Clinical Trial Protocol

A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase III Clinical Study Evaluating the Efficacy and Safety of Favipiravir in the Treatment of patients with COVID-19-Moderate Type

Protocol number: HS216C17-PHASE III

Version: V1.1 dated 27 Mar 2020 *based on China SIT V1.0 dated 17 Feb 2020*

Date: March 27, 2020

Sponsor: ASST FATEBENEFRATELLI SACCO

CRO: Opera CRO Srl, a TIGERMED company

Confidentiality Statement

Protocol Signature Page

I agree to:

- Conduct this study in compliance with the Protocol, the GCP and other applicable laws and regulations.
- Appropriately store all the materials and information provided by ASST FATEBENEFRATELLI SACCO in accordance with the confidentiality requirements, and specifically indicate that these materials and information are confidential when submitting them to the Independent Review Board (IRB) or independent Ethics Committee (IEC).

I have read the Protocol in its entirety, and agree with all its contents.

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Synopsis

Protocol number	HS216C17-PHASE III
Protocol title	A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase III Clinical Study Evaluating the Efficacy and Safety of Favipiravir in the Treatment of patients with COVID-19-Moderate Type
Version	V1.1 dated 27 Mar 2020 *based on China SIT V1.0 dated 17 Feb 2020*
Date	March 27, 2020
Sponsor	ASST FATEBENEFRATELLI SACCO
Clinical trial phase	III
Indication	COVID-19-Moderate type
Objectives	**Primary objective:** To evaluate the efficacy of Favipiravir combined with supportive care for adult patients with COVID-19-Moderate type. **Secondary objective:** To evaluate the safety of Favipiravir combined with supportive care for adult patients with COVID-19-Moderate type.
Study design	This is a multi-center, randomized, double-blind, placebo-controlled (1:1) clinical study to explore the efficacy and safety of Favipiravir in the treatment of adult subjects with COVID-19-Moderate type. Subjects within 10 days of COVID-19 onset will be screened, and be

	randomized as early as possible within 24 hours following screen success. It is planned to randomize 256 subjects in an 1:1 ratio. Subjects in the test group will receive supportive care recommended in the current guidelines+Favipiravir, and subjects in the control group will receive supportive care recommended in the current guidelines+placebo control; the efficacy and safety of Favipiravir versus the placebo in the treatment of COVID-19-Moderate type will be compared. Supportive care is to be selected by the local investigator according to the practice, referring to Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol. Supportive care may not include any antiviral agents other than the study drug, e.g., α- interferon, lopinavir/ritonavir, and ribavirin. Those subjects who have received treatment with antiviral agents can be screened and enrolled provided that these agents are discontinued after enrolment and supportive care is selected by the local investigator according to the practice.
Number of subjects	This study is concerned with a public health emergency. Taking into account the observed clinical recovery status of adults patients with COVID-19-Moderate type treated with the antiviral therapies recommended in the current guidelines, it is estimated that the median time to clinical recovery in the control group would be approximately 14 days, and the addition of test drug could reduce this time to within 9 days (i.e., HR≥1.56); at the two-sided significance level of 0.05 and with an over 80% power, approximately 226 subjects (randomized 1:1 to the test or control group) will be required; considering the size of randomization block and the 10% dropout rate, a total of 256 subjects will actually be required to be enrolled. At least 100 subjects will be enrolled in Italy. This number can be increased in case of elevated monthly recruitment rate in Italy, because the study will use competitive enrolment.

Number of study sites	About 16 sites (of which 8 planned in Italy).
Study duration	From obtaining EC approval until the estimated sample size has been achieved or the epidemic has ended; 3 months as estimated
Eligibility criteria	Inclusion criteria: 1. Voluntarily participating in the clinical study; fully understanding and being fully informed of the study and having signed the Informed Consent Form (ICF); willingness and capability to complete all the study procedures; 2. Age 18-75 years (inclusive) at the time of signing ICF; 3. Being confirmed with COVID-19-Moderate type according to Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol. Based on comprehensive analysis and judgement taking into account both the epidemiological history and clinical manifestations, the diagnosis is to be confirmed for suspected cases/clinically diagnosed cases with all of the following etiological evidences: - Positivity in RT-PCR 2019-nCov test on respiratory tract specimens; - High homology with known gene sequence of 2019-nCov in viral gene sequencing on respiratory tract specimens; Note: The above criterion would be subject to any update of the Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol. In case any new etiologically detection methods/criteria or any new detectable specimens become available after confirmed diagnosis, the new methods or new specimens may or may not be used at the discretion of the investigator.

Note: Sputum specimen is preferred for RT-PCR test of 2019-nCov nucleic acid; the specific type of respiratory tract specimen (e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions) is to be selected based on the conditions of the local laboratory.

The type of specimen and detection method for 2019-nCov should remain consistent for the same subject receiving study treatment.

4. Chest imaging (CT as first option or X-ray if CT not possible)-documented pneumonia; if CT cannot be performed, Pneumonia confirmed by X-ray may be used. The method of chest imaging pneumonia diagnosis must be consistent all through the study period.

5. Patients with pyrexia (axillary ≥37℃ or oral ≥37.5℃, or axillary or rectal≥38℃) or either respiratory rate >24/min and <30/min or cough; For not hospitalized patients, the Investigator should maintain the detection method consistent all through the study period. In addition, the Investigator should maintain the data collection and quality compliant with GCP requirements.

