Clinical study name: Open randomized multicenter comparative study on the efficacy and safety of Areplivir film-coated tablets (PROMOMED RUS LLC, Russia) in patients hospitalized with COVID-19

Investigational product: Areplivir film-coated tablets (PROMOMED RUS LLC, Russia)

Study indication: COVID-19.

Study design: open randomized multicenter comparative.

Study sponsor: PROMOMED RUS LLC, Russia

Study protocol: No. FAV052020

NCT number: NCT04542694

Date and version of the protocol: version 2.0 of 10.06.2020

Clinical development phase: III

Study period:

Q2 2020 - Q4 2020

Sponsor's responsible person: Director General of the management company of PROMOMED RUS, LLC, Smagin Maxim Yurievich

This study, including archiving of key study documents, is performed in accordance with the ICH E6 Good Clinical Practice recommendations and the Rules of Good Clinical Practice approved by the Eurasian Economic Commission.

2. OVERVIEW (SYNOPSIS)

<table>
<tr><td>Sponsor:
PROMOMED RUS LLC, Russia</td><td rowspan="3">Separate study table relating to part of the dossier

Volume:
Pages:</td><td rowspan="3">(For use by national authorized bodies only)</td></tr>
<tr><td>Name of finished product:
Areplivir, film-coated tablets</td></tr>
<tr><td>Active ingredient:
Favipiravir</td></tr>
<tr><td colspan="3">Protocol No.: FAV052020
Clinical study name:
Open randomized multicenter comparative study on the efficacy and safety of Areplivir film-coated tablets (PROMOMED RUS LLC, Russia) in patients hospitalized with COVID-19</td></tr>
<tr><td colspan="3">Investigators, Study site:
The study is conducted at five research centers in the Russian Federation. Detailed information is provided in Section 6.</td></tr>
<tr><td colspan="3">Publication:
A list of scientific papers and publications relevant to this study will be presented in the Clinical Study Final Report.</td></tr>
<tr><td>Study period:
Q2 2020 – Q4 2020</td><td colspan="2">Drug development phase: III</td></tr>
<tr><td colspan="3">Study purpose:
Assess the efficacy and safety of Areplivir versus standard therapy in patients hospitalized with COVID-19.
Study objectives:
• Assess the efficacy of Areplivir versus standard therapy in patients hospitalized with COVID-19.
• Assess the safety of Areplivir versus standard therapy in patients hospitalized with COVID-19.</td></tr>
<tr><td colspan="3">Methodology:
an open randomized multicenter comparative study on the efficacy and safety of Areplivir in patients hospitalized with COVID-19.</td></tr>
<tr><td colspan="3">Number of patients (planned and included in the analysis):
The study will randomize 200 patients. Given the possible non-inclusion of patients at the screening stage, the maximum number of patients to sign the Informed Consent Form in the Patient Information Leaflet and to participate in screening can be no more than 210 people.
This interim report is based on data on 80 patients (40 patients in the Areplivir arm + 40 patients in the standard therapy arm).
Patients who met the inclusion criteria and did not meet the non-inclusion criteria were randomized to 2 groups (treatment arms) in a 1:1 ratio:
Arm 1 (n=100) receives the study drug Areplivir film-coated tablets:
on day 1 of therapy - 1600 mg (8 tablets) 2 times a day;
on days 2-14 of treatment - 600 mg (3 tablets) 2 times a day.
The drug is taken orally every 12 hours, swallowing whole tablet without chewing and washing down with a glass of water. The course of treatment is 14 days.</td></tr>
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Name of finished product: Areplivir, film-coated tablets		
Active ingredient: Favipiravir		

The test drug is administered in hospital setting under supervision of a clinical investigator. The test drug is not handed over to the patient.

Arm 2 (n=100) patients receive standard therapy prescribed in accordance with the recommended treatment regimens included in the Interim Guidelines for the prevention, diagnosis and treatment of new coronavirus infection (COVID-19) approved by the Russian Ministry of Health (revision 6 dated 28.04.2020, or current revision at the time of patient enrollment) by decision of the investigator and taking into account the availability of drugs at the study site.

