

- Concomitant therapy data collection.
- Interviewing a patient about the severity of symptoms (result in points)
- Assessment of vital signs: measurement of BP, HR, body temperature, pulse oximetry (SpO_2) (for outpatients, they should do it by their own) and RR measurement (for outpatients,

a study physician does it using video monitoring).

- SARS-CoV-2 test (PCR)*.
- Assessment of clinical status (WHO scale).
- Chest CT*.
- ECG*.
- Clinical blood test (3 ml)*.
- Blood chemistry test and CRP (6 ml)*.
- Coagulation test (6 ml)*.
- Urine analysis*.
- Registration of AEs/SAEs.
- Control of keeping the patient's diary.

* In the outpatient setting, investigations and biomaterial sampling is carried out in a medical center that has been converted and equipped to work with coronavirus patients where they are transported by specialized transport.

The total volume of blood taken during the visit: 15 ml.

4.6.2.4. End of Treatment Visit (including early termination)

Patients can at any time voluntarily stop the study therapy (withdraw consent), or complete it early, or leave the study early due to various reasons.

For all patients who received at least one dose of the drug and completed the treatment earlier (including those who discontinued early for any reason), the End of Treatment Visit is done. The visit to outpatients is done as soon as possible, no later than 14 days after the decision to terminate the treatment early or to exclude the patient from the study. If the End of Treatment Visit coincides with the date of the previously scheduled visit, the volume of procedures is performed according to the list for the End of Therapy Visit.

Below is a summary list of procedures for the End of Therapy Visit:

- Concomitant therapy data collection.
- Interviewing the patient about the severity of symptoms (result in points).
- Assessment of vital signs (measurement of BP, HR, and body temperature), pulse oximetry (SpO_2), and RR measuring.
- SARS-CoV-2 test (PCR) (only if the patient is still
- "positive" by PCR).
- Assessment of clinical status (WHO scale).
- Registration of AEs/SAEs.
- Providing and archiving copies (digital images) of diaries of hospitalized patients together with primary documentation

These visits when early termination happens are mandatory for all patients, except in cases where a patient is "lost to follow-up" or physically unable to attend the visit. All relevant records must be provided in the primary documentation and CRF.

4.6.2.5. Completion of participation in the study

After the final completion of all follow-up procedures, the patient is considered completely eliminated from the study. When this moment comes, the Study Completion Form is filled in eCRF.

4.7. Description of individual procedures in the study

All planned clinical, laboratory and instrumental procedures and their multiplicity are shown in Table 4.2.

Table 4.4. Multiplicity of clinical, laboratory, and instrumental investigations performed within the study.

Type of the study	Control parameter	Multiplicity	Location
Assessment of clinical status	• Rating on the WHO 8-category scale	×14: - on the screening once, then daily on days 1-10, then during visits on Days 14, 21, 28 once.	The study site or remotely for patients, in the outpatient setting
Assessment of subjective symptoms	• Intoxication • Catarrhal symptoms • Quality of life	×14: - on a single screening, then daily on days 1-10, then on visits on Days 14, 21, 28.	The study site or remotely for patients, in the outpatient setting
Keeping the Patient's Diary	• Concomitant therapy • The fact of taking the study drug/comparison drug • Subjective symptom • The results of the measurement of vital signs, performed independently	×16: - on days 1-14 (daily), then during visits on Days 21 and 28.	Filled in by the patient independently
Vital signs	• BP • HR • body temperature • RR	×33: daily on days 1-10 (body temperature measurement	The study site or remotely for patients, in the outpatient setting

Type of the study	Control parameter	Multiplicity	Location
	• SpO_2	and pulse oximetry should be performed at least 3 times daily), then during visits on Days 14, 21, 28 once.	
Clinical blood test	• hemoglobin • erythrocytes • platelets • leukocytes • neutrophils • lymphocytes • ESR (blood volume – 3 ml)	×4: - at the screening, then during visits on Days 5, 14, 28.	For outpatients, the analysis will be taken either in a medical facility equipped to work with patients with COVID-19 or when specialized teams do a home visit, samples will be sent to the CL. For hospitalized patients, sampling will be performed at the study site, and samples will be sent to the CL.
Blood chemistry panel	• Glucose • ALT • AST • LDH • General bilirubin • Creatinine • CPK • ferritin • lactate • uric acid • CRP (blood volume – 6 ml)	×4: - at the screening, then during visits on Days 5, 14, 28.	For outpatients, the analysis will be taken either in a medical facility equipped to work with patients with COVID-19 or when specialized teams do a home visit, samples will be sent to the CL. For hospitalized patients, sampling will be performed at the study site, and samples will be sent to the CL.
Coagulation test	• activated partial thromboplastin time (APTT) • prothrombin time • fibrinogen • D-dimer	×4: - at the screening, then on Days 5, 14, 28.	For outpatients, the analysis will be taken either in a medical facility equipped to work with patients with COVID-19 or when specialized teams do a home visit, samples will be sent to the CL. For hospitalized patients, the sampling will be

Type of the study	Control parameter	Multiplicity	Location
			performed in the study site, samples sent to the CL.
Urinalysis	• standard set of parameters	×4: - at the screening, then during visits on Days 5, 14, 28.	For outpatients, the analysis will be taken either in a medical facility equipped to work with patients with COVID-19 or when specialized teams do a home visit, samples will be sent to the CL. For hospitalized patients, sampling will be performed at the study site, and samples will be sent to the CL.
SARS-CoV-2 test (PCR)	• high-quality SARS-CoV-2 PCR test	×7: - during visits on Days 3, 5, 7, 10, 14, 21, 28	For outpatients, smear sampling will be performed independently (by the patient), under the supervision of a study physician, or in a medical facility equipped to work with patients with COVID-19, samples will be sent to the CL (non-contact method – in the case of sampling at home). For hospitalized patients, sampling will be performed at the study site, and samples will be sent to the CL.
Instrumental investigations	• Chest CT scan*	×4: - at the screening, then during visits on Days 5, 14, 28.	Specialized CT centers in medical institutions equipped to work with COVID-19 patients will be used for outpatients. For hospitalized patients, CT is performed in the study site.
	• ECG	×4: - at the screening, then during visits on Days 5, 14, 28.	For outpatients, ECG will be performed in a medical facility equipped to work with COVID-19 patients. For hospitalized patients, an ECG will be performed in the study site.
Pharmacokinetics study and	Plasma concentrations of favipiravir	×46-13 fences on sessions Day 1, Day 5, Day 10,	Selection of biological samples for PK study is made only in the study site, further samples

Type of the study	Control parameter	Multiplicity	Location
		1 sampling on days 2–4 and 6–9.	are sent to the pharmacokinetics laboratory
* It is acceptable to use results obtained no more than 4 days before inclusion in the study			

Table 4.5 below shows the estimated amount of blood collected during each visit.

Table 4.5. The amount of blood taken from one participant during the study.

Name of the visit	Types of laboratory tests (multiplicity/blood volume in one sample)	The total volume of blood
Screening	• CBT (1/3 ml) • BCT (1/6 ml) • CBC (1/6 ml)	15 ml
Day 1 Visit	• PK (13/5 ml)	65 ml
Day 2 Visit	• PK (1/5 ml)	5 ml
Day 3 Visit	• PK (1/5 ml)	5 ml
Day 4 Visit	• PK (1/5 ml)	5 ml
Day 5 Visit	• PK (13/5 ml) • CBT (1/3 ml) • BCT (1/6 ml) • CBC (1/6 ml)	80 ml
Day 6 Visit	• PK (1/5 ml)	5 ml
Day 7 Visit	• PK (1/5 ml)	5 ml
Day 8 Visit	• PK (1/5 ml)	5 ml
Day 9 Visit	• PK (1/5 ml)	5 ml
Day 10 Visit	• PK (13/5 ml)	65 ml
Day 14 Visit	• CBT (1/3 ml) • BCT (1/6 ml) • CBC (1/6 ml)	15 ml
Day 28 Visit	• CBT (1/3 ml) • BCT (1/6 ml) • CBC (1/6 ml)	15 ml
The total blood volume that is taken from a single patient during the entire study		**290 ml**

4.7.1. Obtaining written Informed consent

Before starting any of the screening procedures, the study physician must provide the patient with comprehensive information about the study and the conditions of participation, including the following information:

- The clinical study is experimental, the patient's participation in the clinical study is voluntary and they can refuse to participate in the clinical study at any time.
- The purpose of the clinical study, its duration, and the approximate number of participants.

- Treatment options in the clinical study and the probability of random distribution to one of the treatment groups.
- The clinical study procedures, including all invasive procedures.
- Responsibilities of a clinical study participant.
- The expected risks and (or) benefits for the participant of the clinical study, as well as the risks of pregnancy in the patient's sexual partner during participation in the study;
- Other procedures or methods of treatment (in addition to those in the Protocol) that may be available to the participant of the clinical study, as well as their potential benefits and risks.
- Compensation and (or) treatment available to a clinical study participant in the event of harm to their health as a result of participation in the clinical study.
- Expected expenses for a clinical study participant related to their participation in the clinical study (if applicable).
- By signing the patient's information sheet, clinical study participants grant permission for the person designated for monitoring, auditors, independent ethics committees, and authorized bodies to access their medical records.
- The records identifying a clinical study participant will be kept confidential, their disclosure is allowed in accordance with the legislation of the participating countries, and after publishing the results of the clinical study, the confidentiality of the data of a clinical study participant will be preserved.
- Clinical study participants will be immediately informed of new information that may affect their desire to continue participating in the clinical study.
- Individuals who can be contacted for more information about the clinical study and the rights of clinical study participants.
- Possible circumstances and (or) reasons why a person's participation in the clinical study may be discontinued.

Before obtaining voluntary informed consent, the study physician must give a patient sufficient time to decide whether to participate in the clinical study or not. A patient has the right to receive comprehensive and reliable answers to all questions about the clinical study.

After receiving all the necessary information, a patient must sign and date in duplicate the Information sheet with the patient's informed consent form for participation in the study. The investigator also signs and dates the Information sheet with the patient's informed consent form, thereby certifying that the interview with the patient was conducted and consent was obtained and that the patient had the opportunity to ask questions and received complete answers to them. Both copies of the consent will be sent to outpatients by courier in a contactless way.

The patient receives one copy of the Information sheet with the patient's informed consent form, and the second copy is stored by the investigator in the study site along with other study documentation. Due to restrictions caused by the epidemiological situation, for outpatients, at the time of signing the ICF, the second copy cannot be delivered to the study site

(the ICF will be delivered to outpatients by courier service in a contactless way). After signing the ICF, which will be monitored by the investigator using video communication, a patient sends the investigator a photo of all the pages of the informed consent that was just signed. The original ICF can be delivered to the study site only after a time period that ensures the complete elimination of virus particles from paper.

Due to existing sanitary and epidemiological restrictions, the Informed Consent Form signed by patients in the “red” zone cannot be taken outside the “red” zone and properly stored together with the study documents, to ensure compliance with the Principles of GCP the following procedure is provided: a patient signs 2 copies of the Informed Consent Form, provides a copy (digital image) to the study physician, the study physician prints copies in the “green” zone. Upon completion of participation in the study, the patient, with his own hand, makes notes on the confirmation of the fact of signing in the printed copies of the previously signed Informed Consent Form, one copy is handed over to the patient, the second is to be archived in the study site.

After signing the Informed Consent Form, the physician must also give the patient the original insurance policy. The original insurance policy will be sent to outpatients by courier along with the informed consent form.

For inpatients, the individual mandatory life and health insurance policy of the patient, together with the Study Participant's Card, will be held by the study physician for the entire period while a patient is in the “red” zone. This is necessary to ensure the availability of the document, due to the occurrence of an insured event and compliance with the rules of the hygienic and epidemiological regime of the hospital.

4.7.2. Collecting a medical history and demographic data

Based on the records in the patient's medical documentation, as well as the results of the patient interview, the following parameters will be recorded:

Demographic data:

- Date of birth (age).
- Sex.
- Ethnicity and race.
- Evaluation of childbearing potential (use of contraception methods with their indication, data on sterilization, if applicable).

Information about bad habits (smoking and taking alcohol).

Anthropometric data:

- Growth.
- Body weight.

Medical history. Collection of information about past/comorbid diseases (past infectious diseases, chronic infectious and inflammatory diseases, injuries, comorbid somatic diseases) with a known start/end date (if applicable)

Medical history. Collection of medical history (medications that a patient received within 30 days before the start of the

screening examination with an indication of the dosage, dosage frequency, duration of administration, reasons for prescribing and cancellation (if applicable).

4.7.3. Assessment of clinical status according to the WHO scale

The clinical status will be assessed on the basis of the WHO 8-category scale.

Table 4.6. WHO Ordinal Scale for Clinical improvement:

The patient's status	Appearance	Evaluation
Healthy*	Absence of clinical manifestations** and laboratory confirmation of absence of SARS-CoV-2 infection (COVID-19)	0
Outpatient	Activities of daily living are not restricted	1
	Activities of daily living are restricted	2
Hospitalized, moderate form	Oxygen therapy is not required	3
	Oxygen therapy through a mask or nasal cannulas is required	4
Hospitalized, severe form	Non-invasive ventilation or high-flow oxygenation	5
	Intubation, mechanical ventilation	6
	AVL + treatment of organ failure (vasopressors, extracorporeal membrane oxygenation, renal replacement therapy)	7
	Fatal outcome	8
* In the absence of clinical manifestations and laboratory confirmation of the absence of SARS-CoV-2 infection in hospitalized patients, they are also classified as “0”, “Healthy” ** The catarrhal symptom “cough” is allowed to remain, with no more than 1 point of severity		

Frequency and time of execution:

The clinical status will be assessed once at the screening, then daily on days 1–10, then on visits on Days 14, 21, 28 once.

For outpatients, the assessment is performed by the study physician using telemedicine tools; for hospitalized patients, it is performed in a standard way.

4.7.4. Assessment of the severity of symptoms by the study physician

Symptoms will be evaluated by the study physician based on the patient interview using a 4-point scale: 0 points (no complaints), 1 point (mild symptoms), 2 points (moderate symptoms), and 3 points (severe symptoms). The assessment will be made for symptoms such as cough, shortness of breath, myalgia, weakness, headache, etc., as well as restrictions on physical and mental activity. To assess symptoms, the study physician will be provided with questionnaires for evaluating symptoms.

Frequency and time of execution:

The severity of symptoms will be assessed once at the screening, then daily on days 1–10, then once on visits on Days 14, 21, 28.

For outpatients, the assessment is performed by the study physician using telemedicine tools; for hospitalized patients, it is performed in a standard way.

4.7.5. Keeping the Patient's Diary

Each patient on Day 1 visit will be given the Patient's Diary, where they will have to enter the following information about:

- Taking the study drug/comparison treatment (within the first 10 days of the study).
- Results of measuring BP, HR, body temperature, and pulse oximetry (SpO_2).
- The severity of symptoms and complaints that appeared during the day.
- Names, doses, and number of concomitant therapy drugs prescribed by the study physician, or taken at the patient's own discretion.

Frequency and time of execution:

The patient keeps the Patient's Diary for the first 14 days of the study daily and then on days 21 and 28. The study physician checks the Patient's Diary daily for the first 10 days of the study, and then on days 14, 21, and 28. During each following visit, the Diary that was filled in a day before is evaluated. For evaluation, a patient sends copies of their Diary to the study physician using telemedicine technologies.

4.7.6. Vital signs

The assessment of vital signs includes the measurement of:

- Axillary body temperature (in degrees Celsius).
- Blood pressure (BP) (on one hand, in mm Hg).
- Heart rate (using a tonometer).
- RR.
- SpO_2.

In this study, due to the epidemiological situation, the daily contact of study physicians with patients will be limited.

The outpatient population will be treated at home, the inpatient population – in the “red” zone of a hospital. To ensure control of vital signs of patients with the frequency established in the Protocol, as well as the proper fixation and preservation of the obtained data, each patient in the study will be given an individual set of medical devices intended for self-use by a patient: thermometer, electronic tonometer, and portable pulse oximeter. The patient will need to read the operating instructions for each of the devices and use the devices strictly as intended in this study. If necessary, the study physician will give explanations to a patient before using the devices. Additional explanations on the self-measurement of vital signs will be provided in the Patient's Guide. Moreover, the study physician will monitor the accuracy of measuring on a daily basis when contacting a patient (in person or using telemedicine technologies).

The RR measurement will be performed by the Study Physician based on a visual assessment of the movements of the anterior surface of the ribs and upper abdomen during contact with the patient (in person or using telemedicine technologies).

A patient will measure such vital signs as BP and HR independently, after a 5-minute rest in a sitting position. BP (systolic and diastolic BP) and HR will be detected on the same hand using the same device. The measurement will be performed under the supervision of the study physician (in person or using telemedicine technologies) at least once a day.

To determine body temperature, the axillary temperature will be measured. A patient will measure temperature independently, at least 3 times daily.

Blood oxygen saturation (SpO_2) will be assessed using a pulse oximeter (for the most reliable measurement result, patients' hands should be warm, without nail polish). Once a day, the measurement will be performed under the supervision of the Study Physician (in person or using telemedicine technologies), the patient will make the rest of the measurements independently, for at least 3 times daily in total.

The patient will enter the results of BP and HR measurement in the Patient's Diary once a day, immediately after the measurement during the first 14 days of the study, then on days 21 and 28.

The results of temperature measurement and pulse oximetry will be entered in the Patient's Diary immediately after each measurement, at least 3 times daily on days 1–10, once daily on days 11–14, then on days 21 and 28. The maximum values of body temperature and the minimum values of pulse oximetry are entered by the Study Physician in the primary documentation and eCRF.

Frequency and time of execution:

Assessment of vital signs will be performed on days 1–10 daily, with body temperature measurement and pulse oximetry on days 1–10 performed at least 3 times daily; once daily on days 11–13, then assessment of vital signs will be performed once daily on Days 14, 21, 28 visits.

4.7.7. Clinical laboratory tests

During the course of the study, in each subject, blood will be sampled for safety assessment laboratory tests. Laboratory tests will include assessment of the main indicators of clinical blood test, blood chemistry test, including CRP and urinalysis. If necessary, it is allowed to conduct additional laboratory studies to assess the dynamics of changes in the analyzed indicators.

Laboratory analyses are performed in the central contract laboratory. Blood sampling for clinical blood tests, blood chemistry tests, and coagulation tests are performed according to standard methods. Instructions for further sample preparation and sending of bio-samples are given in the laboratory manual.

For outpatients, the samples will be collected either in a medical facility equipped to work with COVID-19 patients, or at home when specialized teams arrive, and then the samples will be sent to the CL. For hospitalized patients, sampling will be performed at the study site, and samples will be sent to the CL.

In case of urgent need (if it is not possible to promptly send the biomaterial to the central laboratory), tests can be performed in local clinical laboratories of study sites, in agreement with the Sponsor.

4.7.7.1. Clinical blood test

A clinical blood test should be performed according to the standard method under fasting conditions (at least 4 hours of abstinence from food). This study includes an assessment of the following hematological parameters:

- hemoglobin (g/l),
- erythrocytes (cells $\times 10^{12}$/l),
- leukocytes (cells $\times 10^{9}$/l),
- platelets (cells $\times 10^{9}$/l),
- neutrophils (cells $\times 10^{9}$/l),
- lymphocytes (cells $\times 10^{9}$/l),
- erythrocyte sedimentation rate (mm/h).

The volume of blood taken is **3 ml**.

Blood sampling for tests is performed according to standard methods.

Frequency and time of execution:

Blood for the clinical tests will be sampled at the screening, then once on Days 14, 21, 28 visits.

4.7.7.2. Blood chemistry panel

A blood chemistry test is performed according to the standard method under fasting conditions (at least 4 hours of abstinence from food, including sweet or alcoholic beverages).

The analysis includes determining the following parameters:

- Glucose
- ALT
- AST
- LDH
- General bilirubin
- Creatinine
- CPK
- ferritin
- lactate
- uric acid.
- C-reactive protein (CRP)

The volume of blood taken is **6 ml.**

Blood sampling for tests is performed according to standard methods.

Frequency and time of execution:

Blood for blood chemistry test will be sampled at the screening, then once during visits on Days 14, 21, 28.

4.7.7.3. Coagulation test

A coagulation test is performed according to the standard method under fasting conditions (at least 8 hours of abstinence from food, including sweet or alcoholic beverages).

The analysis includes determining the following parameters:

- activated partial thromboplastin time (APTT),
- prothrombin time
- fibrinogen
- D-dimer.

The volume of blood taken is **5 ml.**

Blood sampling for tests is performed according to standard methods.

Frequency and time of execution:

Blood for the coagulation test will be sampled at the screening, then once on Days 14, 21, 28 visits.

4.7.7.4. Urinalysis

Urine sampling and analysis will be performed using standard methods.

The following indicators are defined:

- color,
- density,
- protein,
- glucose,
- ketones,
- urobilinogen,
- bilirubin,
- erythrocytes,
- leukocytes,
- pH of urine.

Frequency and time of execution:

Urine analysis will be performed at the screening, then once on Days 14, 21, 28 visits.

4.7.8. SARS-CoV-2 test (PCR)

A smear from the nasopharynx or oropharynx is taken with a sterile swab, which, after taking the material, is placed in a sterile plastic tube with a transport medium (taking into account the recommendations of the manufacturer of the test systems/reagent kits used). To increase the concentration of the virus, nasopharyngeal and oropharyngeal smears should be placed in the same tube. The temperature during the transportation of biological material should be +2...+8 °C. The storage time for samples prior to testing should not exceed 5 days at +2...+ 8 °C, this time can be prolonged when stored at -20 °C or -70 °C.

For outpatients, smear sampling will be performed independently (by the patient), under the supervision of the study physician, or in a medical facility equipped to work with COVID-19 patients, samples will be sent to the CL (non-contact method – in case of taking the samples from home). For hospitalized patients, sampling will be performed at the study site, and samples will be sent to the CL.

Frequency and time of execution:

The analysis will be performed on Days 3, 5, 7, 10, 14, 21, 28 visits. After receiving a negative test result for the presence of the SARS-CoV-2 virus, a second study to confirm the fact of elimination of the virus will be carried out after a minimum of 24 hours. After confirmation of the elimination of SARS-CoV-2 (2 negative tests), sampling will be stopped.

4.7.9. Chest CT scanning

Chest scanning is performed according to the standard program established by the manufacturer, with the patient supine, with his hands behind his head, if possible with a calm, delayed breath. In a study of mechanically ventilated patients, respiratory retention will occur with a short delay in respiratory movements. CT testing of mechanically ventilated patients is performed only if technically feasible, and the patient can be delivered to the unit.

Intravenous contrast is not required but can be used if other pathological conditions are suspected, such as pulmonary embolism.

CT Protocol is formed according to standard rules similar to those in radiographic examinations. However, it uses the terminology adopted in the description of the CT data. The study provides the Manual for CT testing and the obtained data evaluation.

To evaluate CT results, reference evaluation will be performed by the Central Independent Committee for the evaluation of computed tomography data (CIC on CT). The CIC on CT operates in this study in accordance with the Charter.

The CIC on CT was created as part of the TL-FVP-t-01 study to review the following CT data:

- Screening CT scans considered the baseline level for patients in the clinical study.
- CT results obtained during the entire period of the clinical study.

The CIC on CT activities are aimed at ensuring the rights and safety of study participants and timely providing the most complete information on the assessment of their CT results.

The CIC on CT is required to perform its activities in regular contact with representatives of the Sponsor, investigators, or any other person who has direct contact with the study participants or has significant information about the clinical study.

A conflict of interest (scientific, financial, etc.) on the part of CIC on CT members in relation to the ongoing TL-FVP-t-01 study is unacceptable. All members of the CIC on CT must sign a confidentiality agreement provided by the study Sponsor.

For outpatients, CT will be performed in specialized CT centers in medical institutions equipped to work with COVID-19 patients; for hospitalized patients, it will be performed in the study site.

Frequency and time of execution: CT will be performed at the screening, then once on Days 5, 14, 28 visits. In the case of complete resolution of the lung lesions on CT scans on Day 14 visit, according to the conclusion of the CIC, on Day 28 visit, CT may be omitted.

4.7.10. Electrocardiography (ECG)

The ECG in this study will be performed in 12 leads (I, II, III, aVR, aVL, aVF, V1 - V6). The ECG will be recorded after the patient has been lying at rest for at least 10 minutes.

Copies of the ECG will be attached to the patients' CRF. Heart rate will be measured and a conclusion about the norm, the presence of clinically significant or clinically insignificant changes in the patient's ECG will be released.

For outpatients, ECG will be performed in a medical facility equipped to work with COVID-19 patients; for hospitalized patients, it will be performed in the study site.

Frequency and time of execution:

ECG will be performed at the screening, then once on Days 5, 14, 28 visits.

4.7.11. Blood plasma sampling for pharmacokinetics study

To evaluate the pharmacokinetics of the TL-FVP-t, blood sampling to determine the concentrations of favipiravir and its metabolite will be periodically performed in patients.

Detailed instructions for the biomaterial sampling, conducting sample preparation and storage of biomaterials will be presented in the separate Laboratory Manual.

The total volume of blood sampled for pharmacokinetics study will be

220 ml, the volume of one sample is 5 ml.

Blood sampling and sample preparation procedure

Detailed instructions for sampling, sample preparation, and storage of biomaterials will be provided in the separate Laboratory Manual.

The total volume of blood sampled for pharmacokinetics study will be 220 ml, the volume of one sample is 4 ml, before each blood sampling, the first portion of venous blood from the cubital catheter, with a volume of 1 ml, is discarded.

Blood sampling and sample preparation procedure

Blood is sampled through the central or peripheral venous catheter, in accordance with the practice of the study site. 15–30 minutes after the catheter is installed, the first blood sample is taken, then a patient takes the study drug/comparator drug, and then samples are taken according to the specified regimen in 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours.

For the investigation purposes, venous blood in a volume of no more than 5 ml is taken to vacutainers. After blood sampling, the vacutainer with blood is turned over 8–10 times to completely mix the blood with anticoagulants applied to the walls.

The time interval between blood collection, centrifugation, and freezing should not exceed 30 minutes. Blood plasma is separated by centrifugation at 3000 rpm for 10 minutes (conditions can be adjusted after validation of the method). After centrifugation, the test tubes are removed from the centrifuge. The sediment consists of fragments of blood cells and cellular elements. The resulting plasma is located above the blood corpuscles, in contact with them, so you should not shake or tip the tube. At least 1 ml of plasma is transferred to pre-labeled, dry plastic Eppendorf tubes for aliquot A, the remaining plasma is transferred to pre-labeled, dry plastic Eppendorf tubes for aliquot B. Test tubes are immediately placed in storage at a temperature not higher than -20 °C (storage at a temperature up to -80 °C is also allowed). If the sample was not taken, the encrypted blood plasma tube remains empty, which is recorded in the accompanying documentation. During the study, the freezer temperature will be monitored according to the standards of the study site. Responsibility for

the temperature control is taken by the Principal Investigator. The freezer temperature control logs will be located in the "green" zone.

Each test tube must be clearly signed in such a way as to prevent erasing of the applied data. The test tube must indicate:

- study number,
- identification number of the patient (subject ID),
- individual sample number,
- number of the study site,
- place of blood sampling.

The individual sample number is unique and consists of a letter (A or B, which defines part of the sample, and 2 digits: 1st and 2nd – the sampling day, 3rd and 4th digits – the serial number of the sample (sample No. 01 – before taking the drug, sample No. 02 – a sample that was taken 20 minutes after the drug administration, sample No. 03 – a sample taken 40 minutes after the drug administration, and so on, up to the last sample). The unique labeling of test tubes is shown in Table 4.7.

Frequency and time of execution:

According to the study of the pharmacokinetics of the original drug favipiravir, the time to reach the maximum concentrations of favipiravir is 1.5–2 hours. The selection of sampling time points should ensure that several points are obtained for each fragment of the pharmacokinetic curve – at least 3 for the phase of initial concentration increase and at least 5 for the phase of concentration decrease. Therefore, based on this requirement and the available literature data on the pharmacokinetics of favipiravir, the following time points were selected for blood sampling: before administration of the drug, after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours after administration of the drug. These time sampling points will allow the most accurate characterization of the pharmacokinetic profile of the investigated substance, taking into account the expected individual differences in values and time of reaching maximum concentrations.

Table 4.7. Unique labeling of plasma tubes for pharmacokinetics study.

Sampling time	The unique number of the sample									
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**
5 min. before administration	A-01-01 B-01-01	A-02-01 B-02-01	A-03-01 B-03-01	A-04-01 B-04-01	A-05-01 B-05-01	A-06-01 B-06-01	A-07-01 B-07-01	A-08-01 B-08-01	A-09-01 B-09-01	A-10-01 B-10-01
20 minutes	A-01-02 B-01-02				A-05-02 B-05-02					A-10-02 B-10-02
40 minutes	A-01-03 B-01-03				A-05-03 B-05-03					A-10-03 B-10-03
1 hour	A-01-04 B-01-04				A-05-04 B-05-04					A-10-04 B-10-04
1.25 hours	A-01-05 B-01-05				A-05-05 B-05-05					A-10-05 B-10-05
1.5 hours	A-01-06 B-01-06				A-05-06 B-05-06					A-10-06 B-10-06
1.75 hours	A-01-07 B-01-07				A-05-07 B-05-07					A-10-07 B-10-07
2 hours	A-01-08 B-01-08				A-05-08 B-05-08					A-10-08 B-10-08
2.5 hours	A-01-09 B-01-09				A-05-09 B-05-09					A-10-09 B-10-09
4 hours	A-01-10 B-01-10				A-01-10 B-01-10					A-01-10 B-01-10
6 hours	A-01-11 B-01-11				A-01-11 B-01-11					A-01-11 B-01-11
8 hours	A-01-12 B-01-12				A-01-12 B-01-12					A-01-12 B-01-12
12 hours	A-01-13 B-01-13				A-01-13 B-01-13					A-01-13 B-01-13

4.7.12. Procedures for storage and shipment of biological samples

Plasma samples are stored in the study site before being sent to the central pharmacokinetics laboratory. Detailed instructions for storage and shipment will be provided in the separate Laboratory Manual.

The accompanying documentation for frozen samples must be sent with them to the central laboratory.

4.7.13. Method for determining analyte in blood plasma

4.7.13.1. Planning analytical procedures

In the study, it is planned to determine the concentration of favipiravir and its metabolite in the blood plasma of patients after repeated administration of the study drug.

4.7.13.2. Validation of the method

The assay of favipiravir in blood plasma will be performed using a highly sensitive and selective method of high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS) using an internal standard. The extraction of the analyte from the matrix will be carried out by a protein precipitation method or extraction (liquid, solid-phase).