6. The interval between symptoms onset and randomization is no more than 10 days; symptoms onset is primarily based on pyrexia, and can be based on cough or other related symptoms for patients without experiencing pyrexia following onset;

7. For female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pre-treatment serum or urine pregnancy test. Menopause is defined as amenorrhea for at least 12 months without other medical cause, with the following age-specific requirements:

- For female subjects aged <50 years: menopause for at least 12 months following withdrawal of exogenous hormonal therapy, with LH or FSH within the post-menopausal ranges, or having undergone any contraceptive surgery (bilateral oophorectomy or hysterectomy);
- For female subjects aged ≥50 years: menopause for at least 12 months following withdrawal of exogenous hormonal therapy, or having undergone radiotherapy-induced oophorectomy with amenorrhea>1

year, or having undergone chemotherapy-induced menopause with amenorrhea>1 year, or having undergone any contraceptive surgery (bilateral oophorectomy or hysterectomy).

8. Eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment;

9. Not participating in any other interventional drug clinical studies before completion of the present study.

Exclusion criteria:

1. Where, in the opinion of the investigator, participation in this study will not be in the best interest of the subject, or any other circumstances that prevent the subject from participating in the study safely;

2. Refractory nausea, vomiting, or chronic gastrointestinal disorders, inability to swallow the study drug or having undergone extensive bowel resection which may affect adequate absorption of Favipiravir;

3. Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN;

4. Gout/history of gout or hyperuricemia (above the ULN);

5. Oxygen saturation (SPO2)≤93% or arterial oxygen partial pressure (PaO2)/ fraction of inspired O2 (FiO2)≤300 mmHg;

6. Known allergy or hypersensitivity to Favipiravir;

7. Known severe renal impairment [creatinine clearance (CcCl) <30 mL/min] or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis;

CcCl is to be calculated by the following Cockcroft-Gault formula only when the serum creatinine is＞1.5×ULN:

For females:

$$CrCl = \frac{(140 - Age(years)\ X\ Weight\ (kg) X\ 0.85}{72\ X\ Serum\ Cr\ (\frac{mg}{dL})}$$

For males:

$$CrCl = \frac{(140 - Age(years)\ X\ Weight\ (kg) X\ 1.0}{72\ X\ Serum\ Cr\ (\frac{mg}{dL})}$$

8. Possibility of the subject being transferred to a non-study hospital within 72h;

9. Pregnant or lactating women;

10. Having used Favipiravir or participated in any other interventional drug clinical study within 30 days prior to first dose of study drug.

Note: Considering that COVID-19 requires immediate treatment, absence of severe hepatic/renal disorders (e.g., cirrhosis, long-term dialysis) in the medical record can be used as an evidence for eligibility determination. It is recommended that hepatic function and creatinine be examined whenever possible.

Criteria for discontinuation:

Investigator-determined discontinuation

Discontinuation from study refers to where the investigator determines that the subject should discontinue from study/study treatment when the subject has fulfilled any circumstance that makes it no longer appropriate for the subject to continue participating in the study, including:

1. Erroneous inclusion despite failure of inclusion criteria;
2. Where the subject has experienced some comorbidities, complications, or worsening of conditions that makes it no longer appropriate for the subject to continue participating in the study, e.g., laboratory abnormalities, allergic reactions, bronchospasm, severe liver injury, or

	grade III acute kidney injury (AKI) that in the investigator's opinion requires discontinuation of study treatment. 3. Where the subject has received any other treatment than the study treatment which may interfere with the study evaluation; 4. Where the investigator considers that continuation would be detrimental to the subject's wellbeing (e.g., pregnancy); 5. Where the subject has experienced any severe/intolerable AE or SAE making it no longer appropriate for the subject to continue; 6. Poor subject compliance that may interfere with efficacy and/or safety evaluation. Subject's voluntary discontinuation from study In case the subject is no longer willing to participate in the study, as specified in the ICF, he/she has the right to prematurely discontinue from the study at any time during the study; or the subject may not explicitly request for discontinuation but is lost to follow-up as he/she stops receiving any study treatment/procedure, this also constitutes a "discontinuation" (also known as "dropout"). The reason for discontinuation should be collected and recorded whenever possible, e.g., feeling intolerable to some adverse reactions; impossibility to continue study for other reasons; loss to follow-up without providing the reason.
Test drug	**Generic name:** Favipiravir Tablets **Brand name**: Not available **Chemical name:** 6-fluoro-3-hydroxypyrazine-2-carboxamide **Strength:** 200 mg/tablet **Dosage form:** Tablet **Storage conditions:** Store at room temperature **Manufacturer:** Zhejiang Hisun Pharmaceutical Co. Ltd.

	Route of administration: Oral **Dosage and method of administration:** Day 1: 1800mg, BID; Day 2 and thereafter: 600mg, TID, for a maximum of 14 days. Where the subject has experienced an adverse event related to liver injury of grade≥3 (NCI CTCAE v5.0), the dose is to be reduced to 600mg BID. It is at the discretion of the investigator whether or not to perform dose reduction based on how the subject is benefiting from study treatment. The subject should be discontinued from treatment if he/she re-experiences any adverse event related to liver injury of grade≥3 after dose reduction.
Placebo control	**Strength:** 200 mg/tablet **Dosage form:** Tablet **Storage conditions:** Store at room temperature **Manufacturer:** Zhejiang Hisun Pharmaceutical Co. Ltd. **Route of administration:** Oral **Dosage and method of administration:** Day 1: 1800mg, BID; Day 2 and thereafter: 600mg, TID, for a maximum of 14 days. Where the subject has experienced an adverse event related to liver injury of grade≥3 (NCI CTCAE v5.0), the dose is to be reduced to 600mg BID. It is at the discretion of the investigator whether or not to perform dose reduction based on how the subject is benefiting from study treatment. The subject should be discontinued from treatment if he/she re-experiences any adverse event related to liver injury of grade≥3 after dose reduction.
Study procedures	See the Study Flow Chart.
Efficacy variables	**Primary efficacy variable:** 1. Time from randomization to clinical recovery

Defined as: The duration from start of treatment (Favipiravir or placebo) to normalization of pyrexia, respiratory rate and SPO_2 and relief of cough (where there are relevant abnormal symptoms at enrolment) that is maintained for at least 72h.