Standard therapy is administered in hospital setting.

Discharge of patients from a hospital is carried out in accordance with the local practice of the study site in compliance with the current sanitary and epidemiological regime.

Diagnosis and key inclusion criteria:

The study is conducted with the participation of male and female patients aged 18 to 80 years inclusive, hospitalized with COVID-19.

Inclusion criteria:

1. Signing and dating of the Informed Consent Form of the Patient Information Leaflet (PIL) by patients.
2. Men and women aged 18 to 80 years inclusive at the time of signing the Informed Consent Form in PIL.
3. No difficulty with oral medication (e.g. swallowing disorder).
4. Patient diagnosed with "Coronavirus infection caused by SARS-CoV-2 (confirmed)[1], medium severity form*" established in accordance with the Interim Guidelines of the Russian Ministry of Health for the prevention, diagnosis and treatment of a new coronavirus infection (COVID-19), (revision 6 of 28.04.2020).
   **Medium severity form: fever above 38 °C, BR above 22/min, dyspnea during exercise, pneumonia (confirmed by lung CT), SpO2 < 95%, CRP serum level above 10 mg/l.*
5. Patient should be hospitalized no more than 48 hours before the start of the study therapy.
6. Positive PCR result for presence of SARS-CoV-2 RNA at screening phase *(results obtained within 7 days prior to screening are appropriate)*.
7. Patient's consent to use reliable contraceptive methods throughout the study and within 1 month for women and 3 months for men after its completion. Persons eligible for participation in the study:
   - Women who have a negative pregnancy test and use the following contraceptives: barrier method (condom or occlusive cap (diaphragm or cervical/vaulted cap)) or double barrier method of contraception (condom or occlusive cap (diaphragm or cervical/vaulted cap) plus spermicide (foam/gel/film/cream/suppository)). Women incapable of childbearing may also participate in the study

[1] Positive PCR result for SARS-CoV-2 RNA.

(with past history of: hysterectomy, tubal ligation, infertility, menopause more than 1 year).

or

– men with preserved reproductive function who use barrier contraceptives, as well as men with infertility or vasectomy in the past medical history.

Non-inclusion criteria:

1. Hypersensitivity to favipiravir and/or other components of the study drug.
2. Impossibility of CT procedure (for example, gypsum dressing or metal structures in the field of imaging).
3. The need to use drugs from the list of prohibited therapy.
4. Need for treatment in the intensive care unit.
5. Impaired liver function (AST and/or ALT ≥ 2 UNL and/or total bilirubin ≥ 1.5 UNL) at the time of screening.
6. Impaired kidney function (creatinine clearance according to Cocroft-Gaulth formula less than 45 ml/min) at the time of screening.
7. Positive testing for HIV, syphilis, hepatitis B and/or C.
8. Chronic heart failure FC III-IV according to New York Heart Association (NYHA) functional classification.
9. Malabsorption syndrome or other clinically significant gastrointestinal disease that may affect absorption of the study drug (non-correctable vomiting, diarrhea, ulcerative colitis, and others).
10. Malignancies in the past medical history.
11. Alcohol, pharmacological and/or drug addiction in the past medical history and/or at the time of screening.
12. Schizophrenia, schizoaffective disorder, bipolar disorder, or other history of mental pathology or suspicion of their presence at the time of screening.
13. Severe, decompensated or unstable somatic diseases (any disease or condition that threaten the patient's life or impair the patient's prognosis, and also make it impossible for him/her to participate in the clinical study).
14. Any history data that the investigating physician believes could lead to complication in the interpretation of the study results or create an additional risk to the patient as a result of his/her participation in the study.
15. Patient's unwillingness or inability to comply with procedures of the Study Protocol (in the opinion of physician investigator).
16. Pregnant or nursing women or women planning pregnancy.
17. Participation in another clinical study for 3 months prior to inclusion in the study.
18. Other conditions that, according to the physician investigator, prevent the patient from being included in the study.