The method will be validated in accordance with the requirements of the EEU. The parameters of the bioanalytical method used will be described in detail in the report on the development and validation of the bioanalytical method.

The following characteristics of the bioanalytical method should be evaluated during validation:

- selectivity,
- lower limit of quantitation (LLOQ),
- response function and analytical range (reproducibility of calibration curve parameters),
- accuracy,
- precision,
- influence of the matrix (the matrix effects (completeness of elution)),
- stability of the investigated substances in biological samples and stability of the investigated substance(s) and inactive components during storage, in working solutions, in extracts during the entire period of storage and sample preparation.

4.7.13.3. Stability evaluation of biological samples

The stability of the drugs in the blood plasma will be evaluated:

а) during storage – long-term stability study at a temperature no higher than -65 °C.

б) under processing conditions – short-term stability study at room temperature; processed stability

в) stability after three freeze/thaw cycles;

4.7.13.4. Method for determining analyte in blood plasma

Assay of favipiravir in blood plasma will be performed using a validated method of reverse-phase high-performance liquid chromatography and tandem mass spectrometry (RP-HPLC-MS/MS), in accordance with the requirements of the EAEU. The internal method of the pharmacokinetics laboratory will be used.

The lower limit of assay of favipiravir will not exceed 100 ng/ml, while the condition will be met that the lower limit of assay will not exceed 5% of the maximum concentration (C_{max}). The upper limit of quantitation will be selected based on the linearity of the method. If necessary, the dilution integrity will be validated, which will cover the entire range of concentrations in the test samples. The dilution integrity can be evaluated during partial validation of the method.

The final composition of the mobile phase, chromatographic analysis parameters, ionization, fragmentation (MRM), and sample preparation parameters will be selected and optimized during the development of the method.

4.7.14. Registration of adverse events

Adverse events (AE) will be registered by the Investigator during the study according to the procedures presented in the relevant section of the Protocol, on each visit.

During the screening, only SAEs are registered, and other information will be attributed to the subject's medical history.

4.7.15. Assessment of concomitant therapy

Information about concomitant therapy is recorded by the investigator during the study according to the procedures provided in the relevant section of the Protocol, on each visit.

4.7.16. Electronic CRF completion

To work in the electronic CRF system (eCRF), the principal investigator and members of his team will be provided with individual logins and passwords to access.

The electronic CRF (eCRF) must be completed within 5 business days from the date of the visit. The screening data is also entered in the eCRF within 5 business days after the end of the screening.

In the eCRF system, patients are identified only by a unique identification number, and the use of screening numbers when entering patients in the system is not allowed.

For patients who have not passed screening (screen-outs), you do not need to enter data in the electronic CRF.

4.7.17. The procedure for remote contact with a patient using telemedicine technologies

The procedure for remote contact with the patient includes:

- Interviewing a patient about symptoms and complaints.

- Interviewing about the use of concomitant therapy.
- Interviewing about adverse events.
- Monitoring the procedure of measuring vital signs.
- Control of keeping the Patient's Diary, including data on the use of the study drug/comparator drug, the results of measuring vital signs, data on the use of concomitant therapy, the appearance of new complaints, and the assessment of symptoms.
- Control of the procedure of sampling smears from the nasopharynx and oropharynx for PCR diagnostics (if performed on the visit);
- Respiratory rate (RR) assessment.
- Assessment of the severity of symptoms of the disease (in points).
- Evaluation of the clinical condition of patients according to the WHO scale.

To facilitate remote contacts, the study physician will be provided with a checklist with the above questions and questionnaires to assess the severity of symptoms.

4.8. Description of "stopping rules" or "criteria for early withdrawal from the study" for individual subjects, parts of the study, or the entire study

4.8.1. Description of the "stopping rules" for the entire study

The study may be discontinued for the following reasons:

1. By the decision of Drugs Technology LLC for reasons of safety, ethics, compliance with the Protocol, or for other reasons.
2. According to the decision of local ethics committees or regulatory authorities.
3. By the decision of the Independent Data Monitoring Committee (IDMC) after an interim analysis of the safety data.

The sponsor has the right to temporarily suspend the study at any time for reasons including (but not limited to) safety, ethics, or administrative issues. The sponsor has the right to terminate the study at any time if the goals and objectives of the study are not met. In this case, the Sponsor must notify the Investigator or the management of the study site of the temporary suspension or early withdrawal from the study in writing.

If a study is suspended or terminated for reasons related to safety, the Sponsor will immediately inform the Investigator, as well as regulatory authorities and ethics committees.

4.8.2. Description of criteria for early withdrawal from the main part of the study (therapy period) for individual subjects

Patients will be excluded from further participation in the study in the following cases:

1. Detection of gross violations of the inclusion/exclusion criteria after the inclusion of a patient in the study (by the decision of Drugs Technology LLC)[21].

[21] Deviations from the inclusion/exclusion criteria, if justified by the investigator and agreed by the Sponsor, are not a reason for excluding a volunteer from the study.

2. For outpatients, hospitalization due to the increasing severity of symptoms of SARS-CoV-2 infection.
3. Pregnancy in the patient.
4. When study subjects withdraw their consent to participate in the study;
5. If AEs or SAEs, laboratory abnormalities, or comorbidities are found in patients, that, in the opinion of the investigator or sponsor, makes the continuation of the study treatment impossible, or dangerous for patients, or does not meet the interests of the maximum well-being and safety of patients.
6. If a patient is incompliant (in this case, the exclusion of the patient must be agreed with representatives of Drugs Technology LLC, see section 6.3.1 "Assessment of compliance"), or in the case of missing visits 1–5, or systematic gross violation of the planned visits (more than 1 failure to meet the planned time of visits for more than 1 day).
7. In case of termination of the study by the decision of Drugs Technology LLC, local ethics committees or regulatory authorities.
8. In the case of the use of drugs prohibited by the Protocol.
9. If patients die.

The investigator must inform Drugs Technology LLC within 24 hours about the early withdrawal of a patient, indicating the reasons.

In the case of early withdrawal, it is necessary to fill out the End of Study Form in the CRF, the procedures for monitoring patients who left early are described in section 5.4 (list of procedures on each visit).

For more information, see section 11.8 below "Study completion".

4.9. Procedures for ordering, receiving, returning, and accounting for drugs used in the study

For outpatients, the following procedure is provided for ordering, receiving, and returning the study treatment.

Ordering an individual set of the study treatment is carried out by the authorized study physician based on the results of randomization and distribution of the patient to one of the two study groups. The study physician contacts the patient and notifies him of the fact of inclusion in one of the study groups, specifies the time and address of delivery of the individual treatment set. An authorized person from the investigation team sends the received data to the logistics company. The logistics company organizes the delivery of the individual set with temperature control to the door of the patient's apartment, the representative of the logistics company contacts the investigator and informs about the delivery of the cargo when the set is delivered to the patient's door, the representative of the logistics company checks the temperature sensor readings and, if there are no recorded deviations of the temperature conditions, stops the sensor, enters the data in a form agreed with Drugs Technology LLC. A representative of the company in personal protective equipment (mask, gloves) monitors the fact that the patient receives the kit, taking into account the social distance of 2 meters, the temperature sensor readings are provided to the study sponsor on a weekly basis. The fact of transfer of the individual set with the date of delivery and the number of the set is recorded in the accompanying form, all information is entered into the log of transfer of the study drug. The patient fills out a copy of the invoice in

the individual set **not transferring it** to the representative of the logistics company, a copy of the invoice/another accompanying document in electronic form is provided to the staff of the study site or the study physician (the original invoice can be handed over to the representative of the logistics company after the completion of participation in the study on day 28).

The unused study drug will be disposed of at the end of the patient's participation in the study.

For hospitalized patients, the following procedure is provided for ordering, receiving, and returning the investigated treatment.

When confirming successful randomization and distribution of the included patient to one of the groups, the study physician informs an authorized member of the study site about the necessary therapy and the dates of its provision. The authorized member of the investigation team or the study physician reports the required amount of the drug to the logistics company. The logistics company, under the control of the study sponsor, will deliver the required amount of the drug in compliance with the temperature regime. The representative of the study site checks the temperature sensor for the absence of signals about recorded temperature deviations during shipping and records the fact of delivery in the invoice/other accompanying documents. The received drugs are entered into the logs of the study drug accountability in the study site. The drug is given to the patient once on Day 1 for the entire period of treatment. The fact of delivering the study drug to patients is entered into the log. Copies of the logs in electronic form are sent to authorized representatives of the study sponsor on a weekly basis.

At the end of the clinical study in the site, the remains of the drug should be disposed of.

Accounting for the provided treatment should be carried out continuously throughout the study. All study drugs provided by the sponsor must be taken into account, with an explanation of all discrepancies. The principal investigator and/or authorized member of the investigation team is responsible for maintaining accurate records of the supplies of the study drug received from the sponsor, all supplies stored in the study site, and the study drug given to and returned from each patient. It is necessary to keep records that accurately present the accounting of medicinal products at any time.

The following logs are used to record all drugs used in the study:

- Log of the transfer and shipment of the study drug, describing the movement of the drug from the study sponsor to the logistics company warehouse. This log is filled in by the sponsor's representative and contains information about the dates of sending and receiving of the study treatment from the sponsor to the warehouse and unused and/or damaged study drugs from the warehouse to the sponsor at the end of the study
- Log of shipments and transfers of study drugs to all patients. This log is filled in by an authorized representative of the logistics company and contains information about the dates of dispatch, the type of study treatment for outpatients, and its quantity
- Log of drug registration for the study site. This log is maintained by an authorized member of

the investigation team that is responsible for receiving, storing, and distributing the study treatment to patients.

- Patient's Diary. The Patient's Diary must contain information about the use of study drugs on a daily basis, the Patient's Diaries are transferred to the study physician at the end of the clinical study. Information from the Patient's Diaries is considered additional for hospitalized patients and is considered a priority for outpatients when assessing adherence to the treatment

Proper medication accounting includes, in addition to the above, the following:

- Continuous monitoring of the expiration date, if the investigator know the expiration date/retest date of the drug
- Frequent checks of compliance of the actual stock with the documented inventory in the logistics company – estimation of the quantity of available drug in the warehouse
- Control of the fact that all the drugs received are included in the study site's logs and that all the necessary fields are filled in completely, accurately and legibly.

In case of any errors or inconsistencies related to the delivery of the drug, you must immediately notify the sponsor.

During the study, the investigator will be notified of any extension of the expiration date or retest dates of the drugs and/or materials for the clinical study. After receiving an expiration notification during the investigation, the study site must follow all instructions set out in the notification, including disposing of expired clinical study materials and notifying the sponsor of the fact of destruction.

Prior to the closure of the study site and during certain periods of time during the study, the sponsor's designated person will record and approve the materials for the clinical study (using video communication).

Until the end of the study, the investigator must keep all original documentation on the registration, return, and/or destruction of materials for the clinical study, and email copies to the sponsor.

All unused or partially used packages of study drugs should be destroyed at the study site, after approval by the study sponsor. Destruction of the drug must be documented accordingly. Unused packages must not be destroyed until they are fully accounted for (using video communication).

4.9.1. Handling of drugs used in the study

All study products provided to patients should be placed in a dry place, protected from direct sunlight, excluding the free access of children or unauthorized medical personnel in the case of hospitalized patients, with constant room temperature not exceeding +25 ℃.

Patients take the study treatment independently, the study physician can control the procedure of the drug administration (with direct observation of inpatients only, remotely for

outpatients). After patients take the drug, the study physician will monitor the entry of information about the drug administration in the Patient's Diary.

Patients are recommended to take the study drug with approximately 200–350 ml of warm non-carbonated drinking water or water at room temperature. If patients experience unpleasant sensations when taking the drug, they may take another 200 ml of warm still water 10 minutes after the drug administration. It is necessary to adhere to a single administration regime starting from Day 1 and until the last day of receiving the study therapy according to the Study Protocol, for each of the groups. In the case of skipping the dose, the information must also be entered in the Patient's Diary, indicating the reasons. In the case of taking any concomitant and/or symptomatic therapy during the patient's participation in the study, the Patient's Diary should contain information about the name of the drugs, the time of administration, and the dosage on a daily basis. The data entered in the Patient's Diary should be provided to the study physician verbally, as well as for visual control during contacts according to the procedures of the Study Protocol. The completed Patient's Diary must be sent as a copy (digital image) to the study physician at the study site at the end of the patient's participation in the study, or at the request of the study physician, the Principal Investigator.

For outpatients, if the drug is damaged (violation of the integrity of the tablet, falling of the drug extracted from the primary packaging on the floor, etc.), it is necessary to throw the damaged drug and take a new one from the package. for these situations, 3 spare tablets are provided in each package (bottle). This situation should be recorded in the Patient's Diary and reported to the study physician during a contact according to the Study Protocol procedures.

For hospitalized patients, if the drug is damaged during administration, the damaged drug must be removed from the patient and disposed of together with medical waste and replaced with a spare dose from the package. In case of the detection of temperature deviations of the storage conditions in hospitals exceeding those described earlier, the study drug should be placed in a quarantine zone that excludes the possibility of using the quarantine drug in patients. The duration of storage in the quarantine zone should not exceed 10 days, after which the drug should be returned to the sponsor, provided that within 10 days no explanation was received from the sponsor of the study about the possibility of using this drug in patients, if the drug was not in the red zone of the hospital.

4.10. Storing the randomization codes and the procedure of their disclosure

Due to the fact that this clinical study does not involve blinding (i.e., it is open-label), the procedure for disclosure of randomization codes is not provided.

Lists of screening, randomization and study numbers of all included patients will be stored in Drugs Technology LLC.

The Investigator must ensure that patients remain anonymous. In the CRF, patients are identified only by assigned study numbers (IDs).

The Investigator must keep a separate log containing information about screening, randomization, and subject IDs,

and this log is stored in compliance with the rules applicable to confidential documents.

The Investigator must also keep strictly confidential documents that are not intended to be passed on to the Sponsor, such as signed Patient Information Sheets with Informed Consent and primary documentation.

4.11. A list of all data that are registered directly in the CRF (i.e. without prior written or electronic recording) and considered as primary data.

All data that should be indicated in the CRF should be presented in the primary documentation of the study site.

The CRF does not provide for entering any data that is not subject to registration in the primary documentation.

5. INCLUSION AND EXCLUSION OF STUDY PARTICIPANTS

5.1. Inclusion criteria

1. An informed consent form signed by the patient and the study physician.
2. Males and females aged 18 to 60 years.
3. Diagnosis of a mild to moderate coronavirus disease caused by the SARS-CoV-2 (COVID-19) (without respiratory failure). In accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19):
   - Mild form: specific symptoms in the absence of criteria for moderate and severe form.
   - Moderate form: fever above 38 °C; RR more than 22/min; shortness of breath during exercise; pneumonia (exposed by CT of the lungs); SpO2 < 95%; serum CRP more than 10 mg/l).
4. Duration of infection symptoms shall be no more than 6 days (preferably no more than 3 days) before randomization.
5. Infection with the SARS-CoV-2 must be confirmed based on the results of PCR diagnostics (the screening takes into account the patient's existing results, or the test is performed in a study site out of the Protocol).
6. Ability to follow the requirements of the Protocol and fulfill all the clinical study procedures
7. Willingness of participants and their sexual partners with retained childbearing potential to use reliable contraception methods throughout the study and for 3 months after the treatment completion. This requirement does not apply to participants who have undergone surgical sterilization. Reliable methods of contraception involve the use of the first barrier method in combination with one of the following: spermicides, intrauterine spiral/oral contraceptives in a sexual partner.
8. Willingness not to take alcohol throughout the entire period of the study.

Additional inclusion criteria for the PK-subgroup

1. Signed informed consent to participate in further study of pharmacokinetics.
2. Body mass index 18.5–30.0 kg/m^2.

3. The possibility of the patient, in the reasonable opinion of the study physician, to participate in a further study of pharmacokinetics and taking of the necessary amount of blood samples.

5.2. Non-inclusion criteria

1. Age less than 18 or more than 60 years.
2. A patient has been prescribed any etiotropic therapy for SARS-CoV-2 (COVID-19) coronavirus disease before being included in the study.
3. Moderate form with the presence of respiratory failure, severe or extremely severe form of the disease caused by SARS-CoV-2 (COVID-19).
4. The presence of respiratory failure (RR >30/min, SpO2 ≤ 93%) or the need for mechanical ventilation at the screening.
5. Decreased level of consciousness (disorientation in place, time, and self-identity), agitation at the screening.
6. Established hemodynamic instability (systolic BP less than 100 mm Hg or diastolic BP less than 60 mm Hg at the screening.
7. Subtotal diffuse ground-glass induration of pulmonary tissue and pulmonary consolidation combined with reticular changes; involvement of ≥ 75% of lung parenchyma; hydrothorax (CT findings corresponding to CT-4 and higher according to the guidelines of Department of Health of Moscow).
8. Comorbidities:
    a) Chronic obstructive pulmonary disease or moderate to severe asthma.
    a) Severe chronic cardiovascular diseases (rhythm and conduction disorders, artificial heart rhythm driver, myocardial infarction or unstable angina in history, heart failure).
    b) Immunocompromised individuals (HIV, cancer, autoimmune diseases, immunosuppressive therapy).
    c) Severe obesity (body mass index [BMI] 40 or higher).
    d) Diabetes.
    e) Chronic renal failure.
    f) Moderate to severe chronic liver diseases.
9. The presence of any of the following deviations in laboratory findings at the screening: AST or ALT levels greater than 2.5 upper normal levels (UNL), platelet count < $50x10^9$/l.
10. Any medical history that, in the opinion of the investigator, may lead to difficulties in interpreting the results of the study or create an additional risk for the patient as a result of their participation in the study.
11. Performing more than 2 CT diagnostic procedures in the last 6 months prior to randomization into the study (with the exception of chest CT performed no more than 4 days before inclusion in the study).
12. The patient is taking therapy with drugs that significantly inhibit CYP28C, and these drugs cannot be discontinued for the period of the entire study.
13. Malabsorption syndrome or another clinically significant disease of the gastrointestinal tract that may affect the absorption of the study drug (non-correctable vomiting, diarrhea, ulcerative colitis, and others).

14. Pregnancy or breastfeeding; women with a probable pregnancy at the screening; women planning to conceive during the entire period of the study.
15. Known (from the medical history) or suspected alcohol or psychotropic drug abuse; drug dependence, illicit drug addiction.
16. Mental illnesses, including the medical history.
17. A condition or disease that, in the opinion of the investigator or medical monitor, may put the patient's safety at risk or affect the safety assessment of the investigational drug.

5.3. Exclusion criteria

A list of criteria for early withdrawal from the study for individual subjects is provided in section 4.8.2. "Description of criteria for early withdrawal from the main part of the study (in the therapy period) for individual subjects."

The investigator must inform Drugs Technology LLC about the early withdrawal of a patient within 24 hours, indicating the reasons.

5.4. Follow-up of subjects excluded from the study/early withdrawal patients.

If patients have decided to retire from the study or have not completed the study for any reason, then their randomization codes should not be reused.

5.4.1. Monitoring of patients who have not received a single dose of the drug

In the case of the early withdrawal of a patient who has not received any doses of the study drug, the Early Withdrawal Form is filled out on the day of exclusion from the study. Follow-up is performed only in the case of retirement due to SAEs in accordance with the standards of the study site.

Data on patients who leave the study early for any reason and receive at least one dose of the study drug, who have completed at least one safety assessment after the screening, will be included in the safety analysis. If patients were excluded before receiving the first dose of the study drug, they will not be included in the safety analysis.

5.4.2. Monitoring of patients who received at least one dose of the drug

In case of early withdrawal of a patient who received at least one dose of the study drug:

- on the day of exclusion from the study, the Therapy Completion Visit is conducted and the Study Completion Form is filled out. During this visit, the following procedures are performed: vital signs determination, SARS-CoV-2 test (PCR), clinical status assessment (WHO scale) (see section 4.6.2).

These visits when early termination happens are mandatory for all patients, except in cases where a patient is "lost to follow-up" or physically unable to attend the visit. All relevant records must be provided in the primary documentation and CRF.

In the case of exclusion from the study due to the development of AEs/SAEs, further treatment and follow-up of a patient, after the Early Termination Visit,

will be carried out by the investigator in accordance with the study site's standards for the treatment of developed AEs or SAEs.

If patients or their sexual partners become pregnant during the clinical study, they are subject to medical supervision during the entire period of pregnancy, as well as during the 4 weeks of the postpartum period to assess the condition of women and new-born children. Information about the course of pregnancy and its outcome is entered in the primary documentation. During the entire period of pregnancy, together with the obstetrician-gynecologist who is observing the patient, general state of women, data reflecting the nature of the pregnancy, the results of laboratory and instrumental investigations, including ultrasound, will be analyzed. The monitoring of a new-born child will be carried out together with a district pediatrician for 6 months, with the analysis of child's clinical status, data from laboratory and instrumental investigations.

Information about the condition of the patient who left the study should be indicated in the primary documentation and CRF.

Loss to follow-up

Patients who were lost to follow-up should be registered in the eCRF accordingly. In patients who were lost to follow-up, the investigator must demonstrate "appropriate efforts" by recording in the primary documentation the steps taken to establish communication with patients, such as the dates of phone calls, registered letters, etc.

After the final completion of all follow-up procedures, including for reasons of AE/SAE development, pregnancy, etc., patients are considered to be completely excluded from the study. When this moment comes, the Study Completion Form is filled in eCRF.

6. ADMINISTRATION OF MEDICINAL PRODUCTS

6.1. Study products

6.1.1. Mode and duration of administration of the study products

Study participants will be randomly assigned to one of two groups – of the study drug or the comparison drug.

The study drug group

In the study drug group, participants will receive TL-FVP-t (FAVIPIRAVIR-TL) on the first day at a dose of 1800 mg (9 tablets of 200 mg) at intervals of 12 hours (i.e. twice daily), then on days 2–10 at a dose of 800 mg (4 tablets of 200 mg) at intervals of 12 hours (i.e. twice daily). The study drug is taken orally, at least 30 minutes after a meal. At the end of the 10-day period of therapy, patients switch to the follow-up period.

Comparison group

Patients in this group will receive the recommended "standard" etiotropic therapy in accordance with the current version of the Interim Guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study. These drugs include umifenovir, chloroquine, hydroxychloroquine, mefloquine, lopinavir+ritonavir, hydroxyloroquine in combination with azithromycin, interferons (at the time of writing this Protocol). In the comparison group,

patients will receive either umifenovir in combination with interferon-alpha, or chloroquine, or its derivatives (chloroquine/hydroxychloroquine or mefloquine) using standard regimens and dosages according to the guidelines.

The recommended regimens are:

- Hydroxychloroquine: 400 mg twice on the first day (morning, evening), then 200 mg twice daily (morning, evening) for 6 days.
- Chloroquine: 500 mg twice daily for 7 days.
- Mefloquine: Day 1: 250 mg 3 times daily every 8 hours. Day 2: 250 mg twice daily every 12 hours. Days 3–7: 250 mg once daily at the same time.
- Umifenovir: 200 mg 4 times daily for 5–7 days.
- Recombinant interferon-alpha: 3 drops in each nasal passage (3000 IU) 5 times daily for 5 days.

6.1.2. Correction and dechallenge of the study therapy

Dose correction is not provided in this study.

If a patient in the study drug group has grade 3–4 adverse events according to STCAE 5.0 or other significant adverse drug reactions, the use of TL-FVP-t may be discontinued by the decision of the Independent Data Monitoring Committee.

6.1.3. Overdose of the study drug and the comparison drug

There are currently no data on an overdose of favipiravir. For the treatment of Ebola virus infection, favipiravir was used in doses of 6000 mg on the first day of therapy and 2400 mg on subsequent days, with a duration of therapy of up to 10 days, these doses were tolerated satisfactorily.

In this study, an overdose will be considered taking any dose higher than the one prescribed in accordance with the Study Protocol, 1800 mg twice daily on the first day of therapy, 800 mg twice daily on days 2–10. It is acceptable to increase the duration of therapy to 14 days with the retention of a dose of 800 mg twice daily, according to the reasonable opinion of the study physician.

For monitoring purposes, any case of overdose, related or not to any adverse event (serious or non-serious), should be reported to the Principal Investigator, who in turn should inform the representative of Drugs Technology LLC. Information about overdose should be emailed to the Sponsor (safety@drugsformulation.ru) immediately, within 24 hours, in the subject line, it is necessary to specify: to Pharmacovigilance Officer. The Investigator needs to receive an email with the confirmation of the fact that a pharmacovigilance officer was acknowledged with the SAE Report.

6.2. Concomitant therapy and permitted and prohibited drugs

6.2.1. Permitted concomitant therapy

Concomitant therapy. Also, patients in both groups, in addition to the study drug and "standard" etiotropic therapy, may be prescribed concomitant therapy in accordance with the above-mentioned

guidelines. Concomitant therapy is prescribed at the discretion of the study physician and is determined by the actual condition and needs of a patient. It involves symptomatic therapy, pathogenetic therapy and antibacterial therapy (for complicated forms of infection), recommended according to the current version of the Interim guidelines of the MoH of Russia for the prevention, diagnosis, and treatment of coronavirus disease (COVID-19), valid at the time of the study, for patients with mild and moderate disease, as well as corresponding to the standards adopted at the study site.

Symptomatic therapy includes:

- Relief of fever (antipyretic drugs; the recommended drug is acetaminophen, it is permissible to use NSAIDs, for example, ibuprofen).
- Complex therapy of rhinitis and/or rhinopharyngitis (moisturizing/irrigation drugs, nasal decongestants);
- Complex therapy of bronchitis (mucoactive drugs, broncholytic drugs, and other).

Pathogenetic therapy may include antithrombotic and anti-inflammatory drugs.

Detailed symptomatic therapy is described in section 6 of this Protocol. Instructions for the use of symptomatic drugs are contained in the IMU of the corresponding drugs. The use of any symptomatic agents should be indicated in the CRF.

Recommended symptomatic therapy regimens:

Antipyretics: acetaminophen 1,000 mg up to 3 times daily; also allowed the use of NSAIDs, such as ibuprofen.

Mucolytic drugs: Ambroxol syrup 2 ml x 3 times daily.

Bronchodilators: ipratropium bromide, aerosol, 2 inhalations x 3 times daily, when HR is less than 90 beats/min.

Antibiotic therapy (recommended only when signs of bacterial infection appear): Amoxiclav in the absence of contraindications or levofloxacin in standard therapeutic dosages.

Anticoagulants: enoxaparin 4000 IU s/c once daily in the absence of chronic renal failure in history. In case of renal failure with known azotemia – dalteparin 5000 IU s/c x once daily.

For local treatment of rhinitis, pharyngitis, with congestion and/or nasal discharge, start with saline products for local use based on seawater (isotonic, and with congestion – hypertonic). If they are ineffective, nasal decongestants are indicated. In the case of inefficiency or severe symptoms, various solutions with an antiseptic effect can be used.

If necessary, it is allowed to use any symptomatic therapy that is required to the patient in the opinion of the study physician.

In the case of allergic reactions accompanied by general symptoms (fever, arthralgia, myalgia, lymphadenopathy) and/or local manifestations (blistering, exudative polymorphic erythema); in the case of Stephen-Johnson syndrome, intensive treatment is carried out using any medications in accordance with the treatment algorithm for these conditions adopted in the study site. Repeated use of favipiravir, in this case, is strictly contraindicated.

Treatment of adverse events

The Investigator performs therapy of AEs in accordance with the standards of medical care.

All drugs used by patients before the study, and all drugs used by patients or prescribed by the Investigator to stop adverse events, in addition to the test products during the study period (including dietary supplements), will be recorded in the primary documentation and in the clinical report form.

6.2.2. Prohibited concomitant therapy

Group 1 does not allow the use of any drugs that have or are suspected to have antiviral effects against the SARS-CoV-2, with the exception of TL-FVP-t under the study. It is not allowed to use the following drugs as concomitant therapy: umifenovir, recombinant interferon-alpha, recombinant interferon-beta, hydroxychloroquine, chloroquine, mefloquine, azithromycin in combination with hydroxychloroquine, the combination of lopinavir+ritonavir.

To eliminate the risk of drug interactions, if the following medications are necessary – pyrazinamide, repaglinide, famciclovir, sulindac, dechallenge of the study treatment and exclusion of the patient from the study should be considered.

6.2.3. Other restrictions for patients in the study

The Investigator will explain to patients that they must comply with certain restrictions when participating in the study. These restrictions are also detailed in the Patient's Information Sheet with the Informed Consent Form.

During hospitalization, the patient must comply with the rules established in the hospital.

Therapeutic regimen

In this study, the patient is charged with the duty not to skip doses of the study therapy, and to follow all the recommendations of the study physician on therapy and lifestyle.

Every day at the scheduled time, outpatients are required to start communication sessions with the Study Physician, to carry out Protocol procedures under the guidance of the Study Physician, to take study drugs/comparison drugs for supportive therapy as indicated by the Study Physician, to keep the Patient's Diary every day and provide it for remote control by the Study Physician.

Alcohol

Patients should completely avoid taking alcohol during the entire study.

Exercise

During the study, patients should not engage in heavy physical activity and intensive sports.

Contraception

Male patients should use reliable methods of contraception throughout the study. In the case of a distribution to the TL-FVP-t group,

male patients should use reliable methods of contraception for at least 3 months after the last administration of the study drug. Reliable methods of contraception involve the use of the first barrier method (for example, a condom) in combination with one of the following: spermicides or intrauterine spiral/oral contraceptives in a sexual partner.

Female participants should use contraception throughout the study or at least 2 weeks after the last administration of the study treatment/comparison treatment. For female participants, the acceptable methods of contraception in this study include the following:

- Sexual abstinence: if it corresponds to the patient's preferred and habitual lifestyle. [Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods) and interrupted sexual intercourse are not considered acceptable methods of contraception.]
- Sterilization: performing surgical bilateral ovarian removal (with or without removal of the uterus) or tubal ligation at least 6 weeks before the start of the study therapy. If only the ovaries are removed, the woman's reproductive status must be confirmed by a subsequent evaluation of hormone analysis.
- Sterilization of the male partner (with proper documentation of the absence of sperm in the ejaculate after vasectomy) [In women participating in the study, the sexual partner after a vasectomy should be the only partner].
- Using a combination of any two of the methods listed below (a+b):

a) Use of oral, injectable, or implanted hormonal contraceptives.

b) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical cap/vaginal fornix cap) with spermicidal foam/gel/film/cream/vaginal suppository.

When using oral contraceptives, women should constantly use the same drug for at least 3 months before starting the study therapy.