Criteria for normalization or relief:

- Pyrexia (body temperature):axillary≤36.9℃，or oral≤37.4℃，or rectal or axillary≤37.9℃;
- Respiratory rate:≤24/min without oxygen inhalation;
- SPO2:>94% without oxygen inhalation;
- Cough: Subject-perceived improvement or resolution of cough.

Secondary efficacy variables:

1. Time from randomization to negativity in RT-PCR nucleic acid test for 2019-nCov within 28 days of randomization;
2. Incidence of deterioration/aggravation of pneumonia (defined as SPO_2≤93% or PaO_2/FiO_2 ≤300 mmHg or distressed RR≥30/min without oxygen inhalation and requiring oxygen therapy or more advanced breath support) within 28 days of randomization;
3. Time from randomization to resolution of pyrexia (defined the same as for the primary efficacy variable; applicable to subjects with pyrexia at enrolment) within 28 days of randomization;
4. Time from randomization to relief of cough (defined the same as for the primary efficacy variable; applicable to subjects with cough at enrolment) within 28 days of randomization;

   It is recommended that the severity of cough be graded as per NCI-CTCAE v5.0:

   - Mild: Requires non-prescription treatment;
   - Moderate: Requires medication treatment; limits instrumental activities of daily living;

	- Severe: Limits self-care activities of daily living 5. Time from randomization to relief of dyspnoea (defined as subject-perceived improvement or resolution of dyspnoea; applicable to subjects with dyspnoea at enrolment) within 28 days of randomization; 6. Rate of auxiliary oxygen therapy or non-invasive ventilation within 28 days of randomization; 7. ICU admission rate within 28 days of randomization; 8. All-cause mortality within 28 days of randomization.
Safety variables	Post-treatment safety evaluation indicators include laboratory tests, vital signs, physical examinations, 12-lead ECG and AE evaluation, etc. Frequency and severity of AEs will be determined as per NCI-CTCAE v5.0.
Statistical analysis	The specific statistical analysis methods will be specified in and subject to the final Statistical Analysis Plan (SAP). **Analysis sets:** Full Analysis Set: A set consisting of as many randomized subjects meeting the Intent-to-Treat (ITT) principle as possible. Only the randomized subject who have violated any key inclusion/exclusion criteria, have not received any study treatment and for whom no safety, efficacy or 2019-nCov nucleic acid test data are available after randomization will be removed. Per-protocol Set (PPS): A set consisting of subjects in the FAS who have not had any protocol violation that may interfere with efficacy evaluation. Safety Set (SS): A set consisting of all the subjects who have received at least 1 dose of study treatment. **General rules:** Statistical analyses will be performed using SAS 9.4 (or above) software. Continuous variables will be described by mean, standard deviation, median, minimum, and maximum. Categorical variables will be described by number

and percentage of subjects in each category. t-test or Wilcoxon rank-sum test (depending on the data distribution pattern) will be used for inter-group comparison of continuous variables; chi-square test or Fisher exact test (where chi-square test does not apply) will be used for inter-group comparison of categorical variables; Wilcoxon rank-sum test or CMH test will be used for rank data. Unless otherwise specified, all the statistical analyses will be two-sided, and $p<0.05$ (two-sided) would indicate a statistically significant difference in the variable tested.

Subjects disposition:

Subjects disposition will be described for all the subjects who have received screening. Subjects screening, enrolment, discontinuation from study, completion of treatment and follow-up, and inclusion in different analysis sets will be described. Subjects screen failures, screen successes failing to be enrolled, completion of treatment, discontinuation from study and reasons for excluding subjects from each analysis set will be summarized.

Demographics and baseline characteristics:

Subjects demographics and baseline characteristics will be described by descriptive statistics and be listed, using the analysis methods provided in General Rules.

Safety analysis:

Safety analysis will be based on SS. AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) (the latest version at the time of analysis), and will be summarized descriptively by System Organ Class (SOC)/ Preferred Term (PT). The overall incidence and incidences by SOC/PT will be summarized for AEs, adverse reactions, treatment-emergent AEs (TEAEs), study treatment-related AEs, significant AEs, and SAEs. The number of subjects experiencing AEs and number of AE occurrences during the treatment period

	will be summarized by SOC and severity. AEs, adverse reactions, TEAEs, study treatment-related AEs, significant AEs, and SAEs, etc., will be listed. Changes in laboratory tests will be presented by a cross table specifying the changes from abnormal/normal to abnormal/normal before and after treatment. The laboratory test results will be listed. Changes in ECG will be presented by a cross table specifying the changes from abnormal/normal to abnormal/normal before and after treatment. QTc measurements will be described by >450 ms, >480 ms, and >500 ms，and by changes from baseline >30 ms and >60 ms. The ECG results will be listed. Vital signs and physical examinations at each visit will be analyzed and listed, using the analysis methods provided in General Rules. **Efficacy analysis:** Efficacy analyses will be primarily based on FAS, and also be based on PPS. Log-rank test will be used for inter-group comparison of the primary endpoint "time from randomization to clinical recovery", and the hazard ratio (HR) (with its 95% CI) of clinical improvement will be calculated by univariate Cox regression. Intent-to-treat analysis will be used for the primary endpoint. With regard to the secondary efficacy endpoints, log-rank test will be used for inter-group comparison of time from randomization to symptom improvement or seroconversion, and the hazard ratio (HR) (with its 95% CI) of clinical improvement will be calculated by univariate Cox regression. The corresponding statistical methods appropriate for the variable type will be used for comparison of other secondary efficacy endpoints and safety endpoints. t-test or Wilcoxon rank-sum test (depending on the data distribution pattern) will be used for continuous variables; chi-square test or Fisher exact test (where chi-square test does not apply) will be used for categorical variables. Wilcoxon rank-

	sum test or CMH test will be used for rank data. The efficacy data will be listed.