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Active ingredient: Favipiravir		

Investigational medicinal product, dose and mode of administration, batch number:

Investigational medicinal product:

Areplivir, film coated tablets (PROMOMED RUS LLC, Russia), batch 010520 (expiry date 06.2022).

Patients in **Arm 1** take the investigational product Areplivir, film coated tablets:

on Day 1st of treatment - 1600 mg (8 tablets) 2 times a day;

on days 2-14 of treatment - 600 mg (3 tablets) 2 times a day.

The drug is taken orally every 12 hours, swallowing whole tablet without chewing and washing down with a glass of water. The course of treatment is 14 days.

The test drug is administered in hospital setting under supervision of a clinical investigator. The test drug is not handed over to the patient.

Duration of the study:

The total duration of the study for the patient is not more than 31 days, of which the screening period is not more than 2 days.

Visits:

Visit 0 (screening, not more than 2 days);

Visit 1 (randomization, day 1)*;

Visit 2 (day 5);

Visit 3 (day 10);

Visit 4 (day 15)**;

Visit 5 (day 21±1)***;

Visit 6 (study completion, day 28±1)***.

** Visit 1 may coincide with Visit 0.*

*** If a patient is discharged from hospital at an earlier date, the visit will be conducted at the time of discharge (for Arm 2 patients).*

**** If a patient is discharged from hospital at an earlier date, then this patient does not need to visit the study site. Fatalities and serious adverse events (SAE) will be followed-up through telephone contact with the patient.*

Discharge of patients from a hospital is carried out in accordance with the local practice of the study site in compliance with the current sanitary and epidemiological regime.

Efficacy criteria:

The efficacy of therapy is assessed using the following endpoints:

Primary efficacy criterion:

- Time (in days) to improvement in clinical status by categorical ordinal scale of clinical status improvement.
- Rate of clinical status improvement by categorical ordinal scale of clinical status improvement by 2 or more categories at Visit 3.

Secondary efficacy criteria:

- Percentage of patients with elimination* of COVID-19 according to PCR data at Visit 3.
- Time (in days) to end of fever (body temperature < 37.2 ° C for 3 consecutive days without antipyretic medication).
- Assessment of lung injury according to CT data at Visits 4, 5 and 6.
- Percentage of patients transferred to intensive care unit.
- Percentage of cases with non-invasive lung ventilation.
- Percentage of cases with mechanical lung ventilation.
- Incidence of fatal cases.

** Elimination of the virus is defined as two negative laboratory results for the presence of SARS-CoV-2 RNA obtained at an interval of 24 hours.*

Safety criteria:

- Total number of adverse events (AEs) stratified by severity and incidence;
- Incidence of adverse drug reactions;
- Incidence of serious adverse events (SAEs) associated with the use of the study drug/standard therapy;
- Percentage of patients with at least one AE;
- Percentage of patients who discontinuation treatment due to AE.

Statistical methods:

Justification of sample size

The study will randomize 200 patients. Given the possible non-inclusion of patients at the screening stage, the maximum number of patients to sign the Informed Consent Form in the Patient Information Leaflet and to participate in screening will be no more than 210 people.

At the first stage, 40 patients are included in each study arm and the most sensitive efficacy criterion of the two selected is determined, or additional analysis is carried out to select the criterion from secondary ones. Given 40 patients in each of the study arms, the sensitivity of the study to confirm 15% superiority by incidence, supposing the expected response 80% in the test drug arm, will exceed 45%.