6.3. Methods for monitoring compliance of subjects with procedures

You cannot skip Days 1–10 visits, Day 14 visit, or gross violation of the terms of visits on Days 21, 28 (failure to meet the planned time of visits for more than 1 day).

Outpatients are not allowed to skip 2 or more telemedicine sessions.

In the case of gross violations of these conditions, a patient is excluded from the study, and his data are not included in the pharmacokinetic analysis.

6.3.1. Assessment of compliance

TL-FVP-t for the entire course of administration will be issued to patients after randomization on Visit 1. The patient will make a report on taking the drug by filling out the Diary for monitoring the intake of the study treatment and collecting drug packages. Compliance control will be carried out by a Medical investigator, by remote or direct visual control, as well as representatives of the Sponsor when receiving electronic copies of reports.

7. EFFICACY EVALUATION

7.1. List of efficacy parameters

7.1.1. Parameter definitions

The elimination of the virus: the absence of SARS-CoV-2 virus RNA in swabs from the mouth and nasopharynx according to PCR diagnostics (using nucleic acid amplification) in two consecutive investigations conducted at least at intervals of 24 hours.

Severity of symptoms: an assessment of the severity of symptoms in patients in points, formed by the study physician based on the patient's complaints and the physician's clinical impression using the 4-point system (0–3).

Clinical status: a comprehensive assessment of the patient's condition carried out by the study physician based on laboratory and instrumental data and assessment of the severity of symptoms in points based on the physician's clinical impression. Clinical status is assessed in points according to the WHO Ordinal Scale for Clinical Improvement (8-category); improvement in clinical status is defined as a decrease of at least 1 point according to the scale compared to the screening level. The final category on the scale can be set when evaluating data by the Independent Data Monitoring Committee (IDMC).

Body temperature: the axillary temperature will be determined in the study. Temperature normalization is defined as body temperature <37 °C for at least 48 consecutive hours without the use of antipyretics.

Chest CT: chest scanning is performed according to the standard program established by the manufacturer, with the patient supine, with his hands behind his head, if possible with a calm, delayed breath. CT Protocol is formed according to standard rules similar to those in radiographic examinations. However, it uses the terminology adopted in the description of the CT data. The results of chest CT scans in the study will be evaluated by the Central Independent Committee for the evaluation of computed tomography data (CIC on CT).

7.1.2. Endpoints for efficacy evaluation

Primary endpoint:

- Time to improve clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category) (median, in days).
- Time to reach virus elimination (defined as the absence of SARS-CoV-2 based on the results of 2 consecutive PCR tests of smears at intervals of 24 hours at least) (median, in days).

Secondary endpoints:

- The percentage of patients (%) with improved clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category[22]) on day 7 (from the beginning of the therapy).
- Percentage of patients (%) with established virus elimination on days 5 and 7 (from the beginning of the therapy).

[22] Ordinal Scale for Clinical Improvement

- Time to temperature normalization (median, in days).
- Percentage of patients (%) with resolution of changes in the lungs according to CT data on day 14 (from the beginning of the therapy).

Exploratory endpoints:

- Average score on the WHO Ordinal Scale for Clinical Improvement on days 7 and 14 of the study.
- Percentage of patients (%) with improved clinical status (defined as a decrease in the WHO Ordinal Scale for Clinical Improvement by at least 1 category[23]) on day 14 (from the beginning of the therapy).
- Percentage of patients (%) with established virus elimination on study days 3, 10, 14, 21, and 28 (from the beginning of the therapy).
- Time to reversal of individual symptoms (fever, cough, myalgia, weakness, shortness of breath, headache) (median, in days).
- Frequency (%) of hospitalization of patients who were under outpatient observation for a period of 28 days (from the beginning of the therapy).
- Duration of hospitalization of patients for a period of 28 days (from the beginning of the therapy).
- Frequency (%) of ventilator use for a period of 28 days (from the beginning of the therapy).
- Frequency (%) of transfer to the intensive care unit for a period of 28 days (from the beginning of the therapy).
- Frequency (%) of deaths for a period of 28 days (from the beginning of the therapy).

7.1.3. Justification of the selection of parameters for an efficacy evaluation

The selection of the combined endpoint frequency for evaluating efficacy in this study is based on the following factors:

- Favipiravir is a drug of etiotropic, antiviral therapy, the potential for clinical use of which is associated not only with the suppression of the activity of the infectious agent in a particular patient, but also with the prevention of the release of the virus into the environment, and, as a result, reducing the danger of the virus carrier state.
- Considering the poor study of the degree of viremia in the development of severe forms of the disease it seems appropriate in addition to the direct antiviral effect to assess the drug effect on the dynamics of the clinical picture of the disease.
- The use of PCR methods for etiological diagnosis and the 8-category scale for evaluating the clinical improvement of patients with SARS-CoV-2 infection corresponds to the recommended approach to the diagnosis, treatment, and planning of clinical studies of drugs for this nosology.

7.2. Methods and deadlines for evaluating, recording, and analyzing efficacy parameters

7.2.1. Timeline for analyzing efficacy parameters

After 14 days of participation and if at least 54 events have occurred, an interim data analysis will be performed and an interim report will be prepared.

After completion of the study by all included patients, the main report on the study will be prepared.

[23] Ordinal Scale for Clinical Improvement

Methods, the timing of evaluation and registration of efficacy parameters

The following methods will be used for efficacy evaluation:

- Assessment of clinical status by the study physician remotely using telemedicine technologies – at the screening and on days 3, 5, 7, 10, 14, 21, and 28.
- Sampling of biomaterial from the upper respiratory tract to determine the SARS - CoV-2 (by PCR) on days 3, 5, 7, 10, 14, 21, and 28.
- Measurement of body temperature, BP, HR, RR, blood oxygen saturation according to pulse oximetry (SpO2) – daily for the first 10 days, then – on days 14, 21, and 28.
- Assessment of subjective symptoms – daily when interviewed by a study physician for the first 10 days, then on days 14, 21, and 28.
- Chest CT on days 5, 14, and 28.

The patient will also keep The Patient's Diary for the first 14 days, then on days 21 and 28, recording the facts of receiving the study therapy and concomitant therapy drugs, symptoms, results of measurement of body temperature, BP, HR, and SpO_2.

The patient's clinical status will be assessed according to the WHO Ordinal Scale for Clinical Improvement.

The efficacy analysis will be performed in the ITT (full population) and PP (per protocol) populations, the main population of the analysis will be the ITT populations, and the analysis will also be performed for each stratum, if applicable.

- **Complete population analysis (intent-to-treat).** Efficacy evaluation of the main population is defined as the complete population analysis and includes all randomized patients.
- **The "per protocol" population.** The "per protocol" population includes all patients from the intention-to-treat analysis without significant deviations from the Protocol who have received/been administered at least one dose of the study therapy, and who can be evaluated for efficacy.

8. SAFETY EVALUATION

8.1. List of safety parameters

8.1.1. Definitions

8.1.1.1. Adverse event

Adverse event (AE) is an event detected in the subject of a clinical study after the use of a medicinal product, which is unfavorable for health and which also may not have a causal relationship with the use of the drug.

An adverse event is any adverse symptom, including a laboratory deviation from the standard, complaint or disease, the time of occurrence of which does not exclude a causal relationship with the use of the drug, regardless of the presence or absence of such a relationship: from the beginning of

the study drug administration up to 14 days inclusive after the last dose of the drug in a clinical study.

Conditions that already existed at the time of obtaining informed consent should be documented in the eCRF in the section “Medical history”.

8.1.1.2. Serious adverse events

Serious adverse event (SAE) is an adverse medical event that regardless of the drug dose may have the following outcomes:

- It leads to death.
- It creates a threat to life.
- It causes the need for hospitalization or prolonged hospitalization.
- It leads to permanent or severe disability/incapacity.
- It is a congenital abnormality or developmental defect.

If there is any doubt that the information meets the criteria for a serious adverse event, such information should be considered a serious adverse event. An adverse medical event that required medical intervention to prevent the development of the above outcomes should also be considered as meeting the seriousness criteria.

A threat to life is considered an immediate risk of death from a reported event. A life-threatening event does not include one that, if it had occurred in a more severe form, could have caused death, but in the form in which it occurred, it does not cause an immediate risk of death. For example, hepatitis that resolves without signs of liver failure will not be considered life-threatening, despite the fact that hepatitis with a more severe course can lead to death. Similarly, an allergic reaction resulting in Quincke's edema in the face area will not be considered life-threatening, even though Quincke's edema of the larynx, allergic bronchospasm or anaphylaxis may be fatal.

Hospitalization is official admission to hospital. Hospitalization or prolonged hospitalization serves as a criterion that the AE is serious; however, hospitalization itself is not considered a serious adverse event (SAE). If there is no AE, hospitalization or prolonged hospitalization should not be reported by the Investigator as a serious adverse event. This applies to (including but not limited to) the following situations:

- Hospitalization or prolonged hospitalization is necessary for the procedures provided for in the Protocol.
- Hospitalization or prolonged hospitalization is part of routine procedures at this study site (for example, removal of a stent after surgery). A corresponding confirmation must be stored in a folder with the documentation of the study.
- Hospitalization due to a pre-existing condition that did not deteriorate.

Disability is defined as a significant impairment of a patient's ability to lead a normal life.

8.1.1.3. Other safety information subject to special reporting

Certain information that is not considered to be SAE but must be registered and reported to the Sponsor in a special way (within 24 hours) includes:

- The use of the study drug in the case of detected pregnancy in patients or establishing the fact of pregnancy in the patient's partner. If the pregnancy of participants or their partners is confirmed, the administration of the study drug must be stopped immediately.
- Overdose with the study drug, as defined in this Study Protocol, regardless of the development of AEs.
- Unintentional or accidental use of the study drug, regardless of the development of AEs.
- Mistakes of using the drug regardless of the development of AEs (including confusion or possible confusion in the use of drugs).

8.1.1.4. Unexpected adverse reactions and serious unexpected adverse reactions

Unexpected adverse reaction (UAR) is an adverse reaction whose nature or severity does not agree with the available information about the drug (with the data in the Investigator's Brochure).

Serious unexpected adverse reaction (SUAR) is an unexpected adverse reaction that is characterized by signs of SAEs. This type of adverse reaction is subject to special reporting conditions.

8.1.2. Safety assessment endpoints

Secondary endpoints:

- The frequency and severity of all AEs and SAEs.
- The frequency of Grade 3–4 AEs according to CTCAE 5.0.
- All cases of early withdrawal from the study related to AEs/SAEs.

8.2. Methods and timing of assessment, registering and analyzing safety parameters

8.2.1. Timing of safety parameter analysis

After 14 days of participation and if at least 54 events have occurred, an interim data analysis will be performed and an interim report will be prepared.

After completion of the study by all included patients, the main report on the study will be prepared.

If the study members or their partners get pregnant, the information will be tracked for six months from the date of delivery.

8.2.2. Methods and timing of assessment and registration of safety parameters

The safety analysis will include all patients who were administered with the study drug or a comparator drug.

The following will be performed for safety evaluation:

- Collecting complaints, interviewing a patient about subjective symptoms – daily for 10 days of the therapy, then – on days 14, 21, and 28;
- Measurement of body temperature, BP, HR, RR, and SpO_2 – daily for 10 days of the therapy, then – on days 14, 21, and 28.
- Evaluation of laboratory findings will be performed at the screening, then on days 5, 14, and 28:
  - Clinical blood test (hemoglobin, erythrocyte count, leukocyte count, neutrophil count, lymphocyte count, platelet count, ESR).
  - Blood chemistry test (glucose, ALT, AST, LDH, total bilirubin, creatinine, CPK, ferritin, lactate, uric acid, C-reactive protein).
  - coagulation test (activated partial thromboplastin time (APTT), prothrombin time, fibrinogen, D-dimer);
  - Urine analysis.
- ECG will be performed at the screening, then on days 5, 14, and 28.

Based on the data received, the AEs and SAEs will be registered.

The safety assessment will be carried out throughout the study based on the collection of information on the following parameters:

- The frequency of the development of AEs and SAEs registered according to patient complaints and physical examination, neurological examination, clinically significant changes in vital signs (BP, HR, body temperature), clinically significant deviations of laboratory tests and ECG from reference values.
- Changes in vital signs (BP, HR, body temperature, saturation) relative to the baseline level.
- Changes in laboratory findings relative to the baseline level.

The frequency of these procedures during the study is shown in Table 4.2 of Section 4.6.1 "Schedule of visits and procedures". Registration of the AEs/SAEs is carried out in accordance with the Safety Guidelines provided by the Sponsor.

The safety assessment will be conducted using National Cancer Institute Common Terminology Criteria for Adverse Events – NCI CTCAE v. 5.0.

Responsibilities of the Investigator

The Investigator is responsible for registering and timely reporting information about AEs and SAEs. For outpatients, information about any AEs and SAEs is collected using telemedicine technologies during contact with patients.

AEs are registered from the moment of the first administration of the study drug and up to 4 weeks after the last. AEs related to the Protocol procedures are registered from the moment the informed consent is signed. SAEs are registered from the moment of signing the informed consent and up to 4 weeks after the last use of the drug, as well as for a longer period after the last use if the investigator believes that this SAE is associated with the use of the drug or study procedures.

Adverse events that do not meet the seriousness criteria are recorded by the investigator in the primary documentation and in the eCRF and provided to the clinical study monitor/manager at the next scheduled monitoring visit for evaluation.

Serious adverse events (SAEs), especially SUARs, are reported to the Sponsor immediately, within **24 hours**. SAEs Reports are immediately emailed to the Sponsor within 24 hours (**safety@drugsformulation.ru**) with the note "For Pharmacovigilance Officer of Drugs Technology LLC", specifying the Study Protocol number in the subject line. The Investigator needs to receive an email with the confirmation of the fact that a pharmacovigilance officer was acknowledged with the SAE Report. Additional information (copies of laboratory tests, diagnostic procedures, autopsy results in case of death, etc.) will be provided by the investigator in the form of additional messages to the Sponsor no later than 24 hours after receiving a request for additional information on the SAEs from the Sponsor (if available). It is allowed to transfer partially completed primary forms for SAEs, in the form of scans or photocopies, followed by the provision of fully completed forms.

The Investigator must receive confirmation that the information has been received/delivered. Data on ADRs are also provided to the clinical study monitor at the next scheduled monitoring visit.

The investigator must immediately, within a period not exceeding 48 hours from the date of detection (or receipt of information about the SAE detection), report SAEs to the local ethics committee.

Responsibilities of the Sponsor

The sponsor is responsible for evaluating the safety of the study drug during the clinical study. The sponsor is responsible for promptly informing the Investigator, the local ethics committee, and regulatory authorities of any data received that may adversely affect patient safety and the study progress.

The sponsor must submit information about all SUARs to the regulatory authorities and ethics committees within 7 calendar days from the date of detection (or receipt of information about detection) if they resulted in death or posed a threat to life, and within 15 calendar days for the remaining SUARs.

The sponsor must submit other safety information to the regulatory authority and the ethics committee within 15 calendar days, which may change the risk/benefit ratio of the study drug or serve as a basis for changes in the recommendations for its use, as well as the basis for reviewing the possibility of further study.

The Sponsor decides whether to notify the members of the Independent Data Monitoring Committee (IDMC), which will be responsible for periodically reviewing safety and efficacy data and making medical decisions in difficult cases for individual patients (if necessary).

8.3. Requirements for reports, procedures for registering and reporting AEs, as well as the creation of the AE Registration Form

8.3.1. AE/SAE registration

The presence or absence of adverse events since the previous visit is noted on each visit. Any adverse event registered in a patient should be indicated in the primary documentation and

a specially developed form for registering adverse events (CRF). AE registration is carried out from the moment of the first dose administration.

Adverse events are registered and numbered sequentially as they occur. Each AE is reported in the "AE Registration Form". The rules for AE/SAE registration are described in detail in the Safety Guide provided by the Sponsor. Adverse events are registered regardless of the seriousness and the presence of a causal relationship with the study treatment. If the same adverse event happens again, this adverse event is registered as a new one, and a new number is assigned to it.

Conditions that already existed at the time of obtaining informed consent should be documented in the eCRF in the "History" section.

The onset of adverse events should be evaluated using indirect questions on each study visit. Adverse events can also be recorded when patients are self-reported about their presence in the interval between visits, or during a physical examination, laboratory tests, and others. If possible, each adverse event should be evaluated according to the following items:

- Severity (Grade 1–5 CTCAE).
- Duration of the adverse event (start and end date or the fact of its continuation during the monitoring visit).
- Relationship with the study drug (reasonable possibility of a relationship between adverse events and the study drug; Yes or No).
- Actions taken in relation to the study therapy (no actions; correction of the dose of the study drug/temporary suspension of therapy; dechallenge of the study therapy; hospitalization, etc.)
- Use of concomitant medication or non-drug therapy.
- Whether the adverse event is serious, and the definition of a serious adverse event is given in Section 8.1.1.

The seriousness of the adverse event will be assessed in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5 (NCI CTCAE v. 5.0). If this event is not detailed by severity according to CTCAE, it should be classified by the following degrees:

"mild", "moderate", "severe" and "severe, life-threatening", "fatal", which corresponds to degrees 1–5 (see Table 8.1).

Table 8.1. Criteria for assessing the severity of AEs, not detailed in CTCAE 5.

Severity	Criteria
1 (Mild)	Asymptomatic AE detected during examination or laboratory tests; causing mild discomfort and not affecting daily activity. It does not require the intervention of a physician or the use of concomitant therapy.
2 (Moderate)	AE causes discomfort that leads to reduced daily activity (for example, when using the phone, cooking, shopping, or handling money); minimal, non-invasive intervention is required (for example, oral therapy).
3 (Severe)	Inability to work, significantly reduced daily activity; requires assistance in eating, dressing or undressing, assistance with hygiene measures and bowel and bladder functions (but the patient is

Severity	Criteria
	not bedridden). Concomitant therapy is required, and if there is no intervention, hospitalization or intensive care may be required.
4 (Severe life-threatening)	Requires emergency intensive care, dechallenge of the study therapy. If there is no therapeutic intervention, further deterioration can lead to death. (NOTE: in itself, it is not a SAE, see the seriousness criteria)
5 (Fatal)	Death due to the development of AEs. (NOTE: Death is an outcome but not an AE. However, if a fatal outcome develops due to an unknown cause, the term "Death due to an unknown cause" may be used as the name of the adverse event until further information is received.)

Evaluation of the relationship with the study product should be carried out using classification and modified WHO criteria (Table 8.2.). According to this classification, there are 6 degrees of confidence in the relationship. It is considered that an AE belongs to the category of ADR (adverse drug reaction), i.e. it is associated with the study product, if there is at least a minimal possibility of a causal relationship with it, i.e. the degree of relationship includes the categories: definite, probable and possible. In other cases (the relationship is doubtful, tentative, and unclassified), an AE is considered to be unrelated to the study product.

Table 8.2. Classification of the AE relationship assessment regarding the study product, based on the modified WHO criteria.

The existence of a relationship	Degree of relationship	Criteria
Related	Definite relationship (definite)	Clinical manifestations of an AE or violations of laboratory findings occurred during the period of taking the drug, and can not be explained by the presence of existing diseases and the influence of other factors. Manifestations of the AE regress after dechallenge of the drug (dechallenge positive) and occur again when the drug is rechallenged (rechallenge positive).
	Probable relationship	Clinical manifestations of AE or violations of laboratory findings are associated with the time of taking the drug, are unlikely to be related to concomitant diseases or other factors, and regress after dechallenge of the drug (dechallenge positive). The response to rechallenge is unknown.
	Possible relationship (possible)	Clinical manifestations of an AE or violations of laboratory findings are associated with the time of taking the drug but they can be explained by the presence of concomitant diseases or taking other medications and the influence of chemical compounds. Information about the response to drug dechallenge is unclear.

The existence of a relationship	Degree of relationship	Criteria
Unrelated	Doubtful relationship (doubtful)	Clinical manifestations of an AE or violations of laboratory findings occurred in the absence of a clear temporal association with the drug; there are other factors (medications, diseases, chemicals) that may be the cause of the AE.
	Tentative relationship (tentative)	Clinical manifestations and violations of laboratory findings related to an AE that require additional data (for accurate assessment) or these obtained data are currently being analyzed.
	Unclassified relationship (unclassified)	Reports about a suspected AE cannot be evaluated because there is not enough information, or it is contradictory.

All adverse events require adequate treatment. When using concomitant medications or non-drug therapy, they should be documented in the eCRF on the "Concomitant therapy" page.

After detecting an adverse event, it should be monitored until it resolves or until it is considered permanent (stabilization). Adverse event assessments should be performed on each visit (or more frequently, if necessary) to determine any changes in severity, suspected relationship with the study drug, treatment interventions, and its outcome.

Laboratory deviations/deviations of physiological parameters

All laboratory findings outside the established standard values/deviation in physiological parameters that represent adverse events (including Grade 1 according to CTCAE 5.0) and different from the values set during the screening period from the moment the patient was included in the study until the first dose of the study drug administration will be recorded in the CRF in the "Adverse events" section. If possible, the diagnosis should be indicated instead of individual symptoms (for example, anemia, and not a decrease in hemoglobin). Laboratory findings that meet the criteria for adverse events should be monitored until they return to normal or until an adequate explanation is obtained.

8.3.2. Registration of messages about AEs/SAEs

The form for registering adverse events is filled out during the visit (it is acceptable to fill in the form on the same day but after the end of the visit), except for those data that are not available/known at the time of filling in the form. All sections of the form must be filled in. If there is no data due to the inability to obtain it, an entry is made: "Information is not available" or "NA" (not available). However, every effort should be made to obtain all the necessary data on emerging adverse events.

The primary documentation and the AE Registration Form in the eCRF must contain:

- AE No. (a sequence number).

- Visit No.
- Brief description of the AE.
- Seriousness (Yes/No).
- Seriousness criteria.
- Severity according to CTCAE 5.0.
- Start date.
- Resolution date (normalization or the laboratory findings reach the screening values).
- Outcome.
- Actions taken.
- Relationship with the study product (study drug/comparator drug).
- Comments that indicate any clinically significant information related to the occurrence of an AE or its therapy in the Investigator's opinion.

In the case of prescribing drug therapy, the included drugs should be described in the "Concomitant therapy" section of the eCRF, indicating that the drug was used for the purpose of stopping the AE.

The "Degree", "Outcome", "Activities", "Relationship to the study drug" sections are filled in using numeric codes, the values of which are given in the notes. If the AE is identified as serious by the Investigator, not only the AE Registration Form must be filled in but also the form for registering a serious adverse event (in paper form).

For one SAE, one SAE Registration Form is filled in. If the symptoms of a serious adverse event persist on the next visit after registration, then in the CRF, in the "Adverse events" section of the corresponding visit, a mark is made in the checkbox for the presence of adverse events with the note "ongoing". In this case, fill out a new SAE Registration Form with a note in the checkbox "repeated notification".

The following information must be provided in the SAE Registration Form:

1) Clinical study data:
   - Protocol ID.
2) General information about a SAE:
   - Name of the SAE.
   - Initial or repeated notification.
   - the internal SAE number assigned by the Sponsor (it is filled in by the Sponsor).
3) Data about the repeated SAE, investigator, and study site:
   - Full name of the Investigator reporting the SAE.
   - His/her contact information (phone number and email).
   - Name and number of the study site.
   - Full name of the Principal Investigator.
3) Patient data:
   - Patient number.
   - Sex.
   - Body weight.
   - Height.
   - Date of birth.
   - Kidney/liver impairment.
   - Pregnancy.
   - Allergy.
4) Data about the study drug:

- INN and trade name of the study drug.
- Indication.
- Date of first use of the study drug.
- The number of therapy cycles received (if applicable).
- Batch number of the drug (after the use of which the SAE developed).
- Dose (after the use of which the SAE developed).
- Date and time of the start of administration (after which the SAE developed).
- Date and time of the end of the administration (after which the SAE developed).
- Route of administration.
- Dosage and frequency of administration.

5) Data on concomitant therapy used shortly before (for 1 month) and at the time of development of the SAE:
   - INN and trade name of drugs.
   - Indication.
   - Start date of administration.
   - End date of administration.
   - Dosages, frequency, and route of administration.
   - Whether there is a presumed relationship between the SAE and these drugs.
5) Description of the SAE:
   - Description of the SAE with a list of all the necessary symptoms and laboratory and instrumental data, and an indication of the time frame of development.
   - Time after the last administration of the study drug.
   - Data on autopsy in case of death, specifying the cause of death according to anatomic findings. In the absence of the latter, the cause of death is indicated according to the clinical conclusion.
   - Terms of hospitalization, if applicable.
6) Severity (CTCAE 5).
7) Seriousness assessment.
8) Medical history with dates.
9) Laboratory/instrumental data of particular interest at the time of detection of the SAE:
   - Type of the study.
   - Standard.
   - Date of the event.
   - Result.
10) The activities taken to stop the SAE:
   - Drug/non-drug therapy.
     For drug therapy, specify: INN and trade name of the drugs, start and end dates of use, dosage, dosage frequency, and route of administration.
11) Actions taken in relation to the study drug:
   - Dechallenge/dose reduction/no changes, etc.
   - Sample test results after dechalenge and rechallenge of the drug, if applicable.
12) The outcome of the SAE.
13) Signatures.

The investigator **must** sign (signature and surname, first name, patronymic) each sheet of the SAE Registration Form (verification of responsibility for the transmitted information) and only then send it to the Sponsor.

Transfer of primary information about the revealed facts of AEs and SAEs to the Sponsor is allowed in the form of electronic messages, documented information about telephone contacts with patients in the primary documentation.

8.4. Methods and follow-up duration for subjects after the onset of AEs/SAEs

In case of early withdrawal of a patient who received at least one dose of the study drug:

- On the day of withdrawal from the study, an "Early Termination Visit" is conducted and the "Early Termination Form" is filled out. During this visit, the following procedures are performed: general physical examination, determination of physiological parameters, urine analysis, clinical blood test, blood chemistry test, ECG (see Section 4.6.2).
- In the case of withdrawal due to AEs, 14±2 days after the last administration of the test treatment, an "Early Termination Extra Visit" is performed: general physical examination, determination of physiological parameters, urine analysis, clinical blood test, blood chemistry test, ECG (see Section 4.6.2.).

These visits when early termination happens are mandatory for all patients, except in cases where a patient is "lost to follow-up" or physically unable to attend the visit. All relevant records must be provided in the primary documentation and CRF.

In case of withdrawal from the study due to the development of AEs/SAEs, further treatment and monitoring of the patient after the "Early Termination Visit" will be carried out by the investigator in accordance with the standards of treatment of the developed AEs or SAEs adopted in the study site. The patient will be monitored until the AE or SAE is fully resolved, or until the investigator considers the AE to be stable or chronic. In addition, after 14±2 days, the "Early Termination Extra Visit" is performed (the procedures are described above).

In the case of pregnancy in participants or their partners, the study physician should be provided with the contact information of the obstetrician-gynecologist from the antenatal clinic where a pregnant woman is observed. The study physician should monitor the woman during the entire period of pregnancy. Monitoring is carried out using telephone calls made every three months with an obstetrician-gynecologist at the antenatal clinic where the pregnant woman is observed, in order to analyze the general state of the woman, data reflecting the nature of the pregnancy, the results of laboratory and instrumental investigations, including ultrasound scans. The monitoring of the new-born child will be carried out together with the district pediatrician for 6 months. with the analysis of the child's clinical status, data from laboratory and instrumental investigations.

9. THE EVALUATION OF THE PHARMACOKINETICS

9.1. List of pharmacokinetic parameters

9.1.1. Parameter definitions

In order to examine the pharmacokinetics of the study drug, in this research, the concentrations of favipiravir and its main metabolite M1 (the metabolite will be determined if technically feasible) will be determined in the blood plasma of patients in

discrete time intervals. Based on the obtained data, pharmacokinetic concentration-time curves will be constructed for the first and repeated administration of the study drug. The corresponding pharmacokinetic parameters were also calculated.

After the first administration of TL-FVP-t, the following drug parameters will be determined based on the obtained values of the concentration of favipiravir:

C_{max} is the maximum concentration of the substance in the blood of patients during the observation period.

T_{max} is the time when the maximum concentration (C_{max}) of the drug is reached in the blood of patients (if the maximum value is reached at more than one time point, then the T_{max} is the first time point with this value).

$AUC_{(0–12)}$ is the area under the pharmacokinetic concentration-time curve of favipiravir from the moment of drug administration to 12 hours after a single dose of TL-FVP-t. The $AUC_{(0–12)}$ value will be calculated using the linear trapezoid method.

Cl, total clearance, is a parameter that indicates the volume of test tissue that is released from the drug in a unit of time and is determined by the ratio of the drug dose (*DOSE*) to AUC_{0-t}:

$$CL = \frac{\text{DOSE}}{AUC_{0-\text{t}}}$$

V_d is the apparent volume of distribution of medicinal substances; it is the proportional factor between the concentration of the drug in the test tissue and its quantity in the body and reflects the intensity of the drug distribution between the test tissue and other tissues:

$$Vd = CL * MRT$$

K_{el} is a constant of the drug elimination rate; it will be evaluated for each patient based on the slope of a straight linear regression based on several recent (non-zero) log-converted concentration values. The optimal number of values required to construct the regression will be determined using the determination factor (R^2) as follows: first, the last three samples and the last four samples are taken, and the corresponding coefficients of determination $(R_3)^2$ and $(R_4)^2$ are found on them. If $(R_4)^2 \leq (R_3)^2$, then the last 3 samples are used for Kel estimation, and if $(R_4)^2 \geq (R_3)^2$, then the last 5 samples are taken and $(R_5)^2$ is compared with $(R_4)^2$, etc.

$T_{1/2}$ is the half-life of the drug; will be determined by the formula:

$$T_{1/2} = \frac{ln(2)}{K_{el}} = ln(2) * MRT$$

After repeated administration of the drug favipiravir based on the obtained values of the concentration of favipiravir the following indicators of the drug will be determined:

$C_{min,\ ss}$ is the minimum concentration of the substance in the blood of patients when reaching a steady state.

To describe pharmacokinetic parameters, it is planned to use the following characteristics: arithmetic mean, standard deviation, geometric mean, median, minimum and maximum values, quartiles, coefficient of variation.

9.1.2. Endpoints for evaluating pharmacokinetics

Exploratory endpoints:

After a single dose of TL-FVP-t, the following drug parameters will be determined:

- Maximum plasma concentration (C_{max}).
- The area under the pharmacokinetic concentration-time curve for 12 hours ($AUC_{(0-12)}$).
- Time to reach the maximum concentration (T_{max}).
- Apparent elimination half-life ($T_{1/2}$).
- Clearance (Cl).
- Elimination constant (K_{el}).