Study Flow Chart

	Screening & Baseline [1]	Treatment period[2]						Follow-up[3]		Premature discontinuation/End of treatment [4]
Procedure	**B/L**	**d1**	**d3±1**	**d5±1**	**d7±1**	**d10±1**	**d14±1**	**d21±3**	**d28±3**	
Signing ICF	X									
Eligibility assessment	X									
Demographics	X									
Prior medical history and treatment history	X									
Efficacy/safety evaluation										
12-lead ECG (where possible)	X						X			X
Chest imaging[5] (if CT cannot be performed, Pneumonia confirmed by X-ray may be used. The method of chest imaging pneumonia diagnosis must be consistent all through the study period.)	X						X		X	X
Vital signs[body temperature, HR/PR, respiratory rate, and, where possible, blood pressure and SaO_2]	X	X	X	X	X	X	X	X	X	X
Physical examinations	X				X		X		X	X
Clinical symptoms(pyrexia, cough, diarrhoea, dyspnoea)[7]	X	X	X	X	X	X	X	X	X	X
Primary endpoint evaluation			X	X	X	X	X	X	X	X
Type and conditions of breath support		X	X	X	X	X	X	X	X	X
ICU admission status		X	X	X	X	X	X	X	X	X
Survival status		X	X	X	X	X	X	X	X	X
Laboratory assessments										
Hematology[8]	X		X		X		X	X	X	X
Urinalysis[8]	X		X		X		X	X	X	X
Coagulation function[8]	X		X		X		X	X	X	X
Biochemistry[8]	X		X		X		X	X	X	X
Arterial blood gas analysis(when necessary)[9]	X	When deemed necessary by the investigator								
C-reactive protein(CRP)	X				X		X		X	X

	Screening & Baseline [1]	Treatment period[2]						Follow-up[3]		Premature discontinuation/End of treatment [4]
Procedure	**B/L**	**d1**	**d3±1**	**d5±1**	**d7±1**	**d10±1**	**d14±1**	**d21±3**	**d28±3**	
Cytokines[10]	X				X		X		X	X
Pregnancy test (for women of child-bearing potential only)	X									
Respiratory tract specimens[11]	X	X	X	X	X	X	X	X	X	X
Investigational product										
Randomization		X								
Test drug/placebo administration		X	X	X	X	X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X

1. Considering the public heath demand related to this disease and the need to allow the subject to receive treatment timely, no time frame is defined for the baseline, and the examination results that are the closest to randomization before signing ICF would be used for eligibility assessment. However, to ensure consistency of baseline, screening should be completed within 7 days prior to randomization whenever possible. Before signing ICF, the routine examination results obtained at the site within 48h before the first treatment can be used for subject screening.

2. The treatment period is up to 14 days. Treatment is complete when the subject has met the clinical symptoms recovery criteria for the primary efficacy variable/has been negative for 2 consecutive nucleic acid tests (sampling at least 1 day apart; in case the criteria for quarantine release or discharge have been updated, the updated version should prevail) / has voluntarily discontinued, where the subsequent visit examinations should also be collected as much as possible.

3. Follow-up includes clinical efficacy, virology and safety evaluations. During hospitalization in the study site, or at home, for the patients treated at home, the routine assessments will be performed for the subject as per the Protocol; subjects receiving treatment in another hospital (i.e., those subjects who have been transferred to another hospital during treatment, the same hereafter) or who have been discharged within 28 days of first treatment will be followed up via telephone to collect as much relevant data as possible, unless relevant tests are not available as the subject has left the hospital.

4. Where the subject prematurely discontinues treatment for any reason, the End of Treatment (EOT) visit should be completed within 7 days following discontinuation whenever possible (the examinations obtained within the 7 days before discontinuation (after the last treatment) are acceptable).

5. Where applicable, any chest imaging results obtained within 48h after baseline are to be recorded in the eCRF. All the subjects should receive follow-up chest CT or X-ray on the 14th day after enrolment, and, where appropriate, another follow-up chest CT or X-ray on the 28th day after enrolment. Throughout the treatment and follow-up periods, aggravation of any clinical symptoms should be followed up on an ongoing basis, and, where necessary, follow-up chest CT can be performed or other imaging examinations may be used at the discretion of the investigator. The baseline is defined as the chest imaging examinations obtained at subject screening (those chest imaging examinations obtained at the study site for routine disease management (not for the purpose of participating in any clinical trial) before the subject signs ICF may also be used for screening with the permission of the investigator, provided that the examination takes place within 7 days prior to randomization).

6. During the treatment period, vital signs are to be assessed daily; for subjects receiving treatment in another hospital, body temperature, respiratory rate and HR/PR (as well as blood pressure and SaO_2, where possible) are to be monitored daily; blood pressure and SaO_2 are also required for subjects at the study site.

7. Changes in clinical symptoms are to be recorded daily; pyrexia is defined as axillary ≥37℃, or oral ≥37.5℃, or axillary or rectal≥38℃.

8. Hospitalized subjects will receive follow-up examinations on Days 3, 7, 14, 21 and 28, and additional follow-up examinations can be added and recorded in the eCRF Additional Visit page whenever appropriate for the subject's clinical condition.

9. Arterial blood gas analysis may or may not be performed as determined by the investigator according the subject's condition.