Two Independent Proportions (Null Case) Power Analysis

Numeric Results of Tests Based on the Difference: P1 - P2

H0: P1 - P2 ≥ 0. H1: P1 - P2 = D1 < 0. Test Statistic: Z test with pooled variance

Power	Sample Size Grp 1 N1	Sample Size Grp 2 N2	Prop|H1 Grp 1 or Trtmnt P1	Prop Grp 2 or Control P2	Diff if H0 D0	Diff if H1 D1	Target Alpha	Actu Alph
0.4553	40	40	0.6500	0.8000	0.0000	-0.1500	0.0500	0.050

Said statistical power (45%) is acceptable for exploratory stages of the studies aimed to select the duration for endpoint monitoring and to select the endpoint at the second (confirming) stage.
In case change of the planned endpoints, separate adjustment will be made for the multiplicity of comparisons and the required number will be recalculated at the second stage.
The total planned number of patients before the completion of the first stage will be 100 patients in each of the arms.
The estimated calculation until the data of the first stage are obtained is as follows. Given the available data from Chinese researchers, 15% superiority of favipiravir therapy over standard therapy without favipiravir is allowed in relation to the rate of improvement by 2 or more categories on categorical scale by day 10 of treatment. The adopted higher response to standard therapy of 70% is associated with a longer duration relative to the Chinese study (10 days instead of 7 days).

An RCT enrolling patients within 12 days of symptom onset found that favipiravir was superior to arbidol in terms of the clinical recovery rate at day 7 in patients with mild illness (62 [56%] of 111 with arbidol vs 70 [71%] of 98 with favipiravir), but not in those with critical illness (0 vs 1 [6%]). (Chen C. Huang J. Cheng Z. et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020; (published online April 15.) (preprint).

Tests for Two Proportions
Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance
H0: P1 - P2 ≥ 0 vs. H1: P1 - P2 = D1 < 0.

Target Power	Actual Power*	N1	N2	N	P1	P2	D1	Alpha 0.80
0.80170	107	107	214	0.6500	0.8000	-0.1500	0.0500	

* Power was computed using the normal approximation method.

Thus, the minimum number of subjects required for a clinical study is 200 with 100 subjects randomized to each of the two groups.

Statistical analysis

The purpose of statistical analysis is to prove superiority of Areplivir, film-coated tablets (PROMOMED RUS LLC, Russia), over standard therapy in patients hospitalized with COVID-19.
The results of statistical analysis, descriptive statistics and illustrative tables, graphs, lists will be presented in interim and final clinical study reports.

General methods of analysis

Statistical analysis is carried out in accordance with the requirements of the Guideline for Good Clinical Practice (ICH 9) approved by the Eurasian Economic Commission, and other applicable requirements and laws.
Statistical data processing is done by staff not involved in the management of patient participating in the study to create conditions for independent evaluation of the findings.

Sponsor: PROMOMED RUS LLC, Russia **Name of finished product**: Areplivir, film-coated tablets **Active ingredient**: Favipiravir	Separate study table relating to part of the dossier Volume: Pages:	(For use by national authorized bodies only)

Certified statistical software with validated algorithms is used to perform statistical analyses and to ensure proper documenting (StatSoft Statistica 10.0., IBM SPSS Statistics 22).

Descriptive statistics are provided for all efficacy and safety indicators collected during the study. Continuous (quantitative) data are presented using the number of observations, arithmetic mean value, confidence interval (CI) 95% for mean, standard (rms) deviation, median, interquartile span (25th and 75th centiles), minimum and maximum.

Ordinal, categorical and qualitative data are presented as absolute frequencies (number of observations), relative frequencies (percent) and 95% CI (unless otherwise stated).

The check for normality of distribution is carried out by one of the generally accepted methods (***Shapiro-Wilk*** test, ***Kolmogorov-Smirnov*** test). For non-Gaussian distributions, non-parametric methods will be used to compare efficacy and safety indicators.

Significance levels and confidence intervals are calculated as bilateral, the statistical significance of differences is two-sided by default and refers to significance level 0.05 (unless specified otherwise).

Analysis of demographics and other source data

Demographic data (age, sex) and baseline condition data are presented along with summaries in the form of absolute frequencies (number of observations), relative frequencies (percent), or using the arithmetic mean, confidence interval (CI) 95% for mean, standard deviation, median, interquartile span (25th and 75th centiles), minimum and maximum, depending on the type of variable.