After repeated administration of TL-FVP-t, the following drug parameters will be determined:

- The above PK parameters on the days of taking the drug are 5 and 10.
- The minimum concentration in the blood plasma of patients in the steady state ($C_{min\ ss}$).

9.2. Methods and timing of evaluation, registration and analysis of pharmacokinetic parameters

9.2.1. Timing of analysis of pharmacokinetic parameters

The endpoints for evaluating pharmacokinetics will be analyzed after all patients in the subgroup have completed the 10-day treatment period (or after early withdrawal).

After obtaining complete pharmacokinetic data in the study (including PK-metabolite) a supplementary report will be prepared.

9.2.2. Methods, the timing of evaluation, and registration of pharmacokinetic parameters

To evaluate the pharmacokinetics of the drug after a single administration, the selection of sampling points should provide several points for each fragment of the pharmacokinetic curve – at least 3 for the initial increase in concentration and at least 5 for the phase of its decrease. Based on this requirement and the available literature data on the pharmacokinetics of favipiravir, the following time points were selected for blood sampling: before administration of the drug, after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours after taking the drug. In order to characterize the parameters of the pharmacokinetics of the drug with repeated administration, blood sampling periods (0–12 hours) will be repeated during the steady-state period, the estimated time to reach the steady-state period is 4–5 half-lives. The average value of the half-life of favipiravir according to literature data reaches 7 hours, 5 x 7 hours = 35 hours, so it can be argued that the concentration of favipiravir from day 3 of administration of the drug will characterize the PK of the drug in a steady state. To assess C_{min}, blood samples will also be taken daily 5 minutes before the first (morning) intake of the drug. Methods and timing of blood sampling and determination of favipiravir concentrations are described in detail in Section 4.7.

Assay of favipiravir and its main metabolite M1 (the metabolite will be determined if technically feasible) in blood plasma

will be performed using a highly sensitive and selective method of high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS).

10. STATISTICS

10.1. Description of statistical methods to be used

The choice of statistical analysis method will be determined by the type of source data and the type of distribution. The possibility of using a number of statistical methods will be evaluated after data collection is complete, considering the nature of data distribution, sample homogeneity, etc., are unknown in advance. During the analysis, it is possible to expand the list of methods used, if this is necessary for high-quality data processing.

Analysis of efficacy parameters

The analysis will be performed in the ITT and PP populations, the main population of the analysis will be the ITT population, and the analysis will also be performed for each stratum, if applicable (stratification will be performed depending on: severity of the disease (mild, medium), age (<45; ≥ 45 years), the severity of pathology on chest CT (degree 0-1/degree 2–3).

Hypothesis testing will be conducted with one-way 5% and 10% significance levels.

For the primary endpoint, the time to improve clinical status (defined as a decrease of at least 1 point according to the WHO Ordinal Scale for Clinical Improvement) (median, in days) and time to virus elimination (defined as the absence of SARS-CoV-2 based on the results of 2 sequential PCR tests of smears with the intervals not less than 24 hours) (median, in days) as a result of the use of the study treatment and the comparison treatment, and the difference between the corresponding treatment groups will be presented with the appropriate 95% confidence interval (CI).

Categorical data will be processed using frequency tables, the Fisher exact test, the frequency equality test, the Pearson 3^2 test, the Stewart-Maxwell or McNemar test, and the cochrane-Mantel-Heinzel test. Percentages or shares are planned to be used to describe categorical data.

Data describing progression-free survival and overall survival will be analyzed using a log-rank criterion, the Kaplan-Meyer method, and survival tables. Additionally, regression models can be used to assess the impact of factors other than the treatment type.

Safety analysis

The safety parameter analysis will be performed in the population to evaluate the safety parameters.

The AE analysis will be based on an assessment of the frequency of adverse events/serious adverse events. Adverse events reported in the course of the study will be presented by frequency (number of patients with an AE and the number of such AE in the group), grouped by SOC and PT. The AEs will also be presented with a division by severity and relationship to the study drug administration. Frequency comparison between therapy groups will be performed using the exact Fisher test or the Pierson χ^2 test.

To describe quantitative variables distributed according to the normal law, we plan to use the following characteristics: average value,

minimum and maximum values, standard deviation, 95% confidence interval, coefficient of variation. To describe quantitative data distributed according to a different distribution law from the normal one, it is assumed to describe it using the median and quartiles. For quality data, frequencies (fractions and/or percentages) will be provided.

Comparison of clinical and laboratory parameters at the study stages will be performed in patients using the student's t-test (parametric test for two dependent/independent samples), the Mann-Whitney U-test (nonparametric test for two independent samples), the Wilcoxon T-test (nonparametric test for two dependent samples), parametric analysis of variance (ANOVA) for repeated measurements, and the Friedman test (nonparametric test for several dependent samples). The choice of criteria (parametric or nonparametric) will be made after checking the type of data distribution for compliance with the normal distribution law using the Shapiro-Wilk test. For multiple comparisons will be applied to the Benjamini-Yekutieli correction.

Categorical data will be described using percentages and absolute values. Categorical data will be compared using the exact Fisher test, Pearson's χ^2 test, or frequency equality test.

Analysis of pharmacokinetics

All statistical analyses will be made for the PK-analyzed population.

The study will determine the concentrations of favipiravir and its metabolite in the blood plasma of patients in discrete time intervals to build pharmacokinetic concentration-time curves when the study drug is administered repeatedly.

A list of PK-parameters will be calculated:

- After a single administration of TL-FVP-t, the following drug parameters will be determined: maximum plasma concentration (Cmax); area under the pharmacokinetic concentration-time curve from the moment of administration to the last sampling point ($AUC_{(0-12)}$); half-life ($T_{1/2}$); elimination constant (K_{el}), clearance (Cl); and a number of additional parameters.
- After repeated administration of TL-FVP-t will be the following drug parameters: maximum concentration in the blood plasma of patients upon reaching steady state ($C_{max\ ss}$); the time to reach steady state ($T_{max\ ss}$); the minimum concentration in the blood plasma of patients in steady state ($C_{min\ ss}$); the total area under the concentration-time curve within a dosing interval (τ) at steady-state conditions (ss) with repeated drug administration ($AUC_{\tau,ss}$); factor accumulation (Fc).

Otherwise, the same pharmacokinetic parameters specified for a single administration will be determined.

To describe these pharmacokinetic parameters, it is planned to use the following characteristics: arithmetic mean, standard deviation, geometric mean, median, minimum and maximum values, quartiles, coefficient of variation.

Software for statistical analysis

The statistical analysis will be conducted under the supervision of a responsible biostatistician, in accordance with ICH requirements, as well as other applicable requirements and laws.

This multicenter study will be conducted in several study sites. Before starting the analysis, data from all study sites will be combined. Pre-analysis will be conducted aimed to study whether the relevant data belongs to a single General population, as well as the to research the issue of the legitimacy of combining data from different study sites, along with the method of aggregation problem.

Statistical processing of data obtained during the research will be performed using the Statistica package (10.0 or higher), the R programming language for statistical data processing, or other appropriate software.

10.2. Stages of statistical analysis, deadlines for preparing reports

At the end of the study, all 168 patients from the initial enrolment will be evaluated for the final pharmacokinetics and safety endpoints.

10.3. The planned number of subjects, the rationale for the sample size, including reasoning or calculations to justify the statistical power of the study and clinical validity, and the applied significance level

The aim of the study was to study the efficacy and safety of TL-FVP-t in outpatients and hospitalized patients with mild to moderate coronavirus disease (SARS-CoV-2/ COVID-19) compared to the recommended standard treatment. Thus, by its design, it is a superiority study. The primary endpoints will be the median time in days from the start of treatment with the study drug/recommended therapy after inclusion in the study to:

- elimination of the virus (defined as the absence of SARS-CoV-2 based on the results of 2 consecutive PCR smears with an interval of at least 24 hours).
- improvements in clinical status (defined as a decrease of at least 1 point in the WHO Ordinal Scale for Clinical Improvement).

The sample size was calculated using the gsDesign package (version 3.0-1) of the statistical programming language R (version 3.5.3), based on the following preliminary assumptions:

1) Type I error (α) = 0.025 (due to the fact that a one-way superiority hypothesis is being tested, and a two-way 95% confidence interval will be calculated)

2) Type II error (β) = 0.1 (respectively, the power is 90%).

3) Distribution in groups will be made in a ratio of 2 : 1 (favipiravir : recommended therapy)

The sample size for the time to reach virus elimination

According to Cai et al. (2020), the median time to virus elimination in a comparative clinical study of favipiravir versus lopinavir/ritonavir was 4 (2.5–9) and 11 (8–13) days, respectively, provided that patients were included no later than 7 days after the development of symptoms. In these conditions, at least 47 patients should be confirmed to have eliminated the virus.

Fixed design, two-arm trial with time-to-event outcome (Lachin and Foulkes, 1986).

Study duration (fixed):	Ts=30
Accrual duration (fixed):	Tr=1

Uniform accrual:	entry="unif"
Control median:	log(2)/lambda1=11
Experimental median:	log(2)/lambda2=4
Censoring only at study end	(eta=0)
Control failure rate:	lambda1=0.063
Experimental failure rate:	lambda2=0.173
Censoring rate:	eta=0
Power:	100*(1-beta)=90%
Type I error (1-sided):	100*alpha=2.5%
Randomization (Exp/Control):	ratio=2
Sample size based on hazard ratio=2.75 (type="rr")	
Sample size (computed):	n=50
Events required (computed):	nEvents=47

Sample size for time to improve clinical status

Information about the rate of improvement of the clinical status, resolution of clinical manifestations, and virus elimination in patients with non-severe COVID-19 is limited. The possibility of direct use of the literature data is also limited by the fact that the data are provided for observation of patients in real clinical practice, in which patients receive a variety of symptomatic and etiotropic therapy.

Thus, according to Li et al. (2020), in patients with mild to moderate form and "standard" etiotropic therapy, including lopinavir/ritonavir, umifenovir, and other drugs, the median time to virus elimination was 9.0–9.3 days, provided that patients were included in the study for an average of 3–6 days after the development of symptoms. According to the data, the average time from the virus elimination resolution of symptoms is 2.5 days (1.25–4.5), therefore, it can be assumed that the clinical improvement when

the "standard" treatment is used can occur no earlier than 11.5–13.5 days.

The sample size was calculated based on the following assumptions: the median time to improve clinical status is 13 days in the control group and 7 days in the study drug group. Under these conditions, at least 125 patients should have improved clinical status.

Fixed design, a two-arm trial with the time-to-event outcome (Lachin and Foulkes, 1986).	
Study duration (fixed):	Ts=30
Accrual duration (fixed):	Tr=1
Uniform accrual:	entry="unif"
Control median:	log(2)/lambda1=13
Experimental median:	log(2)/lambda2=7
Censoring only at study end	(eta=0)
Control failure rate:	lambda1=0.053
Experimental failure rate:	lambda2=0.099
Censoring rate:	eta=0
Power:	100*(1-beta)=90%
Type I error (1-sided):	100*alpha=2.5%
Randomization (Exp/Control):	ratio=2
Sample size based on hazard ratio=2.75 (type="rr")	
Sample size (computed):	n=140
Events required (computed): nEvents=125	

In this study, it is planned to conduct an interim analysis after the occurrence of at least 40% of the required number of events. The sample size was adjusted using the method of group sequential analysis:

Group sequential design sample size for the time-to-event outcome with sample size 144. The analysis plan below shows events at each analysis. Asymmetric two- sided group sequential design with 90 % power and 5 % Type I Error. Spending computations assume trial stops if a bound is crossed.

				----Lower bounds----		----Upper bounds----	
Analysis	N	Z	Nominal p	Spend+	Z	Nominal p	Spend++
1	**54**	**-0.12**	**0.4525**	**0.0206**	**2.65**	**0.0041**	**0.0041**
2	**129**	**1.64**	**0.9498**	**0.0794**	**1.64**	**0.0502**	**0.0459**
Total				0.1000			0.0500

\+ lower bound beta spending (under H1):
Hwang-Shih-DeCani spending function with gamma = -2.
++ alpha spending:
Hwang-Shih-DeCani spending function with gamma = -4.
Boundary crossing probabilities and expected sample size assume any cross stops the trial
Upper boundary (power or Type I Error)

	Analysis			
Theta	1	2	Total	E{N}
0.0000	0.0041	0.0459	0.05	94.4
0.2618	0.2346	0.6654	0.90	109.4

Lower boundary (futility or Type II Error)

	Analysis		
Theta	1	2	Total
0.0000	0.4525	0.4975	0.95
0.2618	0.0206	0.0794	0.10

An interim analysis of this endpoint is planned after the onset of 54 events (an event, in this case, refers to an improvement in clinical status). In order for the interim analysis to be performed after 14 days of participation, about 69 patients will need to be included in the study. In this case, by day 14 of therapy, the expected number of events will be approximately 42 in the study group and 12 in the control group.

If the value of the Z log-rank test is lower than the critical value (-0.12), it will be concluded that the study treatment is ineffective.

The final analysis will be performed after 129 events occur. Taking into account the fact that not all patients may have improved clinical status by the end of the study, and taking into account the expected withdrawal, it is planned to increase the sample by 30% and include 168 patients in the study (112 patients in the study drug group and 56 patients in the comparison group). At the same time, it is planned to screen no more than 200 patients.

10.4. The applied significance level

To evaluate the primary endpoint, the significance level was chosen to be 2.5% (0.025), and the power was chosen to be 0.9 (90%). The expenditure of the overall error rate was controlled using the method of group sequential analysis.

No interim analysis is planned for the remaining efficacy and safety parameters, so a two-way significance level of 0.05 will be applied for all other analyses.

10.5. Procedures for accounting for missing, unanalyzed, and doubtful data

Procedures for accounting for missing data and improving the accuracy of statistical analysis

All information specified in the eCRF must be confirmed by the relevant data in the primary documentation. During monitoring visits in the study site, the clinical study monitor/manager will analyze the CRF for a lack of necessary data. If there is no data in the CRF and the corresponding information is available in the primary documentation, Questions to investigators and instructions on how to eliminate inconsistencies will be formulated.

The employee who maintains the electronic database checks the database for inconsistencies, erroneous data, or missing data after entering all the data. To collect missing data or correct wrong data, the Database Manager and/or medical expert of Drugs Technology LLC forms queries in the eCRF, which are patient-specific, i.e. separate queries are generated for each patient. When checking the database of the study results, a statistician will conduct a doubtful, missing, and non-analyzed data analysis, which will also result in additional queries to investigators.

Responses to queries must be provided by the investigator no later than 5 business days from the date of forming the query in the eCRF. It is also possible to generate separate queries outside the eCRF system. Copies of such queries with the report should be stored in the study site. and the originals in Drugs Technology LLC.

When receiving answers to questions from investigators, the employee responsible for maintaining the research database checks for inconsistencies, erroneous data entered, or missing data. After the final completion of data collection and entry in all sites, the database is closed, after which statistical processing can begin.

If the detected errors in the data cannot be corrected after the withdrawal of the subjects from the study, during the statistical analysis of data, the sensitivity of the resulting parameters to doubtful data is examined. Information about missing, doubtful, and ineligible for analysis (if applicable) data will be presented in the Clinical Study Report.

Working with withdrawing, excluded patients, and missing data When analyzing pharmacokinetic and safety parameters, no missing data will be added, and no missing data will be taken into account when performing statistical analysis. If any concentration values are missing, this should be displayed accordingly and the reasons indicated (due to loss of test results, errors during sampling, etc.).

When analyzing efficacy parameters if there are missing values the sensitivity analysis will be performed as follows:

1) If there is a small number of omissions, it will be compared to the test results ignoring missing data and the results obtained in the case of the best outcome in omissions in the comparison group and the worst outcome in omissions in the study group. If the results of this

categorical analysis are still maintained, then it is safe to say that the results are stable.

2) If there are a significant number of omissions, then it is possible to use classification methods with training (for example, decision trees, Adaboosting, neural networks, etc.) to predict outcomes at the place of omissions, where all data with known outcomes will be used as a trained sample, and data with unknown outcomes will be used as a test sample. This will take into account factors such as group, initial severity of the disease (mild/moderate), age (≤40 or >40 years).

Working with outliers

In the analysis of pharmacokinetic parameters, the identification of doubtful data and data that are not subject to analysis will be performed by visual analysis of scatter diagrams and boxplot construction. Statistical analysis will be performed for data containing outliers, and then for the sample cleared of outliers.

10.6. Procedures for reporting any deviations from the original statistical plan

If there is a need to change the original clinical study plan, the changes will be described and explained in the Protocol amendment or the interim/final study report.

If the application of initially defined statistical methods is not possible, then the final statistical and general reports justify the changes, with references to the calculations made, statistical indicators, and general analysis of the situation that led to these changes. The decision to make extraordinary deviations (assumptions that modify data) is a privilege of the study Sponsor only and must be explained and justified, including in the text of the final report on the clinical study.

All changes to the original statistical plan and their justification will be reflected in the final study report.

10.7. Selecting subjects for analysis

Population for safety analysis

The safety analysis will be performed in a population of patients who received at least one dose of the test product (study drug or comparison drug).

Population for efficacy analysis

The efficacy analysis will be performed in the ITT-population (intent-to-treat) of all patients included in the study and in the PP-population (per protocol):

- **Complete population analysis (intent-to-treat).** Efficacy evaluation of the main population is defined as the complete population analysis and includes all randomized patients.
- **The "per protocol" population.** The "per protocol" population includes all patients from the full analysis population without significant deviations from the Protocol who have taken at least one dose

of the study treatment, and in which efficacy could be evaluated.

Population for analysis of pharmacokinetic parameters

The PK-analyzed population will include all patients who gave blood samples for the investigation of the drug's pharmacokinetics and for whom the pharmacokinetic profile can be adequately described.

11. DIRECT ACCESS TO PRIMARY DATA/DOCUMENTATION

Primary data are information contained in the original medical records and their copies, describing the results of clinical observations, examinations, and other activities, allowing you to reproduce the progress of a clinical study and evaluate its quality. Primary data are contained in primary documentation (originals or certified copies), as well as in electronic form.

The investigator or organization involved in the study should not prevent direct access to primary data/documentation for study-related monitoring, audit, ethical review, or an inspection by regulatory authorities.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. General information on quality assurance

The sponsor must provide an appropriate quality assurance and control system for conducting this clinical study in accordance with the Study Protocol, principles of Good Clinical Practice, and applicable regulatory requirements.

The study procedures specified in the Protocol must be strictly followed by the Investigator and members of the investigation team.

In order to ensure a proper quality assurance and control system, it is allowed to conduct the study procedures in accordance with the standard operating procedures of the study site, logistics company, or involved medical organizations, provided that they do not contradict the standard operating procedures of the study sponsor. If there is a discrepancy in the procedures, the sponsor's standard operating procedures are considered to take priority unless otherwise specified and there is no notification from the sponsor of the permitted deviation from the standard operating procedure.

12.2. Quality Assurance

In accordance with ICH GCP and regulatory requirements, the Sponsor, a third party on his behalf, regulatory authorities, or ethics Committees may conduct quality assurance audits (inspections) at any time during the study or after the study is completed. The Investigator should provide the auditors with direct access to all relevant documentation, including primary documentation, and allocate their time and the time of their employees to work with the auditors to discuss the results of audits and inspections, as well as other issues.

12.3. Compliance with The Protocol by the Investigator

Before starting the study, the Investigator must fully familiarize himself with the provisions of this Protocol, accept them, and conduct the study in accordance with this Protocol, the ICH GCP, and other applicable regulatory requirements of the participating countries.

During the study, deviations from the Protocol requirements are not allowed without prior written permission from Drugs Technology LLC, the Ministry of Health of the Russian Federation, and Local Ethics Committees, except in cases where this is necessary to prevent any immediate danger to patients.

The Investigator must have sufficient time for the correct execution and completion of the study within the terms agreed with Drugs Technology LLC, as well as have a sufficient number of qualified employees and adequate equipment necessary to perform the study under this Protocol.

Each of the co-investigators participating in the study should be familiar with the Protocol requirements and their responsibilities during the study. The transfer of any of their functions in this study to co-investigators is made by the Principal Investigator in writing in the corresponding section of the Investigator's File.

In each study site, the decision to terminate the patient's participation in the study early must be approved by Drugs Technology LLC.

When the Investigator makes a decision to exclude a patient from the study, he must inform the clinical study manager of Drugs Technology LLC by email indicating the reason for the exclusion of the patient. Drugs Technology LLC within 48 hours, excluding weekends and holidays, from the moment of receipt of the letter informs about the consent to exclude the patient from the study. If the immediate exclusion of a patient from the study is required due to the development of serious adverse events, the investigator informs Drugs Technology LLC about the SAE within 24 hours but does not wait for the consent of Drugs Technology LLC to exclude the patient. from the study.

If patients were lost to follow-up as well as they took doses of the study drugs not covered by the Protocol, the Investigator must inform Drugs Technology LLC within 24 hours after identifying these violations for instructions on further management of patients and registration of the causes of deviations from the Protocol in the Case Report Form/primary documentation.

In case of violation of the above-mentioned approved procedures, as well as repeated deviations from the Protocol, the issue of suspension or final termination of the study at this site will be decided.

12.4. Deviations from the Protocol

Deviation from the Protocol is any change, discrepancy, or departure from the study design or the Study Protocol procedures.

Any deviation from the Protocol during the clinical study should be registered and reflected in the study documentation.

All deviations from the Protocol are classified into significant deviations and minor deviations.

A minor deviation from the Protocol does not significantly affect the rights, safety, and well-being of the patient or the completeness, accuracy, and reliability of the study data.

A significant deviation from the Protocol (or violation of the Protocol) is a deviation that may affect the rights, safety, and well-being of the patient or the completeness, accuracy, and reliability of the study data.

Examples of significant deviations from the Protocol:

- A patient met the exclusion criteria but was not excluded from the study.
- A patient took a prohibited concomitant medication.
- A patient was included in the study, although he did not meet the inclusion criteria.
- Study procedures were conducted without obtaining the patient's written informed consent.
- Violations during CT diagnostics.
- Detection of an unreported SAE.
- Loss due to negligence of data or samples collected for the study, etc.

Significant deviations must be reported to the Ethics Committee, the Independent Data Monitoring Committee (IDMC), and the Central Independent Committee for evaluating CT data in the case of deviations related to CT procedures in the study.

12.5. Responsibility of the Investigator for non-compliance with the Protocol

Failure to comply with the Protocol, SOP, and/or relevant regulatory requirements by the Investigator/study site, CRO, or Sponsor's employees should lead to immediate actions by the Sponsor to ensure compliance.

If serious and/or repeated cases of non-compliance with applicable requirements by the Investigator/medical institution are detected during monitoring or audit, the Sponsor must terminate the participation of the breaching party in the study. If the participation of the Investigator/study site is terminated as a result of serious or repeated cases of non-compliance with applicable requirements, the Sponsor must notify the regulatory authorities.

12.6. Study monitoring

Before the examination, during a remote initiation visit using video communication, an employee of Drugs Technology LLC (clinical study monitor or manager) will review with the Investigators and staff of the study site the Protocol and eCRF, rules of filling of primary documents, rules of contact with patients who tested positive for coronavirus, the compliance with personnel protection measures when taking biological material, organization of contacts and control when interacting with outpatients, the procedure of ordering and dispensing the study treatment, organization of CT examinations, interaction with the Ethics Committee, IDMC, CIC on CT, conditions of the study termination in the site, detection and registration of deviations from the Protocol, the rules of communication with the Study Sponsor.

During the study, the monitor is not allowed to be present in the study site in person. The study will be monitored remotely, electronic copies of available primary documentation, the Investigator's File, and other electronic materials such as CT scans and laboratory data will be checked during the monitoring. The monitor working with the study site will regularly request information in order to check the completeness of patient documentation, assess the accuracy and timeliness of entering information in the CRF, compliance with the Protocol and requirements of Good Clinical Practice, and monitor the patient recruitment process. It is necessary that during the monitor's contacts with the study site using telephone and video communication, key employees of the site are available to assist the monitor and resolve issues that arise. The main communication procedures are listed in the Communication Guide.

The main procedures for remote monitoring during the study are established in accordance with the Standard Operating Procedure of Drugs Technology LLC, unless otherwise specified.

Clinical study monitoring is conducted by the Sponsor on a regular basis in order to:

- Ensuring the protection of patients' rights and health.
- Verification of the accuracy and reliability of the data entered in the eCRF and the data in the primary documentation is provided by checking the electronic copies of the primary documentation.
- Checking of following the procedures of the approved Study Protocol, Amendments to the current version of the Protocol (if applicable), Principles of GCP, and current regulatory requirements by the investigator and members of the investigation group.

The monitoring of the clinical study is carried out according to the approved plan. The clinical study monitor/manager must ensure that the study is properly conducted and documented. The clinical study monitor/manager has the following responsibilities:

- Checking whether the Investigator has the necessary qualifications and sufficient resources, including laboratories, equipment, and personnel, throughout the study.
- Control of the study drug (storage conditions, shelf life, sufficient amount of the drug in the study site, correct prescription of the study drug, accounting of the drug), taking into account the information entered in the accounting logs and electronically submitted for verification.
- Checking compliance of the Investigator with the approved Protocol and all approved amendments to the Protocol (if applicable).
- Monitoring the timely signing of the Patient's Information Sheet and the Informed Consent Form before the start of a patient's participation in the study.
- Providing the Investigator with the current versions of the documents for conducting the clinical study (Protocol, Protocol Amendments (if applicable), investigator's Brochure, Patient's Information Sheet, and Informed Consent Form).
- Providing the investigator and members of the investigation team with adequate information about the study.

- Monitoring the fulfillment of study-related duties by the investigator and members of the investigation team in accordance with the Protocol and other applicable agreements between the Sponsor and the Investigator/medical institution, as well as the independence of performing their assigned duties (finding the facts of the delegation of the Investigator's functions to unauthorized persons).
- Monitoring compliance with the study inclusion criteria by the Investigator.
- Informing Drugs Technology LLC about the rate of subject recruitment to the study.
- Remote control of the accuracy and completeness of data in eCRFs, primary documentation, and other study-related records by comparing them with the provided copies of data.
- Informing the Investigator of any errors, omissions, or illegible entries made in the CRF.
- Checking compliance with the deadlines for reporting adverse events defined in this Protocol.
- Checking the main documents maintained by the Investigator.
- Informing the Investigator about deviations from the Protocol, SOP, and regulatory requirements, and also taking the necessary actions to prevent the recurrence of such deviations.

For each patient participating in the study, the Investigator must keep primary documentation containing data about the patient and records made during visits (medical records from hospitals or clinics), including demographic and medical information, data from laboratory tests, electrocardiograms, and all other tests or examinations. Any information in the CRF must have a primary source in the patient's primary documentation. In addition, the investigator should keep the original Informed Consent Form (a second copy of the signed Informed Consent Form is issued to a patient).

The investigator must ensure that the monitor has access to all patient-related primary documentation to confirm that the primary documentation data matches the data entered in the CRF. The investigator must ensure that the CRF is completed in a timely manner before visiting the monitor or clinical study manager.

To confirm that the study meets the requirements of the Helsinki Declaration, ICH GCP, regulatory requirements of the participating countries, and the Study Protocol, as well as the authenticity, accuracy, and completeness of the data, the study monitor/manager will check the CRF and other study-related documents by verifying the primary data.

At the end of the study, a representative of Drugs Technology LLC (the clinical study monitor/manager) will need to visit the site to conduct the End of Study Visit. At the same time, the necessary documentation will be collected in accordance with the requirements of the SOP of Drugs Technology LLC.

12.7. Audit By The Sponsor

The Sponsor's audit is conducted separately and independently of the routine functions of monitoring and quality control of the clinical study. The purpose of the audit is

assessment of compliance of the study with the Protocol, SOP, and regulatory requirements.

The Sponsor designates independent persons who are not involved in this clinical study to conduct the audit.

The Sponsor must make sure that the auditors are qualified to conduct an audit properly. The auditor's qualifications must be documented.

The Sponsor or authorized organization will develop an audit plan and audit procedures for this study, in accordance with which the audits are performed.

It is allowed to conduct a remote audit of the study, during which the primary documentation will be checked to preserve the confidentiality of patients, applicable forms, logs, etc. In this case, the audit program is developed separately for each study site.

12.8. Termination of the study

Drugs Technology LLC may temporarily or permanently terminate the study for reasons of safety, ethics, compliance with the Protocol, or other reasons. If such a need arises,

Drug Technology LLC will take steps to notify the study site in advance. If the study is temporarily or permanently terminated, Drug Technology LLC and the Investigator must inform the Ethics Committees and regulatory authorities in a timely manner. In these cases, all study data must be transferred to Drugs Technology LLC and all unused study drugs must be returned.

13. ETHICS

13.1. Ethical aspects of the study

The study will be conducted in accordance with the ethical principles set out in the World Medical Association Declaration of Helsinki “Recommendations guiding physicians in biomedical research involving human subjects” (1964-2013) and the ICH GCP rules.

The final version of the Protocol, including the Patient's Information Sheet and the Informed Consent Form, will be submitted for approval to regulatory authorities (the Ministry of Health of the Russian Federation), as well as to the Local Ethics Committee of the study site prior to the start of the study.

All subsequent additions to the Protocol that relate not only to administrative matters must also be approved in accordance with the established procedure before they are applied.

The procedure for obtaining the patient's Informed Consent Form will be conducted prior to the start of any procedures of this study. Information for patients will contain all data about this clinical study that they need to make a meaningful and independent decision of participation.

During the study, all cases of SAEs will be reported within 24 hours to Drugs Technology LLC, which, based on the analysis of reports, may decide to suspend the study. The Ethics Committee will also be informed of any unexpected SAE associated, according to investigators, with the use of the study drug.

Information that identifies patients is confidential and can only be disclosed in cases stipulated by the law and only by a court decision.

All study subjects will be insured in accordance with the Federal law of the Russian Federation No. 61-FZ "On drug circulation" and the Rules of compulsory insurance of life and health of a patient involved in clinical studies of the drug, approved by the Resolution of the Government of Russia No. 714 dated September 13, 2010.

In addition, in this clinical study, it is planned to organize the Central Independent Committee (CIC) for the evaluation of computed tomography (CT) data, whose duties will include a reference assessment of the results of computed tomography of patients throughout the entire period of participation in the study.

The decision on how to manage patients based on CT data will be made at the study site where the patient is recruited, taking into account the conclusion of the CIC on CT. The study plans to set up an Independent Data Monitoring Committee (IDMC), which will be responsible for periodically reviewing safety and efficacy data and making medical decisions in complex cases for individual patients (if necessary).