10. Cytokines include interferon (IFN) -γ, tumor necrosis factor (TNF), interleukin -1(IL-1β), IL-6 and IL-18, which are to be tested whenever possible for the study site.

11. For hospitalized subjects, every effort should be made to collect respiratory tract specimens (e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions, at the discretion of the investigator) at baseline and at 3, 5, 7, 10, 14, 21 and 28 days. During the treatment and follow-up periods, additional respiratory tract specimens can be collected on an ongoing basis as appropriate for the subject's condition. Specimens will be collected until negative for 2 consecutive tests. Where baseline specimen has already been collected before any study treatment, sampling at Day 1 visit can be omitted. Sputum specimen is preferred for test; the specific type of respiratory tract specimen (e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions) is to be selected based on the conditions of the local laboratory; the type of specimen and detection method should remain consistent for the same subject receiving study treatment; in case any new etiologically detection methods/criteria or any new detectable specimens become available afterwards, the new methods or new specimens may or may not be used at the discretion of the investigator.

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List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
AKI	Acute Kidney Injury
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BID	Twice a Day
BUN	Blood Urine Nitrogen
CBC	Complete Blood Count
CK-MB	Creatinine Kinase-MB
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CRP	C-Reactive Protein
CT	Computerized Tomography
DM	Data Manager

Abbreviation	Explanation
eCRF	Electronic Case Report Form
EDC	Electronic Data Collection
FAS	Full Analysis Set
FiO_2	Fraction of Inspired Oxygen
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICU	Intensive Care Unit
IFN-γ	Interferon-γ
IL	Interleukin
INR	International Normalized Ratio
ITT	Intent-to-Treat
LDH	Lactic Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Affairs
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NMPA	National Medical Products Administration
PaO_2	Arterial Partial Oxygen Pressure

Abbreviation	Explanation
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per Protocol Set
PT	Preferred Term
PT	Prothrombin Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SFTSV	Severe Fever with Thrombocytopenia Syndrome Bunyavirus
SOC	System Organ Class
SOP	Standard Operating Procedure
SPO_2	Blood Oxygen Saturation
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
WBC	White Blood Cell Count
TID	Three Times a Day
TNF	Tumor Necrosis Factor
WHO	World Health Organization

1. Study background

1.1 Disease overview

The known coronaviruses can be classified, depending on the serological characteristics and nucleic acid sequence, into the genera α, β, γ and δ, and the coronaviruses that can cause human infection include HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS-CoV [1]. Since December 2019, multiple cases of pneumonia infected with 2019-nCoV were identified in Wuhan, Hubei, China. With the progression of the epidemic, such cases have also been identified across other regions of China as well as overseas. Genotyping showed that it is a novel β coronavirus that has caused this epidemic. On January 12, 2020, World Health Organization formally named the disease leading to the epidemic in Wuhan as COVID-19. 2019-nCoV, a novel coronavirus that has never been identified in humans, has been responsible for COVID-19 that features quick and extensive spread, high infectivity and extensive susceptibility among different populations. On January 20, 2020, COVID-19, as an acute respiratory infectious disease, was assigned as a category B infectious disease subject to the management measures for category A infectious diseases according to Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases. As of February 17, 2020, a total of 70644 confirmed cases (cumulative), 7264 suspected cases, 10937 cured cases (cumulative), and 1772 dead cases had been identified. The COVID-19 epidemic remains at an early stage, its progression is associated with high uncertainty, and no specific treatment has been available.During the first 2020 quarter, the epidemic reached European countries, too. In particular, a total of 35713 confirmed cases (28710 actually positive, 4025 recovered, and 2978 dead cases) were observed in Italy at March 18, 2020. Regarding the actually positive cases only, the inpatients with symptoms are 14363, in intensive care 2257, while 12090 are in home isolation.

2019-nCov is a novel β coronavirus that is enveloped, round or oval, often polymorphic, and 60 - 140nm in diameter. Like influenza viruses, 2019-nCov is a RNA virus. The antiviral agents recommended for COVID-19 in the Protocol for the Diagnosis and Treatment of COVID-19 (Tentative, 5th Edition) include α-interferon and lopinavir/ritonavir. Researchers are making

every effort to search for any agents potentially effective for COVID-19.

1.2 Drug overview

Favipiravir (code T705，brand name AVIGAN) is an anti-influenza A (including H1N1) or anti-influenza B drug initially developed by Fujifilm for the treatment of novel or recurrent influenza (only to be used when other anti-influenza virus treatments are ineffective or the effect is unsatisfactory).

Favipiravir is a non-nucleoside RNA polymerase inhibitor that selectively inhibits RNA polymerases related to influenza virus replication after being metabolized intracellularly and prevents virus proliferation by preventing the replication of viral genetic materials in cells. Studies have shown that Favipiravir has stronger inhibitory activity against influenza virus RdRp and is more sensitive to existing resistant virus strains; and increases the survival rate of animals infected with highly pathogenic H5N1 avian influenza virus. In addition, related fundamental studies have confirmed that Favipiravir is highly active both in vitro and in vivo against the virulent RNA virus families such as filaviridae, bunaviridae, arenaviridae, and togaviridae, as well as the non-virulent RNA virus families such as orthomyxoviridae, paramyxoviridae, picornaviridae, and flaviviridae. Favipiravir can effectively inhibit severe fever with thrombocytopenia syndrome virus (SFTSV) replication in vitro, and has demonstrated good therapeutic effect for SFTSV infection in small animal models as it effectively improved the survival rate of mice infected with SFTSV.

Favipiravir was approved for marketing in Japan in March 2014, and was listed as a strategic reserve drug for the novel influenza epidemic by the Pharmaceuticals and Medical Devices Agency (PMDA) on March 9, 2017.