To test the study group homogeneity hypothesis, at the baseline zero hypotheses (no differences between groups) are tested with Student's ***t-test*** (for interval measures with normal distribution in the study population), ***Mann-Whitney's test*** (for ordinary measures or for interval measures with distribution different from normal) or ***Fisher's exact test*** and χ^2 test (for qualitative indicators).

If statistically significant differences between study arms are found, the magnitude of differences is estimated using confidence intervals.

Analysis of primary efficacy parameter

Primary efficacy endpoints:

One of the primary efficacy parameters is the time (in days) to improvement of patient's clinical status according to the categorical ordinal scale of clinical improvement.

- Time (in days) to improvement in clinical status on a categorical ordinal scale of clinical improvement.

To compare the primary efficacy indicator between arms, the ***Student's t-test*** for independent samples is used. If the necessary assumptions about the normality of distribution of this indicator are not met, the non-parametric ***Mann-Whitney test will be used.*** Also, the ***Kaplan-Meier technique*** and compilation ***survival tables can be used as descriptive methods for studying this efficiency parameter. Gehan-Wilcoxon test, Cox-Mentel test*** or ***Log-Rank test*** can be used to compare the time (in days) to improve the clinical status of the patient between the study groups.

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The proof of the superiority hypothesis is the establishment of a statistically significant time difference (in days) before patient's clinical status improvement between the Areplivir arm and the standard therapy arm.

The next primary efficacy parameter is the percentage of patients who achieved an improvement in clinical status according to the categorical ordinal scale of clinical improvement by 2 or more categories at Visit 3.

- Rate of clinical status improvement by categorical ordinal scale of clinical status improvement by 2 or more categories at Visit 3.

For the analysis of this parameter, an intergroup comparison of percentages is used using a two-sided version of the ***Fischer's exact test*** (or a two-sided version of the χ^2 (chi-square) test, if all the expected values in the cells of the contingency table for this analysis are 5 or more). The percentage of patients who achieved improvement in clinical status on a categorical ordinal clinical improvement scale by 2 or more categories at Visit 3 is presented with a two-sided 95% confidence interval by treatment arm. Hypothesis testing is performed at a 5% significance level. The difference in proportion between treatment arms and the 95% bilateral confidence interval for the difference in proportion calculated by ***Newcomb-Wilson technique is presented.***

The proof of the hypothesis of superiority of Areplivir film-coated tablets (PROMOMED RUS LLC, Russia) is the establishment of a statistically significant difference in the proportions of patients who achieved an improvement in clinical status according to the categorical ordinal scale of clinical improvement by 2 or more categories at Visit 3, between Areplivir arm and standard therapy arm.

Analysis of the primary efficacy parameter is performed in the ITT population (main analysis), and in the PP population (additional analysis). A summary of all efficacy indicators is provided.

Analysis of secondary efficacy parameters

The following efficacy parameters in the protocol are represented by qualitative values:

- Percentage of patients with elimination * COVID-19 according to PCR analysis at Visit 3.
- Percentage of patients transferred to intensive care unit.
- Percentage of cases with non-invasive lung ventilation.
- Percentage of cases with mechanical lung ventilation.
- Incidence of fatal cases.
- Assessment of lung injury according to CT data at Visits 4, 5 and 6.**

** Virus elimination is defined as two negative laboratory tests for SARS-CoV-2 RNA obtained at intervals of 24 hours.*

***An "empirical" visual scale will be used to estimate changes in lung involvement from CT data.*

For the analysis of these parameters, an intergroup comparison of shares is used using a two- sided version of the ***Fischer's exact test*** (or a two-sided version of the χ^2 (chi-square) test, if all the expected values in the cells of the contingency table for this analysis are 5 or more).

The protocol also includes the following endpoint:

- Time (in days) to fever disappearance (body temperature < 37.2 ° C for 3 consecutive days

without antipyretic medication).

For the secondary efficacy parameter "time (in days) to fever disappearance (body temperature < 37.2 °C for 3 consecutive days without antipyretic drugs), a comparison between arms is made using the ***Student's t-test*** or the ***Mann-Whitney test*** (depending on the nature of the distribution of quantitative indicators). Also, ***Kaplan-Meier technique*** and the construction of ***survival tables*** can be used as descriptive methods of study. The ***Gehan-Wilcoxon test, the Cox-Mentel test*** or ***the Log-Rank test*** can be used to compare the time (in days) to the disappearance of fever in the study arms.