13.2. Confidentiality of research participants

The investigator undertakes to maintain confidentiality regarding the patient's identity, the text of this Protocol, as well as all other materials and results of the study.

The Investigator must ensure that patients remain anonymous. In the CRF and other documents provided by Drugs Technology LLC, patients must be identified not by their first and last names, but by assigned identification numbers and/or initials.

The investigator should keep a separate log of patient IDs, last names, addresses, phone numbers, and medical history numbers (if applicable). The investigator must keep strictly confidential data that is not intended to be provided to Drugs Technology LLC.

All research materials that are the property of Drugs Technology LLC can not be transferred to third parties, except in cases stipulated by the legislation of the Russian Federation.

14. DATA MANAGEMENT AND RECORDING

14.1. Records management at the study site

All documents related to the study that were not in the red zone of the site must be archived at the study site or in the central archive of the institution. Documents after direct contact with a hospitalized patient in the red zone, held in conditions of restricted access by staff, are subject to photocopy, after which they are destroyed without transferring the originals to the study physician. Patient's Diaries filled out by outpatients are subject to photocopy and following destruction after receiving the Principal Investigator's permission. Upon completion of participation in the study, patients must certify printed copies of their diaries

with their signature on each page where data are presented. A careful listing of all identification data about study participants is necessary.

According to the ICH GCP definition, required documents include: the signed Protocol and all amendments, copies of completed CRFs, signed Informed Consent Forms for all patients, medical records, diaries, and other primary documentation, approvals by Ethics Committees and regulatory authorities, and all correspondence with them, including approved documents, drug reporting records, study correspondence, and a list of names and addresses of patients. This list is the main one in the documentation that should be kept by the Investigator.

Primary documentation

Primary documentation includes original documents that are relevant to the study, treatment, anamnesis, and description of the patient's condition. For example, these documents include a medical history and discharge records with the results of laboratory tests.

It is the responsibility of the Investigator to keep correct and accurate records of study progress. Primary documentation is maintained according to the rules adopted in the Russian Federation, including registration of primary documentation in the appropriate division of the study site. Entries in the patient's primary documentation are made during each examination of the patient. The required data are transferred to the eCRF within the time limits specified in the Sponsor's/study site's SOPs or other documents.

All entries in the primary documentation must be made in clear, legible handwriting.

If it is necessary to make corrections to the primary documentation, the incorrect entry is crossed out with a single horizontal line, the correct entry is written next to it, then the date of correction, initials and signature of the person who made the corrections are indicated. The use of any means that destroys the previous record or makes it difficult to read is not allowed.

When receiving the results of laboratory and instrumental tests, the Investigator must evaluate, date, and sign them. Forms of laboratory tests and instrumental investigations are considered to be the primary documentation.

14.2. Data confidentiality

Information about research participants will be kept confidential. It will be processed in accordance with applicable laws and regulations. These regulations require informing patients and obtaining their written consent on the following issues:

- What confidential health information will be collected from participants in this study?
- Who will have access to this information, and on what grounds?
- Who will use or disclose this information?
- What rights do study participants have to withdraw consent to use confidential health information?

In the event of withdrawal of consent to the collection or use of confidential health information, the Investigator, in accordance with regulatory standards, retains the ability to use all information collected prior to the withdrawal of consent. Concerning participants who have withdrawn their consent to the collection or use of confidential health information, every effort should be made

to obtain permission to collect at least safety monitoring information (i.e. development or worsening of existing adverse events) at the end of the period of planned study participation.

In order to prevent unauthorized access to confidential information about study participants, the data collection system for this study has built-in safety elements to encrypt all data when it is transmitted in both directions. Access to the system will be controlled using a sequence of individually assigned user identification codes and passwords, which will only be given to authorized employees who have completed mandatory training.

14.3. Data collection

This study uses electronic versions of the CRF (eCRF). These eCRFs were developed using fully validated secure Internet software that meets the regulatory requirements of participating countries (as well as the requirements of Part 11 of Chapter 21 of the US Code of Federal Regulations). Employees of the study site will not be given access to the electronic data entry system until they complete their training. The automatic validation program checks the eCRF for inconsistencies and allows the site's employees to change or verify the entered data.

The Principal Investigator is responsible for the completeness and accuracy of all data entered in the eCRF, as well as for the timeliness of data entry and updating.

The monitor is responsible for checking the eCRF for completeness and accuracy of records, instructing the staff of the study site to make necessary corrections or additions.

Employees of the study sites will take blood plasma samples for pharmacokinetic assessment, after which these samples will be sent to the central laboratory for processing. The results of the analysis of PK-indicators will be sent in the electronic form to Drugs Technology LLC.

14.4. Database maintenance and quality control

In studies using eCRF, employees of Drugs Technology LLC (or a contract research organization (CRO)) will analyze the data entered by the employees of the study site for accuracy and completeness. When discrepancies and missing values are detected, data requests will be created indicating the nature of the problem and the required clarification. These requests will be sent to the study site. The designated study site employee is required to respond immediately to requests and make any necessary changes to the data.

Concomitant and prior therapies are entered into the database by encoding using WHO Model Lists of Essential Medicines, which is based on the Anatomical-Therapeutic-Chemical classification system. Anamnesis/comorbidities and adverse events are encoded using the terminology of the Medical Dictionary for Regulatory Purposes.

Samples and/or data will be processed centrally and the results will be sent electronically to Drugs Technology LLC (or a designated CRO).

At the end of the study, the facts of any deviations from the Protocol will be determined. After completing these steps and confirming the completeness and accuracy of the database, it will be declared closed, and it will be prepared for data analysis. Any changes to the database after it is closed can only be made on the basis of a signed agreement between the Biostatistician and the Head of the clinical development group.

After closing the database, the investigator will receive data on participants on a CD or paper for archival storage in the study site.

14.5. Archiving of documents

By signing this Protocol, the Investigator agrees to comply with the procedures for storing and archiving study documentation. The primary documentation and the Investigator's local file, including the identification list of participants and research-related correspondence, are stored. The main documents of a clinical study must be kept at the study site for at least 15 years after the final version of the clinical study report is submitted to the regulatory authorities.

At the end of this period, the Sponsor will inform the investigator(s) of the date when this documentation can be destroyed.

The study participant's documentation will be archived in accordance with the rules of the study site.

The investigator must inform the Sponsor of the location where the necessary documents are stored, and contact the Drug Technology LLC for its approval before destroying any of them. The Investigator should take measures to prevent accidental or premature destruction of these documents.

The Sponsor is responsible for archiving the Clinical Study Master File.

If the Sponsor terminates the clinical development of the study drug, the Investigator and regulatory authorities must be notified. The Sponsor must inform the Investigator in writing of the need to keep research-related records.

15. FINANCING AND INSURANCE

Patients will not receive payment for participating in this study.

During the study, patients will be insured as participants in the study in accordance with the legislation of the Russian Federation. On the territory of the Russian Federation, patients will be insured in the Russian limited liability company “Absolut Strakhovanie” (Absolute Insurance LLC) (Address: 26 Leninskaya Sloboda str., Moscow, 115280; phone/fax. (495) 987-18-38).

The study physician must familiarize a patient with the terms of the mandatory insurance Contract (including the obligations that must be followed by patients). The study physician must issue the patient with a mandatory life and health insurance policy for the participating of a patient in clinical studies of the drug. If it is necessary to make changes to the mandatory insurance policy, the patient must return the previously issued mandatory insurance policy

that will be replaced with a new one no later than 2 business days.

The insurance policy covers the claims of Patients to the Policyholder only for compensation for damage to life and health caused to them during participation in clinical studies, due to deficiencies of the tested drugs or insufficient information about them, unintentional errors, omissions. Only claims that were first submitted to the Policyholder during the insurance period in respect of events occurring on the territory of the insurance after the Retroactive Date and in connection with the performance of the Insured activity are covered.

If patients' health is damaged as a result of the use of the study drug or medical procedure provided for in the Study Protocol, they will be provided with free qualified medical care in the required amount, paid for by the Insurance company. However, the Insurance company will make the stipulated payments only if the patients comply with all the physician's prescriptions.

The amount of the insurance payment that the Insurer undertakes to pay under the Mandatory Insurance Contract is:

а) In case of death of the insured person related to the study drug, 2 million rubles. The insurance payment in the specified amount is distributed among the beneficiaries in proportion to their number in equal shares.

б) If the insured person's health deteriorates due to the study drug and results in:

Group I disability confirmation – 1.5 million rubles.

Group II disability confirmation – 1 million rubles.

Group III disability confirmation – 500 thousand rubles.

в) If the insured person's health deteriorates due to the study drug and does not result in disability – no more than 300 thousand rubles.

16. PUBLICATIONS

After the study and statistical processing are completed, the obtained data will be published. The investigator should not publish the results of this study, including those obtained at his study site, without the consent of Drugs Technology LLC. Publication of results obtained in a separate study site should not be carried out before the publication of the overall results of the study.

17. REGULATIONS

The main legal framework under which the clinical study will be conducted:

1. Federal law No. 61-FZ dated April 12, 2010 “On the drug circulation.”
2. National standard of the Russian Federation GOST R 52379-2005 “Good Clinical Practice” (approved by Order of the Federal Agency for Technical Regulation and Metrology No. 232-st dated September 27, 2005).
3. Resolution of the Government of the Russian Federation No. 714 dated September 13, 2010 (as amended on October 15, 2014) “On approval of the standard rules for mandatory life and health insurance for

a patient participating in clinical studies of a medicinal product."

4. Order of the Federal Service for Surveillance in Healthcare No. 1071 dated February 15, 2017 "On approval of the Pharmacovigilance Procedure."
5. Order of the Ministry of Health of the Russian Federation No. 200N dated April 1, 2016 "On approval of the Principles of Good Clinical Practice."
6. Appendix 13 to the Order of the Ministry of Industry and Trade of the Russian Federation No. 916 dated June 14, 2013 (as amended on December 18, 2015) "On approval of the Principles of Good Manufacturing Practice for medicinal products in clinical studies."
7. Order of the Ministry of Health and Social Development of Russia No. 703n dated August 23, 2010 "On approval of the notification form for the completion, suspension, or termination of a clinical study of a medicinal product for human use."
8. Order of the Ministry of Health and Social Development of Russia No. 775n dated August 31, 2010 "On approval of the procedure for consideration of a report on the need to make changes to a protocol of a clinical study of a medicinal product for human use."
9. Order of the Ministry of Health and Social Development of Russia No. 748 dated August 26, 2010 "On approval of the procedure for issuing a permit to conduct a clinical study of a medicinal product for human use" (as amended by the Order of the MoH of Russia No. 111n dated March 13, 2015).
10. D
11. ecision of the Council of the Eurasian Economic Commission No. 79 dated November 03, 2016 "On approval of the Principles of Good Clinical Practice of the Eurasian Economic Union."
12. Decision of the Council of the Eurasian Economic Commission No. 87 dated November 03, 2016 "On approval of the Rules of Good Pharmacovigilance Practice of the Eurasian Economic Union."
13. Federal law No. 323-FZ "On the basics of public health protection in the Russian Federation" dated November 21, 2011

Additionally, the following documents will be used:

14. The World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" of 1964 (in the current version).
15. ICH GCP "Good Clinical Practice".
16. ICH E2A "Clinical safety data management: definitions and standards for expedited reporting".

18. APPENDICES

None.

PATIENT INFORMATION LEAFLET
(outpatients)

Version 1.0 of 08/05/2020 (as amended on 19.05.2020)

Clinical study name:

Multicenter Open-Label Randomized Parallel-Group Study of the Efficacy and Safety of TL-FVP-T Compared to Standard Therapy in Patients with Mild to Moderate Coronavirus Disease (SARS-CoV-2/COVID-19)

Protocol No.: TL-FVP-t-01

Study sponsor: Drug Technology LLC
Registered and postal address: 2a Rabochaia str., bld. 31, room 21, 141400 Khimki, Moscow Region, Russia. Tel.: +7 (495) 225-62-00, Fax: +7 (495) 225-62-65. Email: info@drugsformulation.ru.

Investigator's full name: _____

Subject screening number /__/__/-/__/__/

Subject individual identification code:

RF MoH Permit No:	Permit issuance date DDMMYYYY	Serial number of the medical facility as specified in the Permit	Subject's initials, full name	Subject's date of birth DDMMYYYY	Subject unique sequential number

INFORMATION FOR PATIENTS
(outpatient management)

Dear Patient!
Please read this document carefully. You can ask any questions about your participation in this clinical study to the Study Physician. Save this document until termination of the study.

We are grateful to you for your interest in participating in this clinical study. This document provides information about the study that you are going to participate in, if you give your consent and the Study Physician decides that you can be included in the study. Please, ask the Study Physician or the Study Site staff any questions that you have after reading this document, or if you do not understand something in the information provided. You must not sign the Informed Consent Form under duress or until you have received answers to your questions and have made an independent decision about your participation in the study.

You are invited to participate in clinical study of the Favipiravir TL-FVP-t drug , 200 mg film-coated tablets (Drugs Technology LLC, Russia). This clinical study is conducted to evaluate the safety and efficacy of this drug in its treatment of patients with a new coronavirus infection (SARS-CoV-2/COVID-19) of mild and moderate severity.

The study will be conducted in several clinical centers in the Russian Federation.

Name of the clinical center where you are invited to participate in the study is:

_____

_____

_____

(name of the clinical center, Full name of the Investigator, contact phone number)

Data on the study and the study drug are reviewed and approved by the local Ethics Committee:

_____

_____

_____,

(name of the Ethics Committee, contact phone number)
as well as the Ethics Council under the Ministry of Healthcare of the Russian Federation: Rakhmanovsky pereulok, 127994 Moscow, tel.: 8 (495) 625-44-21.

THE STUDY RATIONALE

In December 2019, a major outbreak caused by a new coronavirus occurred in the city of Wuhan (the capital of Hubei province, China). It was determined that this outbreak was caused by a new virus, the severe acute respiratory syndrome type 2 coronavirus (SARS - CoV-2). Numerous clinical cases of SARS-CoV-2 were reported, which spread to more than half of the world's countries over a period of less than 6 months. The lower respiratory tract is the main target of the SARS-CoV-2 infection. The infection can grade into life-threatening complication stage within about 7-10 days after the disease onset, due to rapid spread of the virus, violent release of biological substances from the cells of the human immune system and inflammatory tissue lesion. According to the statistics, 20% of the infected people have the disease in the form of severe viral pneumonia requiring hospitalization. Respiratory failure requiring treatment in the intensive care unit develops in approximately 5% of patients . The high-risk population groups for severe disease course include people aged over 65 years, as well as people suffering from overweight and concomitant diseases: hypertension, diabetes, and cancer.

The new SARS-CoV-2 coronavirus (name was assigned by the International Committee on Virus Taxonomy on February 11, 2020) is a single-stranded RNA virus belonging to the family Coronaviridae, the Beta-CoV lineage. The virus is classified as risk group II, same as some other representatives of this family (SARS-CoV virus, MERS-CoV).

The SARS-CoV-2-induced infection has now become a threat to public health, to people around the world, due to the high transmission potential and unpredictability of disease progression. In Russia, at the end of April, about 80 thousand cases of COVID-19 were registered.

Early use of powerful antiviral agents can be useful for controlling the COVID-19 severity reducing the risk of complications and decreasing the burden on intensive care units. However, there is no approved standard treatment for COVID-19 today. Therefore, searching for effective therapeutic agents among previously developed drugs and study of their effectiveness for treatment of the new coronavirus infection is an urgent need due to the rapid spread of the disease.

CHARACTERISTICS OF THE STUDY DRUG

Currently, there are no registered drugs that have proven efficacy in the new coronavirus infection treatment.

Favipiravir is a broad-spectrum antiviral drug that blocks RNA replication of Riboviria viruses. The effect of Favipiravir has been studied in the treatment of influenza and Ebola virus infections and has been shown to be effective in these diseases. The ability of Favipiravir to exert direct antiviral effect on the new SARS-CoV-2 coronavirus was demonstrated in the study on cell culture infected with this virus.

The first drug with the favipiravir active ingredient (Avigan) was developed by Japanese Company, Toyama Chemical/Fuji Film in 1998. It was registered in Japan and China in 2014 for use in influenza (in cases of ineffectiveness or insufficient effectiveness of other anti-influenza drugs). In Russia today, there is no registered drug with active ingredient Favipiravir.

The Favipiravir safety and efficacy profile (for influenza) has been well studied. Favipiravir is a relatively low-toxicity drug. It is known to use Favipiravir in doses up to 6000 mg per day with no serious dose-limiting toxic effects. The most common adverse events are effects on the gastrointestinal tract, decreased neutrophils in blood, increased hepatic enzymes levels, as well as increased level of uric acid in blood, which are moderate in nature and are not a reason for treatment termination or dose reduction.

Currently, data on the Favipiravir efficacy in the new COVID-19 coronavirus infection are presented by two preliminary clinical studies, which confirmed the potential of this drug for the COVID-19 treatment, although the studies conducted are not sufficient to assess the efficacy of this drug for this indication.

The Drugs Technology LLC (Sponsor of this study) has developed Favipiravir generic drug, FAVIPIRAVIR-TL (internal code of the drug is TL-FVP-t), which in its dosage form (film-coated tablets) and strength (200 mg) fully corresponds to the original drug Avigan. The developed drug FAVIPIRAVIR-TL (TL-FVP-t), 200 mg film-coated tablets, is planned to be used in this clinical study as a study drug for the COVID-19 coronavirus infection treatment.

As a comparator drug this study, one of the drugs of the so-called "standard" etiotropic (antiviral) therapy recommended according to the Interim Guidelines of the Ministry of Healthcare of the Russian Federation, Prevention, Diagnosis and Treatment of Coronavirus Infection (COVID-19), will be used for the treatment of patients with the new coronavirus infection of mild and moderate severity. These drugs include Umifenovir, Chloroquine, Hydroxychloroquine, Mefloquine, Lopinavir+Ritonavir, Hydroxychloroquine in combination with Azithromycin and interferons. In terms of this study, participants randomly assigned to the comparison group will be prescribed either Umifenovir (also known by invented name as Arbidol) in combination with interferon-alpha (intranasal drops), or Chloroquine and its derivatives

(Chloroquine/Hydroxychloroquine or Mefloquine).

In addition to the study drug or comparator drug, you will also receive concomitant therapy, which will be prescribed at the discretion of the Study Physician and determined according to your actual condition and presence of certain symptoms of the underlying disease. It involves symptomatic therapy, pathogenetic therapy and antibacterial therapy (for complicated forms of infection), recommended according to the current version of the Interim Guidelines of the Ministry of Healthcare of the Russian Federation for Prevention, Diagnosis, and Treatment of Coronavirus Disease (COVID-19), valid at the time of the study, for patients with mild and moderate disease, as well as corresponding to the standards adopted at the study site. Recommended concomitant medications include Paracetamol (as an antipyretic), Ambraxol, syrup (for coughing reduction), Ipratropium Bromide, aerosol (if bronchodilatation is required). The specific list of concomitant medications and the administration schedule will be determined by the Study Physician basing on assessment of your condition. Concomitant medications are not provided by the Sponsor.

CLINICAL STUDY AIMS AND OBJECTIVES

The study is exclusively scientific (experimental) in nature (cl. 4.8.10 in GOST R 52379-2005).

Its aim is to compare the efficacy and safety of the Favipiravir TL-FVP-t drug in comparison with the "standard" etiotropic therapy recommended according to the Interim Guidelines of the Ministry of Healthcare of the Russian Federation, Prevention, Diagnosis and Treatment of Coronavirus Infection (COVID-19), for the treatment of patients with the mild and moderate new coronavirus infection.

STUDY ORGANIZER AND INVOLVED INSTITUTIONS

This study is initiated, sponsored and conducted by the Russian company, Drugs Technology LLC. The study will be carried out in medical institutions that are accredited to conduct clinical studies in accordance with the procedure established by applicable legislation.

VOLUNTARY PARTICIPATION IN THE STUDY, SELECTION OF PARTICIPANTS

Participation in this study is entirely voluntary. You don't need to participate in this study to get treatment for your condition. To participate in the clinical study, you have to sign the Informed Consent Form for participation in the clinical study and meet all of the following criteria:

- You have signed the Informed Consent for participation in the study.
- Your age is within the range of 18 to 60 years.
- You have been diagnosed with the coronavirus infection induced by the SARS - CoV-2 virus (COVID-19) having mild or moderate course.
- Up to 6 days have elapsed since the infection symptoms onset before the intended day of the study treatment.
- Presence of SARS-CoV-2 infection is confirmed by PCR diagnostics (if you already have the result of a previous test, this result is taken into account during the screening).
- You are able, according to the Investigator, to fulfil the Protocol requirements.
- You and your sexual partner are willing to use reliable contraception methods throughout the study and for 3 months after the treatment completion. This requirement does not apply to participants who have undergone surgical sterilization. Reliable contraception methods involve the use of the first barrier method in combination with one of the following: spermicides, intrauterine spiral/oral contraceptives.

- You are willing to refuse from taking alcohol throughout the entire period of the study.

You cannot participate in this clinical study if you meet at least one of the criteria listed below:

- You are younger than 18 or older than 60 years.
- You have been already prescribed any etiotropic treatment for SARS-CoV-2 (COVID-19) coronavirus disease before being included in the study.
- You have respiratory failure, severe or extremely severe course of the disease induced by SARS-CoV-2 (COVID-19).
- You have increased respiratory rate, reduced blood oxygenization, there is a need for artificial ventilation.
- You have deviated level of consciousness.
- You have signs of severe circulatory disorders.
- You have pronounced changes in lungs.
- You have at least one of the following comorbidities:
    a) Chronic obstructive pulmonary disease or moderate to severe asthma.
    b) Chronic cardiovascular diseases.
    c) You are mmunocompromised (HIV, cancer, autoimmune diseases, immunosuppressive therapy).
    d) Severe obesity (body mass index [BMI] 40 or higher).
    e) Diabetes.
    f) Chronic renal failure.
    g) Moderate to severe chronic liver diseases.
- You have signs of liver dysfunction or decreased platelets count in blood.
- You have any other diseases or disorders, which, in the opinion of the Investigator, may lead to difficulties in the study results interpretation or pose an additional risk for the patient's heath due to participation in the study.
- You have had more than 2 CT diagnostic procedures within the last 6 months before the randomization into the study (except for the chest CT-scanning performed no more than 4 days before inclusion in the study).
- You are taking medications that are not recommended for use along with the study therapy, and you cannot stop taking these medications for the study duration.
- You are suffering from a significant gastrointestinal condition that may affect the absorption of the study drug.
- You are pregnant or breast-feeding, or plan pregnancy in the study period.
- You are or have been previously addicted to drugs, substances or alcohol.
- You are or have previously been mentally disturbed.

In this regard, the physician will conduct a thorough examination of your health before the study start. The Study Physician may not approve your participation if he/she considers the examination results to be unacceptable for receiving the study treatment.

You may refuse from participation in the study or terminated it at any time, which will not affect the quality of medical care provided to you, either currently or in the future. On terminating participation in the study, the physician will continue to follow-up

Your condition as part of normal medical practice in accordance with the program of state guarantees of free medical care to citizens (Federal law of the Russian Federation No. 323-FZ of November 21, 2011).

During the study, you will be informed in a timely manner of any new data that may affect your safety and your desire to continue participating in this study.

If you decide to withdraw from the study early for any reason, you should immediately notify the Study Physician on your decision.

You can't participate in several studies at the same time.

You will be asked to sign and date the official Informed Consent Form after you have read it and received answers to your questions.

DESCRIPTION OF THE STUDY, TREATMENT AND DIAGNOSTIC PROCEDURES

If you participate in this study, you consent to medical examinations, sampling of biological materials for tests and conduction of the scheduled instrumental and laboratory investigation methods. During the study, you will take the study drug or comparator drug as instructed by the Study Physician.

In this study, it is planned to obtain data from at least 168 male and female patients with mild to moderate course of the new COVID-19 coronavirus infection.

Participants in this clinical study will be randomly assigned in a 2:1 ratio (i.e. about 112 and 56 people) to one of the two groups:

- **The study drug TL-FVP-t (FAVIPIRAVIR-TL) group.**
  Patients in this group will receive oral therapy with TL-FVP-t for 10 days. On the first day of therapy, patients will receive a loading dose of TL-FVP-t, i. e. 1800 mg at 12 hour intervals (i.e. twice a day), further, on days 2 through 10, patients will receive 800 mg at 12 hours intervals (i.e. twice daily).
- **Comparison group:**
  Patients in this group will receive the recommended "standard" etiotropic (antiviral) therapy recommended in accordance with the Interim Guidelines of the Ministry of Healthcare of the Russian Federation, Prevention, Diagnosis and Treatment of Coronavirus Infection (COVID-19), for treatment of patients with mild to moderate new coronavirus infection. In terms of this study, participants in the comparison group will be prescribed either Umifenovir (also known by the invented name Arbidol) in combination with interferon-alpha (intranasal drops), or Chloroquine and its derivatives (Chloroquine/Hydroxychloroquine or Mefloquine) using the recommended standard regimen and strengths.

In addition to the study drug or comparator drug, as noted above, you will also receive concomitant treatment prescribed upon the Study Physician's decision based on the assessment of your condition.

Please note that **before the study start**, **no one** (neither you, your physician or the clinical center staff) **can know** which group you will be assigned to, whether you will be prescribed the study drug (TL-FVP-t) or the recommended

“standard” etiotropic therapy.

This clinical study involves series of Visits; it will be performed according to the following design and include the following procedures:

Screening — preliminary examination of patients

The screening period shall be carried out no longer than 2 days before inclusion in the study.

- During the screening, the Study Physician will assess your compliance with the inclusion/non-inclusion criteria, take your medical history (basing on an interview), and determine your height and weight indicators.
- For female patients, you will receive 2 pregnancy tests along with the Informed Consent Form. One you will be required to perform immediately, the Study Physician will ask you about the results during the screening interview; you will also need to provide the Study Physician with a photo confirmation of the test result. You will receive the second test together with the drug and perform it at the end of the treatment period on Day 14 (for more

information, see the description of the procedures at Day 14 Visit).

- You will undergo ECG tracing and thoracic computed tomography (CT), moreover, body temperature, blood pressure, pulse rate, respiratory rate and blood oxygen saturation (SpO2) will be measured. At the time appointed by the Study Physician, a car that performs specialized transportation will arrive for you. You will be taken to the Medical Center for investigation procedures.
- Your blood will be taken from vein for clinical, biochemical blood tests and for coagulation analysis. You will need to give an urine sample for common urine analysis.
- The Study Physician will ask you questions about prior and concomitant therapy.
- The Study Physician will ask you the questions required to assess your health status and whether you can participate in the study.
- The Study Physician will make decision on the possibility to transfer you to the next stage of the study basing on the evaluation of the tests results and examinations you have already undergone. If the Study Physician reveals that you do not meet the inclusion criteria, your participation in the study will be terminated. If you meet all the selection criteria, the Study Physician will appoint you a Day 1 Visit date.
- You will be informed on the need to comply with the rules of participation in this study and the schedule of procedures and examinations during receiving the study therapy.

The total volume of blood taken during the visit will be 15 mL.

Periods of Treatment and Follow-Up

The schedule of procedures you will need to undergo as part of the study during the periods of treatment and follow-up do not depend on whether you will be treated at home or in a hospital, as well as on the therapy group.

Duration of treatment with the study drug is 10 days, duration of treatment with comparator drug will be determined by the Study Physician, depending on the drug prescribed and your health state, but also will not exceed 10 days. In addition to the study/comparator drug, the Study Physician may prescribe concomitant medications basing on how you feel. The duration of concomitant therapy may exceed 10 days.

During the first 14 days of the study, you shall fill in the Patient's Diary every day and then on days 21 and 28, adding information on:

- taking the study/comparator drug (within the first 10 days of the study);
- results of blood pressure, heart rate, body temperature, pulse oximetry (SpO_2) measurements (the body temperature and SpO_2 shall be measured and the results shall be recorded in the **Diary daily 3 times a day until Day 10, then once a day**);
- complaints occurred during the day;
- names, strengths and quantity of concomitant medications prescribed by the Study Physician, or taken at your sole discretion.

If you are receiving treatment at home, during the entire period of therapy (Days 1 through 10), the Study Physician will contact you daily to collect information about your general state, monitor your condition and monitor the Visits procedures that you will perform yourself (measurements of blood pressure, pulse rate, temperature, pulse oximetry (SpO_2), sampling of oropharyngeal and nasopharyngeal smears for PCR diagnostics of SARS-CoV-2 infection).

The equipment necessary for the procedures (blood pressure monitor, thermometer and pulse oximeter) will be provided by the Sponsor for the period of the study, along with the comparator drug and the Patient's Diary. Blood sampling for monitoring of clinical and biomedical blood parameters, ECG tracing and thoracic CT scanning will be conducted at the outpatient health care facility (HCF), your transfer to the HCF will be organized by the study Sponsor (when travelling you must use the personal protective means provided by the Sponsor such as medical

face mask and gloves; before travelling you will need to carry out standard procedures on your electronic device to leave the place of quarantine, if required, for Moscow, such as obtaining an electronic code, specify visiting a medical facility as purpose for obtaining the code).

In patients undergoing treatment at home, the Study procedures will be carried out as follows:

Day 1 Visit

- In the morning, you will receive a Study Participant Kit, which includes:
  1) packages with the study/comparator drug,
  2) thermometer (1 pc.),
  3) electronic BP monitor (1 pc.),
  4) portable pulse oximeter (1 pc.),
  5) kit for taking biological samples (7 pcs.),
  6) container for urine collecting (2 pcs.),
  7) Patient's Diary (1 pc.),
  8) Personal protective equipment (PPE) kit for transfer to medical facility,
  9) pregnancy test and
  10) Study Participant Technical Guidelines.
- Study Physician will contact you, ask you questions about your general state, complaints, and calculate the respiratory rate (RR).
- You will take the First study/comparator drug dose under the Study Physician supervision.
- You will measure your vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO_2) by yourself under the Study Physician supervision
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 times per day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

Day 2, Day 4, Day 6, Day 8 and Day 9 Visits

- You will take morning dose of the study/comparator drug.
- Study Physician will contact you, ask you questions about your general state, complaints, and calculate the respiratory rate (RR).
- You will measure vital signs (blood pressure, HR and body temperature), pulse oximetry (SpO_2) under the Study Physician supervision.
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the

Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.

- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

Day 3, Day 7, and Day 10 Visits

- You will take morning dose of the study/comparator drug.
- Study Physician will contact you, ask you questions about your general state, complaints, and calculate the respiratory rate (RR).
- You will measure vital signs (blood pressure, HR and body temperature), pulse oximetry (SpO_2) under the Study Physician supervision.
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- You will take oropharyngeal and nasopharyngeal smears by yourself using the Biosample Collection Kit provided by the Sponsor under the Study Physician supervision. You will pack the obtained samples in accordance with the Guidelines and prepare them for shipment by a delivery service*.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

***** Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

Day 5 Visit

- You will take morning dose of the study/comparator drug.
- You will need to collect the urine sample in the Urine Collection Container and pack it according to the Guidelines. You should take the packed container with you to the Medical Center.
- The Study Physician will inform you in advance on the appointed time of your visit to the Medical Center. You should refrain from eating or drinking anything other than clean water for 4 hours before the specified time.
- At the time appointed by the Study Physician, a car that performs specialized transportation will arrive for you. You will be taken to the Medical Center for investigation procedures.
- At the Medical Center, you will undergo blood sampling for laboratory tests, taking oropharyngeal and nasopharengeal smears for PCR investigation, ECG tracing, and thoracic CT scanning. On completion of all procedures, you will be taken home.
- Study Physician will contact you, ask you questions about your general state, complaints, and calculate the respiratory rate (RR).

- You will measure vital signs (blood pressure, HR and body temperature), pulse oximetry (SpO_2) under the Study Physician supervision.
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Patient's Diary filling-in.
- If the nasopharengeal and oropharyngeal smears are not taken at the Medical center, you will take your oropharyngeal and nasopharyngeal smears by yourself using the Biosamples Collection Kit provided by the Sponsor under the supervision of the Study Physician. You will pack the obtained samples in accordance with the Guidelines and prepare them for shipment by a delivery service.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

The total volume of blood taken during the visit will be 15 mL.

Day 14 Visit

- You will need to collect the urine sample in the Urine Collection Container and pack it according to the Guidelines. You should take the packed container with you to the Medical Center.
- The Study Physician will inform you in advance on the appointed time of your visit to the Medical Center. You should refrain from eating or drinking anything other than clean water for 4 hours before the specified time.
- At the time appointed by the Study Physician, a car that performs specialized transportation will arrive for you. You will be taken to the Medical Center for investigation procedures.
- At the Medical Center, you will undergo blood sampling for laboratory tests, ECG-tracing and thoracic CT-scanning. On completion of all procedures, you will be taken home.
- For female patients – you will have to perform a pregnancy test using the second Pregnancy-Test provided to you with the drug. The Study Physician will ask you about the test results during the interviewing, and you shall provide the result photo confirmation to the Physician.
- Study Physician will contact you, ask you questions about your general state, complaints, and calculate the respiratory rate (RR).
- You will measure vital signs (blood pressure, HR and body temperature), pulse oximetry (SpO_2) under the Study Physician supervision.
- You will enter information on the obtained by you values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.

- You will take oropharyngeal and nasopharyngeal smears by yourself using the Biosample Collection Kit provided by the Sponsor under the Study Physician supervision. You will pack the obtained samples in accordance with the Guidelines and prepare them for shipment by a delivery service*.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

The total volume of blood taken during the visit will be 15 mL.

***** Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

Day 21 Visit

- Study Physician will contact you, ask you questions about your general state, complaints, and calculate the respiratory rate (RR).
- You will measure vital signs (blood pressure, HR and body temperature), pulse oximetry (SpO_2) under the Study Physician supervision.
- You will enter information on the obtained by you values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- You will take oropharyngeal and nasopharyngeal smears by yourself using the Biosample Collection Kit provided by the Sponsor under the Study Physician supervision. You will pack the obtained samples in accordance with the Guidelines and prepare them for shipment by a delivery service*.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

***** Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

Day 28 Visit

- You will need to collect the urine sample in the Urine Collection Container and pack it according to the Guidelines. You should take the packed container with you to the Medical Center.
- The Study Physician will inform you in advance on the appointed time of your visit to the Medical Center. You should refrain from eating or drinking anything other than clean water for 4 hours before the specified time.
- At the time appointed by the Study Physician, a vehicle performing specialized transportation (or a taxi, depending on epidemiological indications) will arrive for you. You will be taken to the Medical Center for investigation procedures.
- At the Medical Center, you will undergo blood sampling for laboratory tests, ECG-tracing and thoracic CT-scanning. On completion of all procedures, you will be taken home.
- Study Physician will contact you, ask you questions about your general state, complaints, and calculate the respiratory rate (RR).
- You will measure vital signs (blood pressure, HR and body temperature), pulse oximetry (SpO_2) under the Study Physician supervision.

- You will enter information about the received values in the Patient's Diary.
- You will take oropharyngeal and nasopharyngeal smears by yourself using the Biosample Collection Kit provided by the Sponsor under the Study Physician supervision. You will pack the obtained samples in accordance with the Guidelines and prepare them for shipment by a delivery service*.
- The Study Physician will check whether the Diary is filled in correctly.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

The total volume of blood taken during the visit will be 15 mL.

***** Biomaterials sampling for clinical tests can also be carried out in the medical center, or when specialized brigades from central laboratories (CL) do home visits.

In total, not more than 290 mL of blood will be taken during the study. Such extent of blood loss over a period of 28 days does not pose any danger to your health.

Therapy completion visit (including early drop-out)

You can voluntarily terminate the study therapy at any time (withdraw consent), or terminate it early, or drop-out from the study early for various reasons. In this case, a Therapy Completion Visit will be performed.

- The Study Physician will contact you and ask you questions about your general state and concomitant therapy, your blood pressure, pulse rate, respiratory rate and body temperature, and pulse oximetry (SpO_2).
- You will take oropharengeal and nasopharengeal smears using the Biosample Collection Kit provided by the Sponsor. You will pack the obtained samples in accordance with the Guidelines and prepare them for shipment by a delivery service (at home).
- The Study Physician will ask you questions about your general state and concomitant therapy

SPECIAL INSTRUCTIONS FOR THE STUDY PARTICIPANTS

Please inform the Study Physician about any changes in your general state. Inform the Study Physician in a timely manner if for any reason you are not able to arrive at the study site/medical facility or continue participation in the study. In case of any adverse event occurs, the Study Physician may prescribe additional investigations, additional drugs, send you to hospital or ask you to come to the study site or medical center for additional examination. Contact your Study Physician immediately, if you experience any changes in your general state or other signs of a health disorder, at any time during the study or after it is completed.

In the event of your early drop-out, after taking at least one dose of the study drug, you will undergo procedures of the Early Termination Visit on the day of your drop-out from the study.

If you receive the study therapy, and in case of hospitalization due to aggravation of the SARS-CoV-2 infection, you must inform medical officers the inpatient department you will be admitted to that you are a participant in the Clinical Study and present your Participant Card. You will be excluded from the study, if your clinician in the inpatient department cancels the study therapy or prescribes medications prohibited by the Clinical Study Protocol. If the inpatient department clinician confirms continuation of the previously assigned course of the study therapy, you will need to contact the Study Physician and undergo the procedures of planned visits to

monitor your condition (if it is technically possible).

RESPONSIBILITIES OF THE STUDY PARTICIPANT

Your responsibilities will include strict compliance with the rules and procedures prescribed by the Study Physician and provided for in the Study Protocol. You undertake to report any changes in your health status, regardless of whether it is related to taking the drug or not. You also need to notify the Study Physician of all drugs you took during the study.

As part of this study, you have responsibility take the study/comparison therapy drugs timely and without skipping and to follow all the recommendations of the Study Physician concerning the basic and combination therapy and lifestyle.

You should be aware that you will be prematurely excluded from the study if you miss 2 or more doses of the drug, or 2 or more visits in the study, or do not follow Protocol procedures in full at 2 or more visits.

Before being included in the study, tell the Study Physician about your living conditions, past illnesses, operations, injuries, chronic pathology, allergic reactions, heredity, and medications that you are taking (if applicable).

You should adhere to reliable methods of contraception, which are described below. If you/your partner becomes pregnant, you should immediately inform your Study Physician.

The prohibited or not stipulated by the Protocol drugs include drugs of the following pharmacological classes: Pyrazinamide, Repaglinide, Famciclovir, Sulindac, CYP-2C8 substrate drugs; it is required to consider canceling the study therapy and excluding the patient from the study.

The Study Physician will carefully monitor your condition. If you have any additional health problems (feeling unwell, any new unexpected and unusual symptoms), you should contact your Study Physician urgently. In case of allergic reactions, you will be prescribed the necessary allergy medications. If you experience unexpected adverse events, your physician may decide to exclude you from further participation in the study, which will not affect the quality of medical care provided to you.

Contraception

Please note that by accepting the terms of participation in this study, you consent to use highly effective methods of contraception

Female participants should use contraception throughout the study or at least 2 weeks after the last administration of the study/comparator drug.

A highly effective method of contraception **for women** can be represented by one of the following options:

- Total sex abstinence: if it corresponds to the patient's preferred and habitual lifestyle. [Periodic sex abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods) and interrupted sexual intercourse are not considered acceptable methods of contraception].
- Sterilization: performing surgical bilateral ovarian removal (with or without removal of the uterus) or tubal ligation at least 6 weeks before the start of the study therapy.
- Sterilization of male partner (if there is a single sexual partner).
- Using a combination of any two of the methods listed below (a+b or a+c or b+c):
    a) Use of oral, injectable, or implanted hormonal contraceptives.
    b) Installing an intrauterine device or contraceptive system.
    c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical cap/vaginal fornix cap) with spermicidal foam/gel/film/cream/vaginal suppository.

When using oral contraceptives, women should constantly use the same drug for at least 3

months before starting the study therapy.

In case of assignment to the study drug TL-FVP-t group, male patients should use reliable methods of contraception for at least 3 months after the last administration of the study drug. For the comparison group — at least 2 weeks after last administration of the comparator drug.

Sexually active **men** should use condoms as a method of contraception in combination with one of the following: spermicides, intrauterine device/oral contraceptives in the sexual partner throughout the study, conception during this period is also not allowed. Men after vasectomy (a method of medical sterilization) should also use condoms to prevent the drug transfer with the seminal fluid.

Other Lifestyle Restrictions

Alcohol is not allowed during the entire study.

Due to the fact that against the background of taking Favipiravir or Hydroxychloroquine, photosensitivity reactions may develop (skin redness, rash, peeling, etc. inflammatory reactions with short exposure to sunlight), if you are assigned to the study drug group, we recommend you to avoid intense and prolonged exposure to sunlight, exposure to the sun with your head uncovered and visiting tanning salon while participating in the study.

Lifestyle Recommendations for the Study Period.

During treatment of the SARS-CoV-2 infection, we recommend you to:

- Follow the drinking regime (at least 1 liter of clean water daily, up to 1 liter of tea, liquid food, vegetables and fruits without restrictions).
- Limit the consumption of fatty and fried foods.
- Avoid excessive physical activity.

POSSIBLE RISKS ASSOCIATED WITH PARTICIPATION IN THE STUDY

Due to the experimental nature of any clinical study, the exact result is not known.

Group of Patients Receiving the Study Drug, TL-FVP-t (FAVIPIRAVIR-TL)

The risk of using the Favipiravir drug (TL-FVP-t) is associated primarily with reactions registered in clinical studies of the original drug of favipiravir. In this study, Favipiravir will be used in the form of 200 mg film-coated tablets at loading dose of 1800 mg twice a day on the first day, further, 800 mg twice daily for the next 10 days. The safety profile is expected to match that of the original Favipiravir drug in clinical studies.

Risk of using Favipiravir drug (TL-FVP-t) is associated primarily with the reactions listed in the Table below (information is collected basing on clinical studies of the Favipiravir).

Blood and lymphatic system disorders: decrease in the neutrophil count, lymphocyte ("white" blood cells) count; increase in lymphocyte, monocyte ("white" blood cells) count; decrease in the reticulocyte (precursors of "red" blood cells) count;

Immune system disorders: rash, eczema, itching;

Metabolism and nutrition disorders: increased concentration of uric acid in blood, increased concentration of triglycerides (fats) in blood, presence of glucose in urine, decrease in the potassium concentration in blood;

Nervous system disorders: dizziness;

Ocular disorders: blurred vision, pain in eyes;

Respiratory, thoracic and mediastinal disorders: asthma, pharyngalgia (raw throat), rhinitis (runny nose), nasopharyngitis (nasopharyngeal inflammation);

Gastrointestinal disorders: diarrhea, nausea, vomiting, abdominal pain; abdominal discomfort, duodenal ulcer, hematochezia (fecal blood), gastritis.

hepatobiliary disorder: increased activity of hepatic enzymes (AST, ALT, γ-GTP, alkaline phosphatase), increased bilirubin concentration in blood.

Miscellaneous: increased activity of creatine kinase (muscular tissue enzyme), presence of blood in urine, pigmentation (staining) of urine.

The most common side effects when using Favipiravir in patients in studies were diarrhea, signs of hepatic impairment, including increased activity of hepatic enzymes, decreased neutrophil count, as well as increased uric acid levels in blood. All adverse drug events were moderate and did not lead to premature discontinuation of the drug administration, and quickly stopped after the end of the therapy.

Group of Patients Receiving Comparator Drug

Risks associated with Umifenovir (Arbidol) and Interferon Alpha (nasal drops):

Immune system disorders: *allergic reactions*

Risks associated with Chloroquine/Hydroxychloroquine/Mefloquine:

Blood and lymphatic system disorders: bone marrow function depression, poor blood (anemia, Ehrlich anemia), decrease in the white blood cell count (agranulemia, leukopenia, thrombocytopenia).

Immune system disorders: antitoxin rash, subcutaneous tissue oedema (angioneurotic oedema), broncoconstriction (bronchial spasm).

Metabolism and nutrition disorders: complete absence of appetite (anorexia), decreased blood sugar (hypoglycaemia), relapse of pigment exchange disorders is possible (porphyria).

Mental disorders: emotional instability, nervousness, psychosis, suicidal behavior.

Nervous system disorders: headache, dizziness, convulsions, movement abnormalities.

Ocular disorders: blurred vision, retinal disorders with compromised visual field. These events in incipient forms are usually reversible after the Hydroxychloroquine disengagement.

If the condition remains undiagnosed, and retinal lesions continue to develop further, there may be a risk of their progression even after the drug disengagement. Retinal changes may initially be asymptomatic or manifest as loss of visual fields and color vision disorders. Corneal changes may occur, including oedema and opacity. They can be asymptomatic or cause visual disorders such as the appearance of halos (luminous contour around objects), blurred vision or photophobia. These changes may be transient or reversible after discontinuation of the treatment; central retinal lesions (maculopathy, macular degeneration) that may be irreversible.

Ear and labyrinth disorders: dizziness, tinnitus, hearing loss.

Cardiac disorders: intracardiac conduction disorders in patients with risk factors that may lead to arrhythmias, heart muscle damage (cardiomyopathy) that may result in heart failure and, in some cases, death; cardiac conduction disorders (e. g. His bundle blockade/atrioventricular conduction disorders) and enlargement (hypertrophy) of both ventricles may indicate chronic cardiac toxicity. At drug disengagement, the regression of these changes is possible.

Gastrointestinal disorders: abdominal pain, nausea, diarrhea, vomiting. These symptoms usually disappear immediately after reducing the dose or disengagement of the drug.

Hepatobiliary disorder: liver function test aberrations, fulminant (peracute) hepatic failure.

Skin and subcutaneous tissue disorders: skin rash, itching, skin and mucous membranes discoloration, hair discoloration and hair loss. These changes usually resolve quickly after the treatment discontinuation; blistering rash, including severe forms; skin irritation due to light exposure; exfoliative dermatitis; other severe skin reactions. After the drug disengagement, the outcome is usually favorable.

Musculoskeletal and connective tissue disorders: impairment of skeletal muscles or nerves and muscles (may be reversible after drug intake discontinuation, but it may take several months for complete recovery), tendon reflexes depression and decreased nerve conduction.

Risks associated with use of concomitant medications (occur only if you are prescribed these medications).

Risks Associated with Paracetamol

Blood and lymphatic system disorders, often: postoperative hemorrhages, poor blood (anemia), decrease in blood count (red and/or white blood cells and/or platelets), changes in haemoglobin.

Immune system disorders: allergic reactions (including skin rash, itching, antitoxin rash, subcutaneous tissue oedema (angioneurotic oedema); severe skin reactions, severe allergic reactions.

Mental disorders: insomnia, anxiety.

Nervous system disorders: headache, asthenia, dizziness, motor and emotional excitement, disorientation (at high doses).

Ocular disorders: *adorbital oedema.*

Cardiac disorders: palpitations, chest pain.

Vascular disorders: peripheral oedema, increased or decreased blood pressure.

Respiratory, thoracic and mediastinal disorders: respiratory disorders, abnormal breathing, pulmonary oedema, oxygen deprivation, fluid in pulmonary coat, rale, breathlessness, cough; bronchospasm (in patients with hypersensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs).

Gastrointestinal disorders, often: diarrhea, constipation, digestive disorders, bloating, abdominal pain, nausea, vomiting, dry mouth. *Hepatobiliary disorder:* increased activity of hepatic enzymes; hepatic failure, hepatitises, hepatic necrosis (necrocytosis).

Skin and subcutaneous tissue disorders: *rash.*

Musculoskeletal and connective tissue disorders: muscle spasms, trism.

Renal and urinary disorders: decreased renal urinary output; renal colic, bacteria in urine, kidney tissue lesion.

General disorders and administration site conditions, often: temperature rise, fatigue feeling; feeling generally unwell/faintness.

Effect on the results of laboratory and instrumental tests: decrease in potassium concentration in blood, increase in glucose concentration in blood; blood clotting abnormalities, increased creatinine (mainly in severe hepatopathies and secondary renal impairment).

Risks Associated with Ambroxol (Syrup)

Gastrointestinal disorders: nausea, decreased sensitivity in the oral cavity or pharynx, digestive disorders, vomiting, diarrhea, abdominal pain, dry mouth, pharyngoxerosis.

Immune system disorders, skin and subcutaneous tissue lesions: rash, antitoxin rash, acute drug hypersensitivity drug, subcutaneous tissue oedema (angioneurotic oedema), itching, hypersensitivity.

Nervous system disorders: dysgeusia (taste perversion).

Risks associated with Ipratropium Bromide (dosage form: aerosol)

The most common side effects reported in clinical studies were headache, throat choke, cough, dry mouth, gastrointestinal dysmotility (including constipation, diarrhea, and vomiting), nausea, and dizziness. The following reactions are also possible.

Immune system disorders: acute drug hypersensitivity reactions, hypersensitivity.

Nervous system disorders: headache, dizziness.

Ocular disorders: blurred vision, pupil dilation, increased intraocular pressure, glaucoma, ophthalmalgia, appearance of luminous contour (halo) around objects, conjunctival redness, corneal edema, violations of the ability to see objects at different distances.

Cardiovascular system disorders: heart consciousness, palpitations, heart rhythm disorders (auricular fibrillation), increased heart rate.

Respiratory, thoracic and mediastinal disorders: throat choke, cough, broncoconstriction (bronchospasm, paradoxical bronchospasm), laryngospasm, pharyngeal oedema, pharyngoxerosis.

Gastrointestinal disorders: dry mouth, nausea, gastrointestinal contractive activity

disorder, diarrhea, constipation, vomiting, stomatitis, oral cavity edema.

Skin and subcutaneous tissue disorders: rash, itching, subcutaneous tissue oedema, antitoxin rash.

Renal and urinary disorders: urine retention.

Risks Associated with the Study Procedures

Medical procedures aimed at diagnosing your health status, which are performed according to the standard methods and do not pose any danger to you, but in some cases may be associated with a feeling of some inconvenience or internal discomfort. However, all these procedures are necessary to obtain important information about your health status, and they will be performed by the properly qualified medical professional staff and all actions of physicians and nurses will be performed for the benefit of your safety.

Taking naso-and oropharyngeal smears is a procedure that causes unpleasant, but transient sensations. When taking smears from the oropharynx, vomiting may occur, due to the probe touching the tonsils at the back of the pharynx. When taking smears from the nasopharynx, the probe is lead deep along the lower nasal passage, which can be accompanied by irritation of the nasal mucosa, pinpoint bleeding and also the appearance of a gag reflex.

Electrocardiogram (ECG) tracing is a test that provides valuable information about your heart condition. In order to conduct an electrocardiographic examination, the Study Physician will apply electrodes your chest, as well as on your upper and lower limbs and record the cardiac electrical activity with special equipment. This procedure is absolutely painless, does not involve piercing the body, does not require special training, performed in supine position, in relaxed state. There are no contraindications to this procedure.

Computed tomography (CT) is a safe and painless procedure that allows you to get a detailed image of internal organs and structures, including the lungs. Thoracic CT is included in the standard diagnosis of pneumonia in new coronavirus infection. If you follow the appropriate safety rules, CT does not pose any danger to you.

Blood sampling from the ulnar vein through venipuncture (needle piercing) may cause discomfort, bleeding, or haematoma at the site of needle piercing. Fainting or local infection is rare. The Study Physician will take care of to prevent such events.

Blood sampling from the ulnar vein through venipuncture (needle piercing) and insertion of cubital catheter (thin tube inserted into an ulnar vein and intended for repeated blood sampling) may cause discomfort, bleeding or haematoma (bruising) at the skin needle puncture site. Fainting or local infection is rare. The Study Physician will take care of to prevent such events.

Measurement of blood pressure and heart rate can cause unpleasant, but transient sensations of compression in the forearm area from the tonometer cuff (blood pressure measuring instrument). The staff performing this procedure is aware of the possibility of these feelings and will act in your advantage.

Pulse oximetry may cause unpleasant, but transient sensations of compression in the area of the finger on which the pulse oximeter sensors are placed.

Routine Clinical Examinations. If you participate in this study, you will need to undergo clinical examinations at each study visit. Examinations will be performed using telemedicine technologies if you are undergoing treatment at home, or if you are in the Study Site inpatient department, by visiting the Study Physician in person.

The Study Physician will carefully monitor your condition. If you have any additional health issues (feeling unwell, any new unexpected and unusual symptoms), you should

contact your Study Physician immediately. In case of allergic reactions, you will be prescribed the necessary allergy medications. If you experience unexpected adverse events, the physician may decide to exclude you from further participation in the study, which will not affect the quality of medical care provided to you.

If you have questions about the above, ask the Study Physician to explain them.

BENEFITS OF PARTICIPATING IN THE STUDY

If you decide to participate in this study taking the TL-FVP-t drug or "standard" therapy, you will receive the drugs for the new COVID-19 coronavirus infection treatment at no charge, the probability of assignment to the study Favipiravir drug group will be 2:1.

While participating in the study, you will be provided with thorough medical supervision, including free PCR diagnostics of SARS-CoV-2 infection, CT, ECG tracing, blood and urine tests, as well as daily observation by the Study Physician, which will additionally allow you to assess the state of your body.

The study Favipiravir drug has shown encouraging results in studies of the impact on the SARS-CoV-2 virus in cell culture and in pilot clinical studies in patients with COVID-19, but there is no reliable data on its efficacy and safety when used for this indication. It should be noted that at the moment, there is no such information about any of the drugs used for the treatment of the SARS-CoV-2 infection. Thus, it is assumed that the new data obtained in this study on the efficacy and safety of the Favipiravir TL-FVP-t, 200 mg film-coated tablets, will benefit you and many other patients with the new COVID-19 coronavirus infection.

ALTERNATIVE THERAPY OPTIONS

Currently, there are several drugs that, according to the Interim Guidelines of the Ministry of Healthcare of the Russian Federation for the Prevention, Diagnosis and Treatment of coronavirus infection (COVID-19), can be used to treat patients with the new coronavirus infection. They include Umifenovir, Chloroquine, Hydroxychloroquine, Mefloquine, Lopinavir+Ritonavir, Hydroxyloroquine in combination with Azithromycin, Interferons.

However, the available today information on the results of therapy with these drugs does not allow us to make a clear conclusion about their efficacy or inefficacy, so their use is permissible by the decision of the medical commission in the appropriate manner if the potential benefit to the patient outweighs the risk of their use.

INFORMATION ABOUT LIFE AND HEALTH INSURANCE OF THE STUDY PARTICIPANTS

Mandatory Life and Health Insurance

You will not receive payment for participating in this clinical study. You will not have any additional costs associated with participating in this study.

For the duration of the study, you will be insured as a study participant in accordance with the legislation of the Russian Federation.

The Study Physician must provide a Compulsory Life and Health Insurance Policy of Drug Clinical Study Participant to you. If you need to make changes to the Compulsory Insurance Policy, you should return the previously issued Compulsory Insurance Policy, which will be substituted with a new one no later than 2 business days.

The insurance policy covers the claims of the study participants to the Policyholder solely for compensation for damage to life and health caused to them during participation in the clinical

study due to deficiencies of the study drugs or insufficient information about them, unintentional errors, omissions. Only claims that were first submitted to the Policyholder during the insurance period in respect of events that occurred in the insurance territory after the study start and in connection with the implementation of the insured activity (study) shall be covered.

If your health is damaged as a result of the use of the study drug or medical procedure provided for in the Study Protocol, you will be provided with free qualified medical care in the required amount, paid for by the Insurance company. The Insurance company will make the stipulated payments only if you comply with all the physician's prescriptions.

In the Russian Federation, you will be insured for the study period according to the legislation of the Russian Federation by the Absolut Insurance LLC insurance company. The Study Physician will familiarize you with the terms of the Contract (including the obligations that must be observed by the patients participating in the study). You will be insured under the contract of compulsory life and health insurance of a drug clinical study participant from the moment of signing the patient's Informed Consent Form. The Study Physician shall execute (enter in the Policy form the patient's individual identification code) and give you an Individual Compulsory Life and Health Insurance Policy of Drug Clinical Study Participant. The Compulsory Insurance Policy has a unified form on the territory of the Russian Federation and is a mandatory Appendix to this Information Sheet (in addition, it may be accompanied by the terms of insurance).

If you are undergoing treatment as part of the inpatient, your Individual Compulsory Life and Health Insurance Policy and the Study Participant's Card will be kept by the Study Physician for the entire period while you are staying in the "red zone". This is necessary to ensure the document availability subject to occurrence of an insured event and compliance with the rules of the sanitary and epidemiological regime in the inpatient department.

When an insured event occurs, the Absolute Insurance LLC shall provide payment in accordance with article 44 of the Federal law On Medicine Circulation and the Decree of the Government of the Russian Federation of September 13, 2010 No. 714. The amount of insurance payment under the Contract is:

а) in case of death of the insured person — 2 million rubles. The insurance payment in the specified amount shall be distributed among the beneficiaries in proportion to their number in equal shares;
б) if the insured person's health deteriorates, resulting in:
Group I disability confirmation – 1.5 million rubles.
Group II disability confirmation – 1 million rubles.
Group III disability confirmation – 500 thousand rubles.
в) If the insured person's health deteriorates and does not result in disability – no more than 300 thousand rubles.

The amount of insurance payments may be increased on the basis of a court decision. Additional life and health insurance is not provided in this study.

Restrictions for use of other types of health insurance

Please note that if you have a Voluntary Medical Insurance Policy, the conditions for its implementation may be violated during the period of participation in the study. This circumstance does not prevent you from receiving medical care under the compulsory medical insurance, but it may lead to withdrawal from receiving medical care under the voluntary medical insurance. For more information, if you have a Voluntary Medical Insurance Policy, please contact the insurance company where you are insured under the Voluntary Medical Insurance.

COMPENSATIONS

In case of damage to your health or disease onset as a direct result of prescription of the study drug or medical procedures performed in accordance with the Protocol, you will be provided

with the full necessary examination and treatment of such damage or disease. At the same time, the costs of examination and treatment will be covered by the Absolute Insurance Company LLC. This will happen provided that you have followed all the instructions of the Study Physician, and that the damage is not committed intentionally. After the expert examination, the Absolute Insurance Company LLC will make monetary payments in the amount corresponding to the degree of damage caused in accordance with the Insurance Contract for the clinical study you are invited to participate. If your health deteriorates as a result of participating in the study, you should first contact your physician monitoring you by phone; his/her phone number is indicated in this document.

Treatment costs will not be reimbursed if the damage to health or disease is caused by violation of the Study Physician's instructions regarding the study conduct, including those listed in this Information Sheet.

EXPENSES

The Sponsor Company of this study reimburses expenses associated with the study, i.e. consultations by the Study Physician, instrumental investigations and laboratory tests and other examination types provided for in the Protocol, as well as your transfer to the medical center for the procedures. The study drug, TL-FVP-t (FAVIPIRAVIR-TL), and the comparator drugs such as Umifenovir (Arbidol), Interferon Alpha (nasal drops) and Hydroxychloroquine/Chloroquine/Mefloquine in the amount necessary for conducting the study will be provided free of charge by the Sponsor. Concomitant medications are not provided by the Sponsor. The study does not provide compensation for other personal expenses. In addition, the Sponsor does not reimburse the costs of additional medications and examinations prescribed to you during treatment that are not provided for in the Study Protocol.

SUPPLEMENTARY PAYMENTS

No monetary rewards for patients taking part in the study are provided for.

TERMINATION OF THE STUDY FOR MEDICAL REASONS

The Study Physician may exclude you from the study at any time, regardless of your consent (if there are serious side effects, if you do not follow the instructions of the Study Physician), if he/she believes that it is for your benefit to do so. Before doing this, he/she will explain you the reason and, if necessary, arrange further treatment.

GUARANTEES TO THE STUDY PARTICIPANT RIGHTS PROTECTION

This study is conducted in accordance with the legislation, state standards of the Russian Federation and international guidelines for study of medicinal products in humans. The study was fully reviewed by the relevant supervisory authorities, including assessment of its feasibility, risk/benefit ratio, and ethical assessment, and its conduct was approved by authorized representatives of the Russian Federation.

QUESTIONS AND COMPLAINTS

You will be promptly informed of new information that may affect your wish to continue participating in the study. If you have any questions or claims related to the conduct of this study, as well as for more information about the study and your rights, you can contact your Study

Physician or Chief Investigator.

PRIVACY

In order to ensure medical confidentiality and your personal data privacy, your medical data in the study will be marked with an individual code, without specifying personal identification data, such as your name or initials. The code linking your personal data to the records will be stored by your physician in a secure and confidential location at the study site. Only your physician can reveal this code. When publishing the results of the study your personal information will not be disclosed. If the study materials are delivered to your home, the address will be sent to the courier by your physician. The study Sponsor does not receive this information. The information gathered about you during this study may be reviewed by authorized persons for the study purposes and/or in connection with regulatory matters. The persons authorized to access to your medical data include representatives of the Sponsor, Drugs Technology LLC, conducting this study, members of the Ethics Council, Local Ethics Committee of the institution, as well as, if necessary, other representatives of regulatory authorities. These individuals are required to maintain the confidentiality of the information they receive to the same extent as your Study Physician.