On June 21, 2016, Fujifil authorized Zhejiang Hisun Pharmaceutical Co. Ltd. to develop, manufacture and distribute the anti-influenza virus drugs with “Favipiravir” patent in China, and no imported version of Favipiravir has been available in Chinese market.

A recent collaborative study by Wuhan Institute of Virology, CAS and Academy of Military Medical Sciences showed that Favipiravir could effectively inhibit replication of 2019-nCov at live virus level, with the median effective concentration (EC50) of 61.88 μM. In addition,

Favipiravir showed good safety profile in vitro, with the cellular median lethal concentration (LC50) greater than 400 and the selection index greater than 646. Based on the above, the investigators assume that Favipiravir could exert certain preventive and inhibitory effects for COVID-19.

Zhejiang Hisun Pharmaceutical Co., Ltd. obtained the National Medical Products Administration drug registration approval for China in February 2020, and mass production has been achieved, and the clinical drug supply can be guaranteed.

On March 2020, considering the concomitant public health emergency, Zhejiang Hisun Pharmaceutical Co. Ltd. donated Favipiravir as free-of-charge drug to ASST FATEBENEFRATELLI SACCO (Milano, Italy) to perform the present no profit clinical trial in Italy.

1.2.1 Preclinical pharmacodynamics studies

(I) In vitro activity

(1) Activity against influenza viruses

Favipiravir has demonstrated potent antiviral activity against all types of influenza A, B and C, as well as against the strains resistant to the existing medications (amantadine hydrochloride, oseltamivir phosphate, zanamivir hydrate). In addition, Favipiravir showed therapeutic effect against various types and subtypes of highly pathogenic influenza viruses (including H5N1) in mouse infection models, as well as in infection models of immunodeficient mouse.

In vitro activity against influenza viruses: The EC50 of Favipiravir against the seasonal influenza viruses A(H1N1), A(H3N2) and B, including the strains resistant to amantadine, oseltamivir and zanamivir, was 0.03~0.79μg/ml , 0.07~0.94 μg/ml and 0.09~0.83 μg/ml, respectively. The EC50 of T-705 against the 2009 novel influenza viruses A(H1N1), A(H2N2) and A(H7N2) was 0.06~3.53 μg/ml. A variety of these influenza virus stains were resistant to amantadine, oseltamivir and zanamivir, and the EC50 of T-705 for 4 strains resistant to amantadine, oseltamivir and zanamivir was 0.09~0.47 μg/ml. In a phase III clinical trial where influenza virus stains were isolated before and after T-705 treatment, Favipiravir demonstrated

the EC50 of 0.045~3.8 μg/ml for the 332 strains isolated before treatment, and no reduced sensitivity after treatment. As mentioned above, Favipiravir has demonstrated broad-spectrum activity against various types of influenza virus, and no cross-resistance in the existing strains of influenza viruses.

(2) Activity against Ebola virus

In a German report, the in vitro IC50, IC90 and IC99 of Favipiravir for Ebola virus (Zaire，Mayinga 1976 strain，infecting vero E6 cells) were 67 μM, 110 μM and 186 μM, respectively. While there has been no literature report on its selection index, our experimental data suggest that Favipiravir 10mM did not demonstrate toxicity, indicating that the selection index of Favipiravir might be high (>140 as estimated based on our data).

(3) Preliminary evaluation of activity of Favipiravir against 2019-nCov

In the virus proliferation inhibition test, the test compound could effectively inhibit the viral genome replication in the infected supernatant at the concentrations of 100 μM, 33 μM, 11.1 μM, and 3.7 μM. Cytotoxicity test showed that treatment with the test compound did not alter cell viability at the concentrations of 0.14-100 μM, indicating that the test compound did not induce cytotoxicity at any concentration. The Favipiravir EC50=61.88 μM，CC50 > 400 μM, SI > 6.46.

(II) In vivo activity

(1) Activity against influenza viruses

Favipiravir 30mg/kg, p.o., once daily for 5 days demonstrated therapeutic effect in mice infected with influenza viruses A/Victoria/3/75(H3N2) and A/Osaka/5/70(H3N2). The Favipiravir dose resulting in 90% inhibition of virus proliferation in lungs of mice infected with A/Osaka/5/70(H3N2) was 16 mg/kg/day. For mice infected with A/DUCK/MN/1525/81(H5N1), treatment at 30 mg/kg/day for 5 days also demonstrated therapeutic effect, while oseltamivir phosphate at 20 mg/kg/day (2 folds the clinical exposure dose) did not produce therapeutic effect after 5 days of treatment. In a study in mouse infection models induced by the assumedly highly pathogenic influenza virus

A/Vietnam/UT3040/2004(H5N1), treatment at 30~60 mg/kg/day, p.o., for 5 days demonstrated therapeutic effect, which was better with 7 days of treatment; in comparison, oseltamivir phosphate at 20 mg/kg/day did not produce marked therapeutic effect even when the treatment period was extended from 5 days to 7 days. Treatment at 300 mg/kg/day showed therapeutic effect in mice infected with A/New Caledonia/20/99 (H5N1) or B/Sichuan/37/99 when the first treatment was delayed to 60h or 72h after infection, and in mice infected with A/DUCK/MN/1525/81(H5N1) when the first treatment was delayed to 120h after infection.

In the SCID mouse models with immunodeficiency and susceptibility to severe disease that were infected with A/Aichi/2/68(H3N2), treatment at 30mg/kg/day, p.o., for 14 days demonstrated therapeutic effect, while oseltamivir phosphate at 30 mg/kg/day, p.o., did not produce therapeutic effect after 14 days of treatment.