Analysis of secondary efficacy parameters is performed in the ITT population (main analysis), and in the PP population (additional analysis).

In case of developing acute respiratory distress syndrome and the need to switch patient to mechanical ventilation, the investigational drug is canceled, but the patient is not withdrawn from the study. Patients are under follow-up until Visit 6, the data are taken into account to assess efficacy in the ITT population.

Safety Analysis

Safety criteria

Safety assessment includes the following parameters:

- Total number of adverse events (AEs) stratified by severity and incidence;
- Incidence of adverse drug reactions;
- Incidence of serious adverse events (SAEs) associated with the use of the study drug/standard therapy;
- Percentage of patients with at least one AE;
- Percentage of patients who discontinuation treatment due to AE.

Cross-group comparisons are performed for all safety indicators. The comparison of groups on frequency indicators is carried out using the ***Fischer's exact test*** or the χ^2 (chi-square) test, depending on the expected value in the cells of contingency table. For quantitative laboratory results, comparisons between groups at relevant visits are made using the ***Student's t-test*** or the ***Mann-Whitney test*** (depending on the nature of the distribution of quantitative indicators).

For analysis of all safety parameters the safety population was used.

In case of developing acute respiratory distress syndrome and the need to switch patient to mechanical ventilation, the investigational drug is canceled, but the patient is not withdrawn from the study. Patients are under follow-up until Visit 6, the data are taken into account to assess efficacy in the ITT population.

Interim analysis

In the first stage, 40 patients were included in each group (study arm). Given 40 patients in each of the study arms, the sensitivity of the study to confirm 15% superiority by incidence, supposing the expected response 80% in the test drug arm, will exceed 45%.

Two Independent Proportions (Null Case) Power Analysis
Numeric Results of Tests Based on the Difference: P1 - P2
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0.4553	40	40	0.6500	0.8000	0.0000	-0.1500	0.0500	0.050

Said statistical power (45%) is acceptable for exploratory stages of the studies aimed to select the duration for endpoint monitoring and to select the endpoint at the second (confirming) stage.
In case change of the planned endpoints, separate adjustment will be made for the multiplicity of comparisons and the required number will be recalculated at the second stage.

Significance level used in the clinical study

Significance levels and confidence intervals are calculated as bilateral, the statistical significance of differences is two-sided by default and refers to significance level 0.05 (unless specified otherwise).

Stopping criteria for the clinical study

This protocol does not contain any statistical criteria for stopping the clinical study.

Accounting for missing data, data not to be analyzed and questionable data

In the case of for missing data, data not to be analyzed and questionable data, appropriate statistical analysis methods are applied. Patients who will not be able to complete the course of therapy according to the protocol are included in the analysis of the main endpoint using the last observation carried forward (LOCF) method. This means that measures taken as criteria for efficacy will be assessed for such patients at the time of dropping out of the study.

Procedures for reporting any deviations from the original statistical plan

All deviations from the final version of the statistical analysis plan will be described and substantiated in the final clinical study report.

Population analysis

The statistical analysis includes the following patient populations:

1. ***Safety population***: patients who have received at least one dose of the study drug and for whom there is an assessment of condition and/or AE for at least one time point after administration.
2. ***Population of all patients included in the study (Intent-to-treat, ITT)***: patients who received at least one dose of the drug in the study and for whom there is data for at least one visit after the baseline (Visit 0).
3. ***Population of patients who completed the study as per the Protocol (Per protocol, PP)***: patients who have completed the study as per the Study Protocol.

In case of developing acute respiratory distress syndrome and the need to switch patient to mechanical ventilation, the investigational drug is canceled, but the patient is not withdrawn

from the study. Patients are under follow-up until Visit 6, the data are taken into account to assess efficacy in the ITT population.