By signing the Informed Consent Form, you consent to collection, use and processing of your personal data obtained in the course of the study. At the end of the study, your data will be stored safely in the archival repository and, if necessary, their confidential destruction will be arranged. You have the right to access and correct your personal data during the course of the study before the data related to this study is archived, under the terms of confidentiality. If you need to make corrections to your personal data, you should contact your Study Physician, who has access to such data. On completion of the study and transferring the data to the database, all the transmitted data will be encoded, without the ability to identify you. The electronic database will be stored for at least 5 years from the date of writing the final study report or publishing the study results. If you have another attending physician, your Study Physician may inform your attending physician that you are participating in the study upon your consent.

ACCESS TO DATA OBTAINED DURING CLINICAL STUDY

We inform you that you have the right to access information about your health status, results of examinations and tests.

Some of your data will be available to the following people during the study and after its completion:

Surname, first name and patronymic, date of birth, gender, weight, height, blood and urine test data, health data during the period of participation in the study, data on the amount of the drug administered — to the Study Physician, the clinical study monitor and other representatives of the clinical study Sponsor (at any time of the study and after its termination).

For verification of procedures and/or clinical study data, the original medical records will be directly accessible to monitors, clinical study auditors, representatives of the Local Ethics Committee and the Ethics Council under the Ministry of Healthcare of the Russian Federation, as well as official representatives of the authorized healthcare agencies to the extent permitted by law. However, the confidentiality of this data will not be violated, and the records that identify you will be kept secret and can only be disclosed to the extent permitted by law. When publishing the study results, the confidentiality of your personal data (surname, first name, patronymic, date of birth) will not be violated. This study assumes that medical information is transmitted electronically, and the transmitted data will not contain your personal information or information that allows to identify you other than the code assigned in the study.

By signing this Consent, you become a participant in the clinical study. However, you do not lose any rights that belong to you by law, including the right for qualitative and timely medical care.

If you agree to participate in the study, please sign this document on the last page. The Informed Consent is drawn up in two copies, one of which remains with the Study Physician, and the second you can take with you.

CONTACT INFORMATION

Keep this document in case you need to read it again later.

Ethics Council of the Ministry of Healthcare of the Russian Federation:

Address and directions: 3 Rakhmanovsky pereulok, Moscow, 127994. The nearest metro stations are Tsvetnoy Bulvar, Trubnaia, and Chekhovskaia.
Ethics Council Chairman — member of the Russian Academy of Sciences, Professor Alexander Grigorvich Chuchalin, contact phone number: +7 (495) 625-44-21.

Study Site
Address and directions

_____

Surname, first name, patronymic of the Study Physician, contact phone numbers

_____

Surname, first name, patronymic of the Chief Investigator

_____

Local Ethics Committee
Address

_____

Surname, first name, patronymic of the Local Ethics Committee Chair and his/her contact phone number

_____

The Study Sponsor and the organization conducting the study:
Drugs Technology LLC

Location address: 2a Rabochaia str., bld. 31, room 21, Khimki, 141400, Moscow region Tel.: +7 (495) 225-62-00, Fax: +7 (495) 225-62-65. E-mail: info@drugsformulation.ru Business hours: 9:00 to 18:00 daily, except for weekends and holidays.

INFORMED CONSENT FORM FOR PARTICIPATION IN CLINICAL STUDY

Multicenter Open-Label Randomized Parallel-Group Study of the Efficacy and Safety of TL-FVP-T Compared to Standard Therapy in Patients with Mild to Moderate Coronavirus Disease (SARS-CoV-2/COVID-19)

I, the undersigned,

(Full name)

am informed by the Study Physician

(Full name)

about all aspects of the planned clinical study of the Favipiravir TL-FVP-t drug (Drugs Technology LLC, Russia).

I obtained information on the objectives and nature of the clinical study of the Favipiravir TL-FVP-t, 200 mg film-coated tablets, information on the favipiravir TL-FVP-t drug, its expected efficacy and safety, the benefits and risks of participating in the clinical study, my rights and responsibilities and my rights and responsibilities as a participant in the study.

I am warned about possible adverse events and side effects and about necessary actions in case of unexpected events when using the Favipiravir TL-FVP- drug.

I have had the opportunity to discuss all my questions with the Study Physician, and I am satisfied with the answers I received.

I am informed that I will be included in the study only after I will undergo full examination in accordance with the Study Protocol, and my medical and physical condition will meet the conditions for inclusion in this study.

I voluntarily and knowingly agree to participate in the Favipiravir TL-FVP-t clinical study, and I am informed that I have the right to refuse to participate in the study or at any time and to terminate participating in this study without explanation.

I agree to follow the instructions correctly, voluntarily cooperate with the Study Physician, and immediately inform him/her of any changes in my health. I agree to the use of acceptable, highly effective, and highly protected contraceptive methods described in the Patient's Information Sheet within the time frame specified in the Patient's Information Sheet.

I am informed that if my health is damaged due to direct administration of the study product or medical procedure provided for in the Clinical Study Design, I will be provided with all necessary medical care, the costs of which will be reimbursed by the Absolute Insurance Company LLC. The amount of compensation may be revised if the deterioration of health occurred due to non-compliance with the instructions of the Study Physician.

I am informed that my medical and personal data will be confidential and can only be disclosed to official representatives while maintaining anonymity.

I am informed that my medical and personal data will be transmitted using electronic systems, including digital copies of images (jpeg, pdf, etc.).

I am informed that I have the right to access information about my health status and results of all investigations and tests.

I am informed that there are no monetary payments for this study.

By signing this Informed Consent Form, I give my permission to access the medical data obtained in the clinical study of the Favipiravir TL-FVP-t to the drug developer institution, organization responsible for conducting the clinical study, representatives of the Ethics Council under the Ministry of Healthcare of the Russian Federation and the Local Ethics Committee, and official representatives of the Ministry of Healthcare of the Russian Federation.

I signed and dated the Patient's Information Sheet along with the Informed Consent Form on 24 pages in 2 copies; I received 1 copy of the signed and dated Patient's Information Sheet on 24 pages:

Patient's signature:
Date (dd/mm/yyyy): _____ Time (in 24-hour format):
Patient's surname and initials (in block letters):

I, the undersigned, confirm that the Patient signed this document has been provided with the detailed explanation of all aspects of the study, and that the Patient understands what this study is about, as well as the risks and benefits associated with his/her participation in this clinical study.

Investigator's signature:
Date (dd/mm/yyyy): _____ Time (in 24-hour format):
Investigator's surname and initials (in block letters):

Executed in 2 copies: 1 copy for the Patient, 1 copy for the Investigator.

PATIENT INFORMATION LEAFLET
(inpatients)

Version 1.0 of 08/05/2020 (as amended on 19.05.2020)

Clinical study name:

Multicenter Open-Label Randomized Parallel-Group Study of the Efficacy and Safety of TL-FVP-T Compared to Standard Therapy in Patients with Mild to Moderate Coronavirus Disease (SARS-CoV-2/COVID-19)

Protocol No.: TL-FVP-t-01

Study sponsor: Drug Technology LLC
Registered and postal address: 2a Rabochaia str., bld. 31, room 21, 141400 Khimki, Moscow Region, Russia. Tel.: +7 (495) 225-62-00, Fax: +7 (495) 225-62-65. Email: info@drugsformulation.ru.

Investigator's full name: _____

Subject screening number /__/__/-/__/__/

Subject individual identification code:

RF MoH Permit No:	Permit issuance date DDMMYYYY	Serial number of the medical facility as specified in the Permit	Subject's initials, full name	Subject's date of birth DDMMYYYY	Subject unique sequential number

INFORMATION FOR PATIENTS
(inpatient department)

Dear Patient!
Please read this document carefully. You can ask any questions about your participation in this clinical study to the Study Physician. Save this document until termination of the study.

We are grateful to you for your interest in participating in this clinical study. This document provides information about the study that you are going to participate in, if you give your consent and the Study Physician decides that you can be included in the study. Please, ask the Study Physician or the Study Site staff any questions that you have after reading this document, or if you do not understand something in the information provided. You must not sign the Informed Consent Form under duress or until you have received answers to your questions and have made an independent decision about your participation in the study.

You are invited to participate in clinical study of the Favipiravir TL-FVP-t drug , 200 mg film-coated tablets (Drugs Technology LLC, Russia). This clinical study is conducted to evaluate the safety and efficacy of this drug in its treatment of patients with a new coronavirus infection (SARS-CoV-2/COVID-19) of mild and moderate severity.

The study will be conducted in several clinical centers in the Russian Federation.

Name of the clinical center where you are invited to participate in the study is:

_____

_____

_____

(name of the clinical center, Full name of the Investigator, contact phone number)

Data on the study and the study drug are reviewed and approved by the local Ethics Committee

_____

_____

_____,

(name of the Ethics Committee, contact phone number)
as well as the Ethics Council under the Ministry of Healthcare of the Russian Federation: Rakhmanovsky pereulok, 127994 Moscow, tel.: 8 (495) 625-44-21.

THE STUDY RATIONALE

In December 2019, a major outbreak caused by a new coronavirus occurred in the city of Wuhan (the capital of Hubei province, China). It was determined that this outbreak was caused by a new virus, the severe acute respiratory syndrome type 2 coronavirus (SARS - CoV-2). Numerous clinical cases of SARS-CoV-2 were reported, which spread to more than half of the world's countries over a period of less than 6 months. The lower respiratory tract is the main target of the SARS-CoV-2 infection. The infection can grade into life-threatening complication stage within about 7-10 days after the disease onset, due to rapid spread of the virus, violent release of biological substances from the cells of the human immune system and inflammatory tissue lesion. According to the statistics, 20% of the infected people have the disease in the form of severe viral pneumonia requiring hospitalization. Respiratory failure requiring treatment in the intensive care unit develops in approximately 5% of patients . The high-risk population groups for severe disease course include people aged over 65 years, as well as people suffering from overweight and concomitant diseases: hypertension, diabetes, and cancer.

The new SARS-CoV-2 coronavirus (name was assigned by the International Committee

on Virus Taxonomy on February 11, 2020) is a single-stranded RNA virus belonging to the family Coronaviridae, the Beta-CoV lineage. The virus is classified as risk group II, same as some other representatives of this family (SARS-CoV virus, MERS-CoV).

The SARS-CoV-2-induced infection has now become a threat to public health, to people around the world, due to the high transmission potential and unpredictability of disease progression. In Russia, at the end of April, about 80 thousand cases of COVID-19 were registered.

Early use of powerful antiviral agents can be useful for controlling the COVID-19 severity reducing the risk of complications and decreasing the burden on intensive care units. However, there is no approved standard treatment for COVID-19 today. Therefore, searching for effective therapeutic agents among previously developed drugs and study of their effectiveness for treatment of the new coronavirus infection is an urgent need due to the rapid spread of the disease.

CHARACTERISTICS OF THE STUDY DRUG

Currently, there are no registered drugs that have proven efficacy in the new coronavirus infection treatment.

Favipiravir is a broad-spectrum antiviral drug that blocks RNA replication of Riboviria viruses. The effect of Favipiravir has been studied in the treatment of influenza and Ebola virus infections and has been shown to be effective in these diseases. The ability of Favipiravir to exert direct antiviral effect on the new SARS-CoV-2 coronavirus was demonstrated in the study on cell culture infected with this virus.

The first drug with the favipiravir active ingredient (Avigan) was developed by Japanese Company, Toyama Chemical/Fuji Film in 1998. It was registered in Japan and China in 2014 for use in influenza (in cases of ineffectiveness or insufficient effectiveness of other anti-influenza drugs). In Russia today, there is no registered drug with active ingredient Favipiravir.

The Favipiravir safety and efficacy profile (for influenza) has been well studied. Favipiravir is a relatively low-toxicity drug. It is known to use Favipiravir in doses up to 6000 mg per day with no serious dose-limiting toxic effects. The most common adverse events are effects on the gastrointestinal tract, decreased neutrophils in blood, increased hepatic enzymes levels, as well as increased level of uric acid in blood, which are moderate in nature and are not a reason for treatment termination or dose reduction.

Currently, data on the Favipiravir efficacy in the new COVID-19 coronavirus infection are presented by two preliminary clinical studies, which confirmed the potential of this drug for the COVID-19 treatment, although the studies conducted are not sufficient to assess the efficacy of this drug for this indication.

The Drugs Technology LLC (Sponsor of this study) has developed Favipiravir generic drug, FAVIPIRAVIR-TL (internal code of the drug is TL-FVP-t), which in its dosage form (film-coated tablets) and strength (200 mg) fully corresponds to the original drug Avigan. The developed drug FAVIPIRAVIR-TL (TL-FVP-t), 200 mg film-coated tablets, is planned to be used in this clinical study as a study drug for the COVID-19 coronavirus infection treatment.

As a comparator drug this study, one of the drugs of the so-called "standard" etiotropic (antiviral) therapy recommended according to the Interim Guidelines of the Ministry of Healthcare of the Russian Federation, Prevention, Diagnosis and Treatment of Coronavirus Infection (COVID-19), will be used for the treatment of patients with the new coronavirus infection of mild and moderate severity. These drugs include Umifenovir, Chloroquine, Hydroxychloroquine, Mefloquine, Lopinavir+Ritonavir, Hydroxychloroquine in combination with Azithromycin and interferons. In terms of this study, participants randomly assigned to the comparison group will be prescribed either Umifenovir (also known by invented name as Arbidol) in combination with interferon-alpha (intranasal drops), or Chloroquine and its derivatives (Chloroquine/Hydroxychloroquine or Mefloquine).

In addition to the study drug or comparator drug, you will also receive concomitant therapy,

which will be prescribed at the discretion of the Study Physician and determined according to your actual condition and presence of certain symptoms of the underlying disease. It involves symptomatic therapy, pathogenetic therapy and antibacterial therapy (for complicated forms of infection), recommended according to the relevant version at the time of the study

Interim Guidelines of the Ministry of Healthcare of the Russian Federation for the Prevention, Diagnosis and Treatment of Coronavirus Infection (COVID-19) for patients with mild to moderate course, as well as corresponding to the standards adopted at the study site. Recommended concomitant medications include Paracetamol (as an antipyretic), Ambraxol, syrup (for coughing reduction), Ipratropium Bromide, aerosol (if bronchodilatation is required). The specific list of concomitant medications and the administration schedule will be determined by the Study Physician basing on assessment of your condition. Concomitant medications are not provided by the Sponsor.

CLINICAL STUDY AIMS AND OBJECTIVES

The study is exclusively scientific (experimental) in nature (cl. 4.8.10 in GOST R 52379-2005).

Its aim is to compare the efficacy and safety of the Favipiravir TL-FVP-t drug in comparison with the "standard" etiotropic therapy recommended according to the Interim Guidelines of the Ministry of Healthcare of the Russian Federation, Prevention, Diagnosis and Treatment of Coronavirus Infection (COVID-19), for the treatment of patients with the mild and moderate new coronavirus infection.

STUDY ORGANIZER AND INVOLVED INSTITUTIONS

This study is initiated, sponsored and conducted by the Russian company, Drugs Technology LLC. The study will be carried out in medical institutions that are accredited to conduct clinical studies in accordance with the procedure established by applicable legislation.

VOLUNTARY PARTICIPATION IN THE STUDY, SELECTION OF PARTICIPANTS

Participation in this study is entirely voluntary. You don't need to participate in this study to get treatment for your condition. To participate in the clinical study, you have to sign the Informed Consent Form for participation in the clinical study and meet all of the following criteria:

- You have signed the Informed Consent for participation in the study.
- Your age is within the range of 18 to 60 years.
- You have been diagnosed with the coronavirus infection induced by the SARS - CoV-2 virus (COVID-19) having mild or moderate course.
- Up to 6 days have elapsed since the infection symptoms onset before the intended day of the study treatment.
- Presence of SARS-CoV-2 infection is confirmed by PCR diagnostics (if you already have the result of a previous test, this result is taken into account during the screening).
- You are able, according to the Investigator, to fulfil the Protocol requirements.
- You and your sexual partner are willing to use reliable contraception methods throughout the study and for 3 months after the treatment completion. This requirement does not apply to participants who have undergone surgical sterilization. Reliable contraception methods involve the use of the first barrier method in combination with one of the following: spermicides, intrauterine spiral/oral contraceptives.
- You are willing to refuse from taking alcohol throughout the entire period of the study.
  For inclusion in the pharmacokinetics subgroup

- Your body mass index is in the range of 18.5 to 30.0 kg/m_2.
- - According to the Study Physician, you have the opportunity to participate in additional pharmacokinetics study and necessary number of blood sampling procedures.

You cannot participate in this clinical study if you meet at least one of the criteria listed below:

- You are younger than 18 or older than 60 years.
- You have been already prescribed any etiotropic treatment for SARS-CoV-2 (COVID-19) coronavirus disease before being included in the study.
- You have respiratory failure, severe or extremely severe course of the disease induced by SARS-CoV-2 (COVID-19).
- You have increased respiratory rate, reduced blood oxygenization, there is a need for artificial ventilation.
- You have deviated level of consciousness.
- You have signs of severe circulatory disorders.
- You have pronounced changes in lungs.
- You have at least one of the following comorbidities:
    a) Chronic obstructive pulmonary disease or moderate to severe asthma.
    b) severe chronic cardiovascular diseases;
    c) You are mmunocompromised (HIV, cancer, autoimmune diseases, immunosuppressive therapy).
    d) Severe obesity (body mass index [BMI] 40 or higher).
    e) Diabetes.
    f) Chronic renal failure.
    g) Moderate to severe chronic liver diseases.
- You have signs of liver dysfunction or decreased platelets count in blood.
- You have any other diseases or disorders, which, in the opinion of the Investigator, may lead to difficulties in the study results interpretation or pose an additional risk for the patient's heath due to participation in the study.
- You have had more than 2 CT diagnostic procedures within the last 6 months before the randomization into the study (except for the chest CT-scanning performed no more than 4 days before inclusion in the study).
- You are taking medications that are not recommended for use along with the study therapy, and you cannot stop taking these medications for the study duration.
- You are suffering from a significant gastrointestinal condition that may affect the absorption of the study drug.
- You are pregnant or breast-feeding, or plan pregnancy in the study period.
- You are or have been previously addicted to drugs, substances or alcohol.
- You are or have previously been mentally disturbed.

In this regard, the physician will conduct a thorough examination of your health before the study start. The Study Physician may not approve your participation if he/she considers the examination results to be unacceptable for receiving the study treatment.

You may refuse from participation in the study or terminated it at any time, which will not affect the quality of medical care provided to you, either currently or in the future. On completion of your participation in the study, your Physician will continue to monitor your condition as part of normal medical practice in accordance with the program of state guarantees of free medical care to citizens (Federal law of the Russian Federation No. 323-FZ of November 21, 2011).

During the study, you will be informed in a timely manner of any new data that may affect your safety and your desire to continue participating in this study.

If you decide to withdraw from the study early for any reason, you should immediately notify the Study Physician on your decision.

You can't participate in several studies at the same time.

You will be asked to sign and date the official Informed Consent Form after you have read it and received answers to your questions.

DESCRIPTION OF THE STUDY, TREATMENT AND DIAGNOSTIC PROCEDURES

If you participate in this study, you consent to medical examinations, sampling of biological materials for tests and conduction of the scheduled instrumental and laboratory investigation methods. During the study, you will take the study drug or comparator drug as instructed by the Study Physician.

In this study, it is planned to obtain data from at least 168 male and female patients with mild to moderate course of the new coronavirus infection.

Participants in this clinical study will be randomly assigned in a 2:1 ratio (i.e. about 112 and 56 people) to one of the two groups:

- **The study drug TL-FVP-t (FAVIPIRAVIR-TL) group.**
  Patients in this group will receive oral therapy with TL-FVP-t for 10 days. On the first day of therapy, patients will receive a loading dose of TL-FVP-t, i. e. 1800 mg at 12 hour intervals (i.e. twice a day), further, on days 2 through 10, patients will receive 800 mg at 12 hours intervals (i.e. twice daily).
- **Comparison group:**
  Patients in this group will receive the recommended "standard" etiotropic (antiviral) therapy recommended in accordance with the Interim Guidelines of the Ministry of Healthcare of the Russian Federation, Prevention, Diagnosis and Treatment of Coronavirus Infection (COVID-19), for treatment of patients with mild to moderate new coronavirus infection. In terms of this study, participants in the comparison group will be prescribed either Umifenovir (also known by the invented name Arbidol) in combination with interferon-alpha (intranasal drops), or Chloroquine and its derivatives (Chloroquine/Hydroxychloroquine or Mefloquine) using the recommended standard regimen and strengths.

In addition to the study drug or comparator drug, as noted above, you will also receive concomitant treatment prescribed upon the Study Physician's decision based on the assessment of your condition.

Please note that **before the study start**, **no one** (neither you, your physician or the clinical center staff) **can know** which group you will be assigned to, whether you will be prescribed the study drug (TL-FVP-t) or the recommended "standard" etiotropic therapy.

This clinical study involves series of Visits; it will be performed according to the following design and include the following procedures:

Screening — preliminary examination of patients

The screening period shall be carried out no longer than 2 days before inclusion in the study.

- During the screening, the Study Physician will assess your compliance with the inclusion/non-inclusion criteria, take your medical history (basing on an interview), and determine your height and weight indicators.
- For female patients, you will receive 2 pregnancy tests along with the Informed Consent Form. The test you will be required to perform immediately, the Study Physician will ask you about the results during the screening interview; you will also need to provide the Study Physician with a photo confirmation of the test result. You will receive the second

test together with the drug and perform it at the end of the treatment period on Day 14 (for more information, see the description of the procedures at Day 14 Visit).

- You will undergo ECG tracing and thoracic computed tomography (CT), moreover, body temperature, blood pressure, pulse rate, respiratory rate and blood oxygen saturation (SpO_2) will be measured.
- Your blood will be taken from vein for clinical, biochemical blood tests and for coagulation analysis. You will need to give an urine sample for common urine analysis.
- The Study Physician will ask you questions about prior and concomitant therapy.
- The Study Physician will ask you the questions required to assess your health status and whether you can participate in the study.
- The Study Physician will make decision on the possibility to transfer you to the next stage of the study basing on the evaluation of the tests results and examinations you have already undergone. If the Study Physician reveals that you do not meet the inclusion criteria, your participation in the study will be terminated. If you meet all the selection criteria, the Study Physician will appoint you a Day 1 Visit date.
- You will be informed on the need to comply with the rules of participation in this study and the schedule of procedures and examinations during receiving the study therapy.

The total volume of blood taken during the visit will be 15 mL.

Periods of Treatment and Follow-Up

The schedule of procedures you will need to undergo as part of the study during the periods of treatment and follow-up do not depend on whether you will be treated at home or in a hospital, as well as on the therapy group.

Duration of treatment with the study drug is 10 days, duration of treatment with comparator drug will be determined by the Study Physician, depending on the drug prescribed and your health state, but also will not exceed 10 days. In addition to the study/comparator drug, the Study Physician may prescribe concomitant medications basing on how you feel. The duration of concomitant therapy may exceed 10 days.

During the first 14 days of the study, you shall fill in the Patient's Diary every day and then on days 21 and 28, adding information on:

- taking the study/comparator drug (within the first 10 days of the study);
- results of blood pressure, heart rate, body temperature, pulse oximetry (SpO_2) measurements (the body temperature and SpO_2 shall be measured and the results shall be recorded in the **Diary daily 3 times a day until Day 10, then once a day**);
- complaints occurred during the day;
- names, strengths and quantity of concomitant medications prescribed by the Study Physician, or taken at your sole discretion.

You will measure blood pressure, heart rate, body temperature, pulse oximetry (SpO2), take oropharengeal and nasopharengeal smears for PCR diagnostics of SARS-CoV-2 infection by yourself.The necessary equipment (BP monitor, thermometer and pulse oximeter) will be provided to you by the Sponsor for the study period, along with the comparator drug and the Patient's Diary.

You will undergo blood sampling procedures to monitor clinical and biomedical parameters of blood, ECG tracing and thoracic CT scanning, in accordance with the Study Protocol and routine practice of the center.

If you are randomized to the study drug group, blood samples will be taken periodically during the treatment period to evaluate the pharmacokinetics of Favipiravir.

Due to the sanitary and epidemiological rules, the Informed Consent Form that you signed before being included in the study cannot be removed from the "red" zone and stored with the other study documents. To ensure compliance with the rules of good clinical practice, an electronic copy of the signed copy of the Informed Consent Form will be taken, which the Study Physician

will print out in the "green" zone and will continue to keep it until your discharge from the hospital. Upon discharge, you will be provided with 2 copies of the previously signed Informed Consent Form for signature. You will confirm with your signature that these documents are copies of the Form you signed before your including in the study.

In patients undergoing treatment in the hospital, the study procedures will be carried out as follows:

Day 1 Visit

- In the morning, you will receive a Study Participant Kit, which includes:
  1) packages with the study/comparator drug,
  2) thermometer (1 pc.),
  3) electronic BP monitor (1 pc.),
  4) portable pulse oximeter (1 pc.),
  5) Patient's Diary (1 pc.),
- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will take your first dose of the study/comparator drug.
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO_2).
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.
- You will undergo sampling for PK-study at the following time points: 5 minutes before taking the study drug, then after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours.
- At the time of sampling, cubital catheter will be inserted in your arm, which will be removed after sampling at the 12 o'clock point.

The total volume of blood taken during the visit will be 15 mL.

Day 2, Day 4, Day 6, Day 8 and Day 9 Visits

- You will take morning dose of the study/comparator drug.
- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO_2).
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the

Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.

- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.
- You will undergo sampling for PK-study at the following time points: 5 minutes before the next (morning) intake of TL-FVP-t.

Total blood volume taken during each visit will be 5 mL (25 mL for 5 visits).

Day 3 and Day 7 Visits

- You will take morning dose of the study/comparator drug.
- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO2).
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- You will undergo taking of oro- and nasopharengeal smears for PCR diagnostics using the Biosample Collection Kit provided by the Sponsor.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.
- You will undergo sampling for PK-study at the following time points: 5 minutes before the next (morning) intake of TL-FVP-t.

Total blood volume taken during each visit will be 5 mL (10 mL for 2 visits).

Day 5 Visit

- You will take morning dose of the study/comparator drug.
- You will undergo blood sampling for laboratory tests, taking of oro- and nasopharengeal smears for PCR diagnostics (using the Biosample Collection Kit provided by the Sponsor), ECG tracing, thoracic CT scanning, and common urine analysis
- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO2).
- You will enter information on the drug taking and the obtained by you values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.

- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.
- Sampling for PK-research at the following time points: 5 minutes before the morning intake of the test drug, then after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours.
- At the time of sampling, cubital catheter will be inserted in your arm, which will be removed after sampling at the 12 o'clock point.

The total volume of blood taken during the visit will be 80 mL.

Day 10 Visit

- You will take morning dose of the study/comparator drug.
- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO2).
- You will enter information on the drug taking and the obtained values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- You will undergo taking of oro- and nasopharengeal smears for PCR diagnostics using the Biosample Collection Kit provided by the Sponsor.
- During the day, you will take the study/comparator drug, according to the Physician's prescriptions, and enter information on the drug administration in the Patient's Diary.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.
- Sampling for PK-research at the following time points: 5 minutes before the morning intake of the test drug, then after 20 minutes; 40 minutes; 1 hour; 1.25; 1.5; 1.75; 2; 2.5; 4; 6; 8; 12 hours.
- At the time of sampling, cubital catheter will be inserted in your arm, which will be removed after sampling at the 12 o'clock point.

The total volume of blood taken during the visit will be 15 mL.

Visit Day 14

- For female patients – you will have to perform a pregnancy test using the second Pregnancy-Test provided to you with the drug. The Study Physician will ask you about the test results during the interviewing, and you shall provide the result photo confirmation to the Physician.
- You will undergo blood sampling for laboratory tests, taking of oro- and nasopharengeal smears for PCR diagnostics (using the Biosample Collection Kit provided by the Sponsor), ECG tracing, thoracic CT scanning, and common urine

analysis

- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO2).
- You will enter information on the obtained by you values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications taken at your own discretion in the Patient's Diary.

The total volume of blood taken during the visit will be 15 mL.

Day 21 Visit

- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO2).
- You will enter information on the obtained by you values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- You will undergo taking of oro- and nasopharengeal smears for PCR diagnostics using the Biosample Collection Kit provided by the Sponsor.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.

Day 28 Visit

- You will undergo blood sampling for laboratory tests, taking oropharyngeal and nasopharengeal smears for PCR investigation, ECG tracing, and thoracic CT scanning, sampling urine for common urine analysis.
- The Study Physician will ask you questions about your health, complaints, and calculate the respiratory rate (RR).
- You will undergo measurement of vital signs (blood pressure, heart rate and body temperature), pulse oximetry (SpO2).
- You will enter information on the obtained by you values in the Patient's Diary, and the Study Physician will monitor correctness of the Diary filling-in.
- During the day, you will take concomitant medications, in accordance with the Physician's prescriptions, and enter information on the drugs administration in the Patient's Diary.
- During the day, you will make repeated measurements of body temperature and SpO_2 (at least 3 measurements a day in total), and enter information on the results in the Patient's diary.
- You will enter information on complaints that occur during the day and medications

taken at your own discretion in the Patient's Diary.
The total volume of blood taken during the visit will be 15 mL.

In total, not more than 290 mL of blood will be taken during the study. Such extent of blood loss over a period of 28 days does not pose any danger to your health.

If you are discharged earlier than Day 28, you will be able to complete further study Visit procedures at home or when visiting the study center.

Therapy completion visit (including early drop-out)

You can voluntarily terminate the study therapy at any time (withdraw consent), or terminate it early, or drop-out from the study early for various reasons. In this case, a Therapy Completion Visit will be performed.

- The Study Physician will measure your blood pressure, heart rate, respiratory rate and body temperature, pulse oximetry (SpO2).
- You will undergo taking of oro- and nasopharengeal smears for PCR diagnostics using the Kit provided by the Sponsor
- The Study Physician will ask you questions about your general state and concomitant therapy

SPECIAL INSTRUCTIONS FOR THE STUDY PARTICIPANTS

Please inform the Study Physician about any changes in your general state. Inform the Study Physician in a timely manner if for any reason you are not able to continue participation in the study.

In case of any adverse event occurs, the Study Physician may prescribe additional investigations, additional drugs. Contact your Study Physician immediately, if you experience any changes in your general state or other signs of a health disorder, at any time during the study or after it is completed.

In the event of your early drop-out, after taking at least one dose of the study drug, you will undergo procedures of the Early Termination Visit on the day of your drop-out from the study.