In conclusion, Favipiravir 30 mg/kg/day p.o. demonstrated therapeutic effect in A/Victoria/3/75(H3N2), A/Osaka/5/70(H3N2), A/DUCK/MN/1525/81(H5N1) and A/Vietnam/UT3040/2004(H5N1) infection tests, as well as in SCID mice infected with A/Aichi/2/68(H3N2). When investigating the effect of Favipiravir treatment given in divided doses on its therapeutic effect in the A/Osaka/5/70(H3N2) infection model, over 3 doses a day showed inhibitory effect on virus proliferation in lungs as compared to 1 dose a day.

(2) Activity against Ebola virus

For in vivo activity evaluation, two commonly used inbred mouse (C57 and 129) models with type I interferon receptor deficiency was challenged intranasally with Ebola virus (Zaire, mayinga strain) and received treatment by intragastric administration. At the 100% lethal challenge dose in the placebo group, Favipiravir 300 mg/kg/d given at 6~13 days after challenge resulted in 100% survival, with significant improvements in body weight, ALT, AST, and viremia, etc. At the same challenge dose and treatment dose, treatment at 8~14 days after challenge resulted in slightly improved survival duration, while all the animals in the treatment group eventually died, indicating that overly late Favipiravir treatment would not produce protective effective.

For in vivo activity evaluation, 129 mice with both type I and type II interferon receptor

deficiency was infected with E718 strain through aerosol and received, starting from 1h after infection, treatment at 150 mg/kg twice a day (300 mg/kg/d) continuously for 14 days. All the animals in the placebo group died, while all the animals in the treatment group survived with good improvement in body weight.

The above studies suggest that Favipiravir is effective against Ebola virus both in vitro and in vivo; earlier treatment could produce better therapeutic effect; treatment would generally not be effective when given beyond 6 days after infection.

1.2.2 Toxicological studies

No severe adverse reactions have been observed clinically, and the incidence of moderate adverse reactions is comparable to oseltamivir phosphate. The common adverse reactions include elevated blood uric acid, liver dysfunction, vomiting, anorexia, nausea, joint pain, limb pain, residual urine and paresthesia, etc., which could recover after treatment withdrawal.

In the 1-month oral treatment studies in rats and dogs and the 2-week oral treatment study in monkeys, Favipiravir showed toxic effect on the hemopoietic tissues (decreased RBC parameters associated with reduced medullary hematopoiesis), the liver (increased ALP, ALT, AST, total bilirubin and liver weight，and vacuolar degeneration of hepatic cells), and the testicles.

Results of the 1-month oral toxicity study in rats, 1-month oral toxicity study in dogs and 2-week oral toxicity study in monkeys showed that the main target organs of Favipiravir are hemopoietic tissues, liver and testicles.

In addition, light yellow coloring of furs (originally white) and paws was observed in the >80 mg/kg/day dose groups in the 1-month oral toxicity study in rats and the >100 mg/kg/day dose groups in the 1-month oral toxicity study in dogs. While coloring was also observed in other toxicity studies, the colored tissues in these two studies were not observed with the disorders such as shedding and elongation abnormality, and no histological abnormalities were observed in the skin under the colored fur or paw. The coloring was a reversible change that would resolve after treatment withdrawal, and is therefore not of much toxicological significance.

1.2.3 Favipiravir human pharmacokinetics study

In healthy male Japanese subjects (n=100), single administration of Favipiravir 2400 mg p.o. resulted in the mean C_{max} and AUC of 92.17 mg/mL and 1297.56 mg.h/mL, respectively, and the median T_{max} and mean half life of 3h and 4.5h, respectively. Multiple administrations of Favipiravir 400mg (BID) resulted in the mean C_{max} and AUC of 43.83 mg/mL and 244.31 mg.h/mL, respectively, and the median T_{max} and mean half life of 0.6h and 5.2h, respectively.

2. Objectives

2.1Primary objective

To evaluate the efficacy of Favipiravir combined with supportive care for adult patients with COVID-19-Moderate type.

2.2 Secondary objective

To evaluate the safety of Favipiravir combined with supportive care for adult patients with COVID-19-Moderate type.

3. Subjects selection and discontinuation

3.1 Inclusion criteria

1. Voluntarily participating in the clinical study; fully understanding and being fully informed of the study and having signed the Informed Consent Form (ICF); willingness and capability to complete all the study procedures;

2. Age 18-75 years (inclusive) at the time of signing ICF;

3. Being confirmed with COVID-19-Moderate type according to Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol. Based on comprehensive analysis and judgement taking into account both the epidemiological history and clinical manifestations, the diagnosis is to be confirmed for suspected cases (for provinces other than Hubei) or suspected cases/clinically diagnosed cases (for Hubei province) with all of the following etiological evidences:

   - Positivity in RT-PCR 2019-nCov test on respiratory tract specimens;
   - High homology with known gene sequence of 2019-nCov in viral gene sequencing on respiratory tract specimens.

Note: The above criterion would be subject to any update of the Protocol for the Diagnosis and Treatment of COVID-19. In case any new etiologically detection methods/criteria or any new detectable specimens become available after confirmed diagnosis, it is at the discretion of the investigator whether or not to use the new methods or new specimens.

Note: Sputum specimen is preferred for RT-PCR test of 2019-nCov nucleic acid; the specific type of respiratory tract specimen (e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions) is to be selected based on the conditions of the local laboratory.

The type of specimen and detection method for 2019-nCov should remain consistent for the same subject receiving study treatment.