If you are transferred to another hospital, you must inform the medical officers of the hospital where you will be admitted that you are a participant in the clinical study and present your Participan'st Card. You will be excluded from the study, if your clinician in the inpatient department cancels the study therapy or prescribes medications prohibited by the Clinical Study Protocol. If the inpatient department clinician confirms continuation of the previously assigned course of the study therapy, you will need to contact the Study Physician and undergo the procedures of planned visits to monitor your condition (if it is technically possible).

RESPONSIBILITIES OF THE STUDY PARTICIPANT

Your responsibilities will include strict compliance with the rules and procedures prescribed by the Study Physician and provided for in the Study Protocol. You undertake to report any changes in your health status, regardless of whether it is related to taking the drug or not. You also need to notify the Study Physician of all drugs you took during the study.

As part of this study, you have responsibility take the study/comparison therapy drugs timely and without skipping and to follow all the recommendations of the Study Physician concerning the basic and combination therapy and lifestyle.

You should be aware that you will be prematurely excluded from the study if you miss 2 or more doses of the drug, or 2 or more visits in the study, or do not follow Protocol procedures in full at 2 or more visits.

Before being included in the study, tell the Study Physician about your living conditions,

past illnesses, operations, injuries, chronic pathology, allergic reactions, heredity, and medications that you are taking (if applicable).

You should adhere to reliable methods of contraception, which are described below. If you/your partner becomes pregnant, you should immediately inform your Study Physician.

Drugs of the following pharmacological classes **are considered to be unauthorized or not stipulated in the Protocol:**

- Pyrazinamide, Repaglinide, Famciclovir, Sulindac, CYP-2C8 substrate drugs; it is necessary to consider canceling the study therapy and excluding the patient from the study.

The Study Physician will carefully monitor your condition. If you have any additional health problems (feeling unwell, any new unexpected and unusual symptoms), you should contact your Study Physician urgently. In case of allergic reactions, you will be prescribed the necessary allergy medications. If you experience unexpected adverse events, the physician may decide to exclude you from further participation in the study, which will not affect the quality of medical care provided to you.

Contraception

Please note that by accepting the terms of participation in this study, you consent to use highly effective methods of contraception. Female participants should use contraception throughout the study or at least 2 weeks after the last administration of the study/comparator drug.

A highly effective method of contraception for women can be represented by one of the following options:

- Total sex abstinence: if it corresponds to the patient's preferred and habitual lifestyle. [Periodic sex abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods) and interrupted sexual intercourse are not considered acceptable methods of contraception].
- Sterilization: performing surgical bilateral ovarian removal (with or without removal of the uterus) or tubal ligation at least 6 weeks before the start of the study therapy.
- Sterilization of male partner (if there is a single sexual partner).
- Using a combination of any two of the methods listed below (a+b or a+c or b+c):
    a) Use of oral, injectable, or implanted hormonal contraceptives.
    b) Installing an intrauterine device or contraceptive system.
    c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical cap/vaginal fornix cap) with spermicidal foam/gel/film/cream/vaginal suppository.

When using oral contraceptives, women should constantly use the same drug for at least 3 months before starting the study therapy.

In case of assignment to the study drug TL-FVP-t group, male patients should use reliable methods of contraception for at least 3 months after the last administration of the study drug. For the comparison group — at least 2 weeks after last administration of the comparator drug.

Sexually active **men** should use condoms as a method of contraception in combination with one of the following: spermicides, intrauterine device/oral contraceptives in the sexual partner throughout the study, conception during this period is also not allowed. Men after vasectomy (a method of medical sterilization) should also use condoms to prevent the drug transfer with the seminal fluid.

Other Lifestyle Restrictions

Alcohol is not allowed during the entire study.

Due to the fact that photosensitivity reactions (skin redness, rash, peeling, etc. inflammatory reactions at short exposure to sunlight) may develop against the background of taking Favipiravir or Hydroxychloroquine, if you are assigned to the study drug group, we recommend you to avoid intense and prolonged exposure to sunlight, being in the sun with head uncovered, visiting a tanning room while participating in the study.

Lifestyle Recommendations for the Study Period.

During treatment of the SARS-CoV-2 infection, we recommend you to:

- Follow the drinking regime (at least 1 liter of clean water daily, up to 1 liter of tea, liquid food, vegetables and fruits without restrictions).
- Limit the consumption of fatty and fried foods.
- Avoid excessive physical activity.

POSSIBLE RISKS ASSOCIATED WITH PARTICIPATION IN THE STUDY

Due to the experimental nature of any clinical study, the exact result is not known.

Group of Patients Receiving the Study Drug, TL-FVP-t (FAVIPIRAVIR-TL)

The risk of using the Favipiravir drug (TL-FVP-t) is associated primarily with reactions registered in clinical studies of the original drug of favipiravir. In this study, Favipiravir will be used in the form of 200 mg film-coated tablets at loading dose of 1800 mg twice a day on the first day, further, 800 mg twice daily for the next 10 days. The safety profile is expected to match that of the original Favipiravir drug in clinical studies.

Risk of using Favipiravir drug (TL-FVP-t) is associated primarily with the reactions listed in the Table below (information is collected basing on clinical studies of the Favipiravir).

Blood and lymphatic system disorders: decrease in the neutrophil count, lymphocyte ("white" blood cells) count; increase in lymphocyte, monocyte ("white" blood cells) count; decrease in the reticulocyte (precursors of "red" blood cells) count;

Immune system disorders: rash, eczema, itching;

Metabolism and nutrition disorders: increased concentration of uric acid in blood, increased concentration of triglycerides (fats) in blood, presence of glucose in urine, decrease in the potassium concentration in blood;

Nervous system disorders: dizziness;

Ocular disorders: blurred vision, pain in eyes;

Respiratory, thoracic and mediastinal disorders: asthma, pharyngalgia (raw throat), rhinitis (runny nose), nasopharyngitis (nasopharyngeal inflammation);

Gastrointestinal disorders: diarrhea, nausea, vomiting, abdominal pain; abdominal discomfort, duodenal ulcer, hematochezia (fecal blood), gastritis. *hepatobiliary disorder*: increased activity of hepatic enzymes (AST, ALT, γ-GTP, alkaline phosphatase), increased bilirubin concentration in blood.

Miscellaneous: increased activity of creatine kinase (muscular tissue enzyme), presence of blood in urine, pigmentation (staining) of urine.

The most common side effects when using Favipiravir in patients in studies were diarrhea, signs of hepatic impairment, including increased activity of liver enzymes, decreased neutrophil count, and increased blood uric acid levels. All adverse drug events were moderate and did not lead to premature discontinuation of the drug administration, and quickly stopped after the end of the therapy.

Group of Patients Receiving Comparator Drug

Risks associated with Umifenovir (Arbidol), Interferon Alpha (nasal drops):

Immune system disorders: *allergic reactions*

Risks associated with Chloroquine/Hydroxychloroquine/Mefloquine:

Blood and lymphatic system disorders: bone marrow function depression, poor blood (anemia, Ehrlich anemia), decrease in the white blood cell count (agranulemia, leukopenia, thrombocytopenia).

Immune system disorders: antitoxin rash, subcutaneous tissue oedema (angioneurotic oedema), broncoconstriction (bronchial spasm).

Metabolism and nutrition disorders: complete absence of appetite (anorexia), decreased

blood sugar (hypoglycaemia), relapse of pigment exchange disorders is possible (porphyria).

Mental disorders: emotional instability, nervousness, psychosis, suicidal behavior.

Nervous system disorders: headache, dizziness, convulsions, movement abnormalities.

Ocular disorders: blurred vision, retinal disorders with compromised visual field. These events in incipient forms are usually reversible after the Hydroxychloroquine disengagement.
If the condition remains undiagnosed, and retinal lesions continue to develop further, there may be a risk of their progression even after the drug disengagement. Retinal changes may initially be asymptomatic or manifest as loss of visual fields and color vision disorders. Corneal changes may occur, including oedema and opacity. They can be asymptomatic or cause visual disorders such as the appearance of halos (luminous contour around objects), blurred vision or photophobia. These changes may be transient or reversible after discontinuation of the treatment; central retinal lesions (maculopathy, macular degeneration) that may be irreversible.

Ear and labyrinth disorders: dizziness, tinnitus, hearing loss.

Cardiac disorders: intracardiac conduction disorders in patients with risk factors that may lead to arrhythmias, heart muscle damage (cardiomyopathy) that may result in heart failure and, in some cases, death; cardiac conduction disorders (e. g. His bundle blockade/atrioventricular conduction disorders) and enlargement (hypertrophy) of both ventricles may indicate chronic cardiac toxicity. At drug disengagement, the regression of these changes is possible.

Gastrointestinal disorders: abdominal pain, nausea, diarrhea, vomiting. These symptoms usually disappear immediately after reducing the dose or disengagement of the drug.

Hepatobiliary disorder: liver function test aberrations, fulminant (peracute) hepatic failure.

Skin and subcutaneous tissue disorders: skin rash, itching, skin and mucous membranes discoloration, hair discoloration and hair loss. These changes usually resolve quickly after the treatment discontinuation; blistering rash, including severe forms; skin irritation due to light exposure; exfoliative dermatitis; other severe skin reactions. After the drug disengagement, the outcome is usually favorable.

Musculoskeletal and connective tissue disorders: impairment of skeletal muscles or nerves and muscles (may be reversible after drug intake discontinuation, but it may take several months for complete recovery), tendon reflexes depression and decreased nerve conduction.

Risks associated with use of concomitant medications (occur only if you are prescribed these medications).

Risks Associated with Paracetamol

Blood and lymphatic system disorders, often: postoperative hemorrhages, poor blood (anemia), decrease in blood count (red and/or white blood cells and/or platelets), changes in haemoglobin.

Immune system disorders: allergic reactions (including skin rash, itching, antitoxin rash, subcutaneous tissue oedema (angioneurotic oedema); severe skin reactions, severe allergic reactions.

Mental disorders: insomnia, anxiety.

Nervous system disorders: headache, asthenia, dizziness, motor and emotional excitement, disorientation (at high doses).

Ocular disorders: *adorbital oedema.*

Cardiac disorders: palpitations, chest pain.

Vascular disorders: peripheral oedema, increased or decreased blood pressure.

Respiratory, thoracic and mediastinal disorders: respiratory disorders, abnormal breathing, pulmonary oedema, oxygen deprivation, fluid in pulmonary coat, rale, breathlessness, cough; bronchospasm (in patients with hypersensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs).

Gastrointestinal disorders, often: diarrhea, constipation, digestive disorders, bloating, abdominal pain, nausea, vomiting, dry mouth. *Hepatobiliary disorder:* increased activity of

hepatic enzymes; hepatic failure, hepatitises, hepatic necrosis (necrocytosis).

Skin and subcutaneous tissue disorders: *rash.*

Musculoskeletal and connective tissue disorders: muscle spasms, trism.

Renal and urinary disorders: decreased renal urinary output; renal colic, bacteria in urine, kidney tissue lesion.

General disorders and administration site conditions, often: temperature rise, fatigue feeling; feeling generally unwell/faintness.

Effect on the results of laboratory and instrumental tests: decrease in potassium concentration in blood, increase in glucose concentration in blood; blood clotting abnormalities, increased creatinine (mainly in severe hepatopathies and secondary renal impairment).

Risks Associated with Ambroxol (Syrup)

Gastrointestinal disorders: nausea, decreased sensitivity in the oral cavity or pharynx, digestive disorders, vomiting, diarrhea, abdominal pain, dry mouth, pharyngoxerosis.

Immune system disorders, skin and subcutaneous tissue lesions: rash, antitoxin rash, acute drug hypersensitivity drug, subcutaneous tissue oedema (angioneurotic oedema), itching, hypersensitivity.

Nervous system disorders: dysgeusia (taste perversion).

Risks associated with Ipratropium Bromide (dosage form: aerosol)

The most common side effects reported in clinical studies were headache, throat choke, cough, dry mouth, gastrointestinal dysmotility (including constipation, diarrhea, and vomiting), nausea, and dizziness. The following reactions are also possible.

Immune system disorders: acute drug hypersensitivity reactions, hypersensitivity.

Nervous system disorders: headache, dizziness.

Ocular disorders: blurred vision, pupil dilation, increased intraocular pressure, glaucoma, ophthalmalgia, appearance of luminous contour (halo) around objects, conjunctival redness, corneal edema, violations of the ability to see objects at different distances.

Cardiovascular system disorders: heart consciousness, palpitations, heart rhythm disorders (auricular fibrillation), increased heart rate.

Respiratory, thoracic and mediastinal disorders: throat choke, cough, broncoconstriction (bronchospasm, paradoxical bronchospasm), laryngospasm, pharyngeal oedema, pharyngoxerosis.

Gastrointestinal disorders: dry mouth, nausea, gastrointestinal contractive activity disorder, diarrhea, constipation, vomiting, stomatitis, oral cavity edema.

Skin and subcutaneous tissue disorders: rash, itching, subcutaneous tissue oedema, antitoxin rash.

Renal and urinary disorders: urine retention.

Risks Associated with the Study Procedures

Medical procedures aimed at diagnosing your health status, which are performed according to the standard methods and do not pose any danger to you, but in some cases may be associated with a feeling of some inconvenience or internal discomfort. However, all these procedures are necessary to obtain important information about your health, they will be performed by medical personnel with the necessary qualifications, and all actions of medical officers and nurses will be performed in the interests of your safety.

Taking naso-and oropharyngeal smears is a procedure that causes unpleasant, but transient sensations. When taking smears from the oropharynx, vomiting may occur, due to the probe touching the tonsils at the back of the pharynx. When taking smears from the nasopharynx, the probe is lead deep along the lower nasal passage, which can be accompanied by irritation of the nasal mucosa, pinpoint bleeding and also the appearance of a gag reflex.

Electrocardiogram (ECG) tracing is a test that provides valuable information about your heart condition. In order to conduct an electrocardiographic examination, the Study Physician will apply electrodes your chest, as well as on your upper and lower limbs and record the cardiac electrical activity with special equipment. This procedure is absolutely painless, does not involve

piercing the body, does not require special training, performed in supine position, in relaxed state. There are no contraindications to this procedure.

Computed tomography (CT) is a safe and painless procedure that allows you to get a detailed image of internal organs and structures, including the lungs. Thoracic CT is included in the standard diagnosis of pneumonia in new coronavirus infection. If you follow the appropriate safety rules, CT does not pose any danger to you.

Blood sampling from the ulnar vein through venipuncture (needle piercing) may cause discomfort, bleeding, or haematoma at the site of needle piercing. Fainting or local infection is rare. The Study Physician will take care of to prevent such events.

Blood sampling from the ulnar vein through venipuncture (needle piercing) and insertion of cubital catheter (thin tube inserted into an ulnar vein and intended for repeated blood sampling) may cause discomfort, bleeding or haematoma (bruising) at the skin needle puncture site. Fainting or local infection is rare. The Study Physician will take care of to prevent such events.

Measurement of blood pressure and heart rate can cause unpleasant, but transient sensations of compression in the forearm area from the tonometer cuff (blood pressure measuring instrument). The staff performing this procedure is aware of the possibility of these feelings and will act in your advantage.

Pulse oximetry may cause unpleasant, but transient sensations of compression in the area of the finger on which the pulse oximeter sensors are placed.

Routine Clinical Examinations. If you participate in this study, you will need to undergo clinical examinations at each study visit. Examinations will be performed using telemedicine technologies if you are undergoing treatment at home, or if you are in the Study Site inpatient department, by visiting the Study Physician in person.

The Study Physician will carefully monitor your condition. If you have any additional health problems (feeling unwell, any new unexpected and unusual symptoms), you should contact your Study Physician urgently. In case of allergic reactions, you will be prescribed the necessary allergy medications. If you experience unexpected adverse events, the physician may decide to exclude you from further participation in the study, which will not affect the quality of medical care provided to you.

If you have questions about the above, ask the Study Physician to explain them.

BENEFITS OF PARTICIPATING IN THE STUDY

If you decide to participate in this study using TL-FVP-t drug or "standard" therapy, you will receive drugs for the treatment of the new COVID-19 coronavirus infection free of charge; the probability of assignment to the Favipiravir study drug group will be 2:1.

While participating in the study, you will be provided with thorough medical supervision, including free PCR diagnostics of SARS-CoV-2 infection, CT, ECG tracing, blood and urine tests, as well as daily observation by the Study Physician, which will additionally allow you to assess the state of your body.

The study Favipiravir drug has shown encouraging results in studies of the impact on the SARS-CoV-2 virus in cell culture and in pilot clinical studies in patients with COVID-19, but there is no reliable data on its efficacy and safety when used for this indication. It should be noted that at the moment, there is no such information about any of the drugs used for the treatment of the SARS-CoV-2 infection. Thus, it is assumed that the new data obtained in this study on the efficacy and safety of the Favipiravir TL-FVP-t, 200 mg film-coated tablets, will benefit you and many other patients with the new COVID-19 coronavirus infection.

ALTERNATIVE THERAPY OPTIONS

Currently, there are several drugs that, according to the Interim Guidelines of the Ministry

of Healthcare of the Russian Federation for the Prevention, Diagnosis and Treatment of coronavirus infection (COVID-19), can be used to treat patients with the new coronavirus infection. They include Umifenovir, Chloroquine, Hydroxychloroquine, Mefloquine, Lopinavir+Ritonavir, Hydroxyloroquine in combination with Azithromycin, Interferons.

However, the available today information on the results of therapy with these drugs does not allow us to make a clear conclusion about their efficacy or inefficacy, so their use is permissible by the decision of the medical commission in the appropriate manner if the potential benefit to the patient outweighs the risk of their use.

INFORMATION ABOUT LIFE AND HEALTH INSURANCE OF THE STUDY PARTICIPANTS

Mandatory Life and Health Insurance

You will not receive payment for participating in this clinical study. You will not have any additional costs associated with participating in this study.

For the duration of the study, you will be insured as a study participant in accordance with the legislation of the Russian Federation.

The Study Physician must provide a Compulsory Life and Health Insurance Policy of Drug Clinical Study Participant to you. The Insurance Policy covers the claims of the study participants to the Policyholder solely for compensation for the damage caused to their life and health during participation in the clinical study, due to deficiencies of the study drugs or insufficient information about them, unintentional errors, omissions. Only claims that were first submitted to the Policyholder during the insurance period in respect of events that occurred in the insurance territory after the study start and in connection with the implementation of the insured activity (study) shall be covered.

If your health is damaged as a result of the use of the study drug or medical procedure provided for in the Study Protocol, you will be provided with free qualified medical care in the required amount, paid for by the Insurance company. The Insurance company will make the stipulated payments only if you comply with all the physician's prescriptions.

In the Russian Federation, you will be insured for the study period according to the legislation of the Russian Federation by the Absolut Insurance LLC insurance company. The Study Physician will familiarize you with the terms of the Contract (including the obligations that must be observed by the patients participating in the study). You will be insured under the contract of compulsory life and health insurance of a drug clinical study participant from the moment of signing the patient's Informed Consent Form. The Study Physician shall execute (enter in the Policy form the patient's individual identification code) and give you an Individual Compulsory Life and Health Insurance Policy of Drug Clinical Study Participant. The Compulsory Insurance Policy has a unified form on the territory of the Russian Federation and is a mandatory Appendix to this Information Sheet (in addition, it may be accompanied by the terms of insurance).

If you are undergoing treatment as part of the inpatient, your Individual Compulsory Life and Health Insurance Policy and the Study Participant's Card will be kept by the Study Physician for the entire period while you are staying in the "red zone". This is necessary to ensure the document availability subject to occurrence of an insured event and compliance with the rules of the sanitary and epidemiological regime in the inpatient department.

When an insured event occurs, the Absolute Insurance LLC shall provide payment in accordance with article 44 of the Federal law On Medicine Circulation and the Decree of the Government of the Russian Federation of September 13, 2010 No. 714. The amount of insurance payment under the Contract is:

a) in case of death of the insured person — 2 million rubles. The insurance payment in the specified amount shall be distributed among the beneficiaries in proportion to their number in equal shares;

б) if the insured person's health deteriorates, resulting in:
Group I disability confirmation – 1.5 million rubles.
Group II disability confirmation – 1 million rubles.
Group III disability confirmation – 500 thousand rubles.
в) If the insured person's health deteriorates and does not result in disability – no more than 300 thousand rubles.

The amount of insurance payments may be increased on the basis of a court decision. Additional life and health insurance is not provided in this study.

Restrictions for use of other types of health insurance

Please note that if you have a Voluntary Medical Insurance Policy, the conditions for its implementation may be violated during the period of participation in the study. This circumstance does not prevent you from receiving medical care under the compulsory medical insurance, but it may lead to withdrawal from receiving medical care under the voluntary medical insurance. For more information, if you have a Voluntary Medical Insurance Policy, please contact the insurance company where you are insured under the Voluntary Medical Insurance.

COMPENSATIONS

In case of damage to your health or disease onset as a direct result of prescription of the study drug or medical procedures performed in accordance with the Protocol, you will be provided with the full necessary examination and treatment of such damage or disease. At the same time, the costs of examination and treatment will be covered by the Absolute Insurance Company LLC. This will happen provided that you have followed all the instructions of the Study Physician, and that the damage is not committed intentionally. After the expert examination, the Absolute Insurance Company LLC will make monetary payments in the amount corresponding to the degree of damage caused in accordance with the Insurance Contract for the clinical study you are invited to participate. If your health deteriorates as a result of participating in the study, you should first contact your physician monitoring you by phone; his/her phone number is indicated in this document.

Treatment costs will not be reimbursed if the damage to health or disease is caused by violation of the Study Physician's instructions regarding the study conduct, including those listed in this Information Sheet.

EXPENSES

The Sponsor Company of this study reimburses expenses associated with the study, i.e. consultations by the Study Physician, instrumental investigations and laboratory tests and other examination types provided for in the Protocol, as well as your transfer to the medical center for the procedures. The study drug, TL-FVP-t (FAVIPIRAVIR-TL), and comparator drugs Umifenovir (Arbidol), Interferon Alpha (nasal drops) and Hydroxychloroquine/Chloroquine/Mefloquine in the amount necessary for the study will be provided free of charge by the Sponsor. Concomitant medications are not provided by the Sponsor. The study does not provide compensation for other personal expenses. In addition, the Sponsor does not reimburse the costs of additional medications and examinations prescribed to you during treatment that are not provided for in the Study Protocol.

SUPPLEMENTARY PAYMENTS

No monetary rewards for patients taking part in the study are provided for.

TERMINATION OF THE STUDY FOR MEDICAL REASONS

The Study Physician may exclude you from the study at any time, regardless of your consent (if there are serious side effects, if you do not follow the instructions of the Study Physician), if he/she believes that it is for your benefit to do so. Before doing this, he/she will explain you the reason and, if necessary, arrange further treatment.

GUARANTEES TO THE STUDY PARTICIPANT RIGHTS PROTECTION

This study is conducted in accordance with the legislation, state standards of the Russian Federation and international guidelines for study of medicinal products in humans. The study was fully reviewed by the relevant supervisory authorities, including assessment of its feasibility, risk/benefit ratio, and ethical assessment, and its conduct was approved by authorized representatives of the Russian Federation.

QUESTIONS AND COMPLAINTS

You will be promptly informed of new information that may affect your wish to continue participating in the study. If you have any questions or claims related to the conduct of this study, as well as for more information about the study and your rights, you can contact your Study Physician or Chief Investigator.

PRIVACY

In order to ensure medical confidentiality and your personal data privacy, your medical data in the study will be marked with an individual code, without specifying personal identification data, such as your name or initials. The code linking your personal data to the records will be stored by your physician in a secure and confidential location at the study site. Only your physician can reveal this code. When publishing the results of the study your personal information will not be disclosed. If the study materials are delivered to your home, the address will be sent to the courier by your physician. The study Sponsor does not receive this information.

The information gathered about you during this study may be reviewed by authorized persons for the study purposes and/or in connection with regulatory matters. Those authorized to have access to your medical data include representatives of the Sponsor (Drugs Technology LLC), conducting this study, members of the Ethics Council, Local Ethics Committee of the institution, as well as, if necessary, other representatives of regulatory authorities. These individuals are required to maintain the confidentiality of the information they receive to the same extent as your Study Physician.

By signing the Informed Consent Form, you consent to collection, use and processing of your personal data obtained in the course of the study. At the end of the study, your data will be stored safely in the archival repository and, if necessary, their confidential destruction will be arranged. You have the right to access and correct your personal data in the course of the study until the data associated with this study is archived on a confidential basis. If you need to make corrections to your personal data, you should contact your Study Physician, who has access to such data. On completion of the study and transferring the data to the database, all the transmitted data will be encoded, without the ability to identify you. The electronic database will be stored for at least 5 years from the date of writing the final study report or publishing the study results. If you have another attending physician, your Study Physician may

inform your attending physician that you are participating in the study upon your consent.

ACCESS TO DATA OBTAINED DURING CLINICAL STUDY

We inform you that you have the right to access information about your health status, results of examinations and tests.

Some of your data will be available to the following people during the study and after its completion:

Surname, first name and patronymic, date of birth, gender, weight, height, blood and urine test data, health data during the period of participation in the study, data on the amount of the drug administered — to the Study Physician, the clinical study monitor and other representatives of the clinical study Sponsor (at any time of the study and after its termination).

For verification of procedures and/or clinical study data, the original medical records will be directly accessible to monitors, clinical study auditors, representatives of the Local Ethics Committee and the Ethics Council under the Ministry of Healthcare of the Russian Federation, as well as official representatives of the authorized healthcare agencies to the extent permitted by law. However, the confidentiality of this data will not be violated, and the records that identify you will be kept secret and can only be disclosed to the extent permitted by law. When publishing the study results, the confidentiality of your personal data (surname, first name, patronymic, date of birth) will not be violated. This study assumes that medical information is transmitted electronically, and the transmitted data will not contain your personal information or information that allows to identify you other than the code assigned in the study.

By signing this Consent, you become a participant in the clinical study. However, you do not lose any rights that belong to you by law, including the right for qualitative and timely medical care.

If you agree to participate in the study, please sign this document on the last page. The Informed Consent is made in two copies, one of which remains with the Study Physician, and the second you can take with you (in this case, its verified copy).

CONTACT INFORMATION

Keep this document in case you need to read it again later.

Ethics Council of the Ministry of Healthcare of the Russian Federation:

Address and directions: 3 Rakhmanovsky pereulok, Moscow, 127994. The nearest metro stations are Tsvetnoy Bulvar, Trubnaia, and Chekhovskaia.
Ethics Council Chairman — member of the Russian Academy of Sciences, Professor Alexander Grigorvich Chuchalin, contact phone number: +7 (495) 625-44-21.

Study Site
Address and directions

Surname, first name, patronymic of the Study Physician, contact phone numbers

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Surname, first name, patronymic of the Chief Investigator

Local Ethics Committee
Address

Surname, first name, patronymic of the Local Ethics Committee Chair and his/her contact phone

number

The Study Sponsor and the organization conducting the study:
Drugs Technology LLC

Location address:
2a Rabochaia str., bld. 31, room 21, Khimki, 141400, Moscow region
Tel.: +7 (495) 225-62-00, Fax: +7 (495) 225-62-65.
E-mail: info@drugsformulation.ru
Business hours: 9:00 to 18:00 daily, except for weekends and holidays.

INFORMED CONSENT FORM FOR PARTICIPATION IN CLINICAL STUDY

Multicenter Open-Label Randomized Parallel-Group Study of the Efficacy and Safety of TL-FVP-T Compared to Standard Therapy in Patients with Mild to Moderate Coronavirus Disease (SARS-CoV-2/COVID-19)

I, the undersigned,

(Full name)

am informed by the Study Physician

(Full name)

about all aspects of the planned clinical study of the Favipiravir TL-FVP-t drug (Drugs Technology LLC, Russia).

I obtained information on the objectives and nature of the clinical study of the Favipiravir TL-FVP-t, 200 mg film-coated tablets, information on the favipiravir TL-FVP-t drug, its expected efficacy and safety, the benefits and risks of participating in the clinical study, my rights and responsibilities and my rights and responsibilities as a participant in the study.

I am warned about possible adverse events and side effects and about necessary actions in case of unexpected events when using the Favipiravir TL-FVP- drug.

I have had the opportunity to discuss all my questions with the Study Physician, and I am satisfied with the answers I received.

I am informed that I will be included in the study only after I will undergo full examination in accordance with the Study Protocol, and my medical and physical condition will meet the conditions for inclusion in this study.

I voluntarily and knowingly agree to participate in the Favipiravir TL-FVP-t clinical study, and I am informed that I have the right to refuse to participate in the study or at any time and to terminate participating in this study without explanation.

I agree to follow the instructions correctly, voluntarily cooperate with the Study Physician, and immediately inform him/her of any changes in my health. I agree to the use of acceptable, highly effective, and highly protected contraceptive methods described in the Patient's Information Sheet within the time frame specified in the Patient's Information Sheet.

I am informed that if my health is damaged due to direct administration of the study product or medical procedure provided for in the Clinical Study Design, I will be provided with all necessary medical care, the costs of which will be reimbursed by the Absolute Insurance Company LLC. The amount of compensation may be revised if the deterioration of health occurred due to non-compliance with the instructions of the Study Physician.

I am informed that my medical and personal data will be confidential and can only be disclosed to official representatives while maintaining anonymity.

I am informed that my medical and personal data will be transmitted using electronic systems, including digital copies of images (jpeg, pdf, etc.).

I am informed that I have the right to access information about my health status and results of all investigations and tests.

I have been notified of the need to comply with anti-epidemic measures and accept the conditions of transportation for conducting the study procedures.

I am informed that there are no monetary payments for this study.

By signing this Informed Consent Form, I give my permission to access the medical data obtained in the clinical study of the Favipiravir TL-FVP-t to the drug developer institution, organization responsible for conducting the clinical study, representatives of the Ethics Council under the Ministry of Healthcare of the Russian Federation and the Local Ethics Committee, and official representatives of the Ministry of Healthcare of the Russian Federation.

I signed and dated the Patient's Information Sheet along with the Informed Consent Form on 24 pages in 2 copies; I received 1 copy of the signed and dated Patient's Information Sheet on

24 pages:

Patient's signature:
Date (dd/mm/yyyy): _____ Time (in 24-hour format):
Patient's surname and initials (in block letters):

I, the undersigned, confirm that the Patient signed this document has been provided with the detailed explanation of all aspects of the study, and that the Patient understands what this study is about, as well as the risks and benefits associated with his/her participation in this clinical study.

Investigator's signature:
Date (dd/mm/yyyy): _____ Time (in 24-hour format):
Investigator's surname and initials (in block letters):

Executed in 2 copies: 1 copy for the Patient, 1 copy for the Investigator.