4. Chest imaging (CT as first option or X-ray if CT not possible)-documented pneumonia; if CT cannot be performed, Pneumonia confirmed by X-ray may be used. The method of chest imaging pneumonia diagnosis must be consistent all through the study period;

5. Patients with pyrexia (axillary ≥37℃ or oral ≥37.5℃, or tympanic or rectal≥38℃) or either respiratory rate >24/min and <30/min or cough; For not hospitalized patients, the Investigator should maintain the detection method consistent all through the study period. In addition, the Investigator should maintain the data collection and quality compliant with GCP requirements.

6. The interval between symptoms onset and randomization is no more than 10 days; symptoms onset is primarily based on pyrexia, and can be based on cough or other related symptoms for patients without experiencing pyrexia following onset;

7. For female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pre-treatment serum or urine pregnancy test. Menopause is defined as amenorrhea for at least 12 months without other medical cause, with the following age-specific requirements:

   - For female subjects aged <50 years: menopause for at least 12 months following withdrawal of exogenous hormonal therapy, with LH or FSH within the post-menopausal ranges, or having undergone any contraceptive surgery (bilateral oophorectomy or hysterectomy);
   - For female subjects aged ≥50 years: menopause for at least 12 months following withdrawal of exogenous hormonal therapy, or having undergone radiotherapy-induced oophorectomy with amenorrhea>1 year, or having undergone chemotherapy-induced menopause with amenorrhea>1 year, or having undergone any contraceptive surgery (bilateral oophorectomy or hysterectomy).

8. Eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment;

9. Not participating in any other drug clinical studies before completion of the present study.

3.2 Exclusion criteria

1. Where, in the opinion of the investigator, participation in this study will not be in the best interest of the subject, or any other circumstances that prevent the subject from participating in the study safely;

2. Refractory nausea, vomiting, or chronic gastrointestinal disorders, inability to swallow the study drug or having undergone extensive bowel resection which may affect adequate absorption of Favipiravir;
3. Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN;
4. Gout/history of gout or hyperuricemia (above the ULN);
5. Oxygen saturation (SPO2)≤93% or arterial oxygen partial pressure (PaO_2)/ fraction of inspired O2 (FiO_2)≤300 mmHg;
6. Known allergy or hypersensitivity to Favipiravir;
7. Known severe renal impairment [creatinine clearance (CcCl) <30 mL/min] or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis;

CcCl is to be calculated by the following Cockcroft-Gault formula only when the serum creatinine is＞1.5×ULN:

For females:

$$CrCl = \frac{(140 - Age(years)\ X\ Weight\ (kg) X\ 0.85}{72\ X\ Serum\ Cr\ (\frac{mg}{dL})}$$

For males:

$$CrCl = \frac{(140 - Age(years)\ X\ Weight\ (kg) X\ 1.0}{72\ X\ Serum\ Cr\ (\frac{mg}{dL})}$$

8. Possibility of the subject being transferred to a non-study hospital within 72h;
9. Pregnant or lactating women;
10. Having used Favipiravir or participated in any other clinical study within 30 days prior to first dose of study drug.

Note: Considering that COVID-19 requires immediate treatment, absence of severe hepatic/renal disorders (e.g., cirrhosis, long-term dialysis) in the medical record can be used as an evidence for eligibility determination. It is recommended that hepatic function and creatinine be examined whenever possible.

3.3 Criteria for discontinuation

Investigator-determined discontinuation

Discontinuation from study refers to where the investigator determines that the subject should discontinue from study/study treatment when the subject has fulfilled any circumstance that makes it no longer appropriate for the subject to continue participating in the study, including:

1. Erroneous inclusion despite failure of inclusion criteria;
2. Where the subject has experienced some comorbidities, complications, or worsening of conditions that makes it no longer appropriate for the subject to continue participating in the study, e.g., laboratory abnormalities, allergic reactions, bronchospasm, severe liver injury, or grade III acute kidney injury (AKI) that in the investigator's opinion requires discontinuation of study treatment.
3. Where the subject has received any other treatment than the study treatment which may interfere with the study evaluation;
4. Where the investigator considers that continuation would be detrimental to the subject's wellbeing (e.g., pregnancy);
5. Where the subject has experienced any severe/intolerable AE or SAE making it no longer appropriate for the subject to continue;
6. Poor subject compliance that may interfere with efficacy and/or safety evaluation.

Subject's voluntary discontinuation from study

In case the subject is no longer willing to participate in the study, he/she, as specified in the ICF, has the right to prematurely discontinue from the study at any time during the study; or the subject may not explicitly request for discontinuation but is lost to follow-up as he/she stops receiving any study treatment/procedure, this also constitutes a "discontinuation" (also known as "dropout"). The reason for discontinuation should be collected and recorded whenever possible, e.g., feeling intolerable to some adverse reactions; impossibility to continue study for other reasons; loss to follow-up without providing the reason.

3.4 Handling of discontinued subjects

The investigator must enter the reason for discontinuation in the CRF, and make every effort to contact the subject, complete all the assessments that could possibly be completed (at premature discontinuation/EOT visit), and complete the relevant CRF, recording the time of the last treatment whenever possible. For those subjects discontinued due to an AE that was assessed upon follow-up as being related to the investigational product, this must be recorded in the CRF and be communicated to the sponsor. CRFs should be retained for any discontinued subjects, regardless of the reason, and the result of the last test can be carried forward for full analysis of efficacy and adverse reactions.

Study-related toxicities and SAEs ongoing at the time of discontinuation must be followed up until resolution, unless in the investigator's opinion it is impossible to resolve due to the nature of the subject's underlying disease.

Following discontinuation of study treatment, the investigator must follow up any preexisting or newly emerging AEs within 14 days following last study treatment, and report any new AEs or SAEs occurring during this interval (SAEs must be reported to the sponsor within 24h) and follow them up until resolution. After a subject is discontinued from study, the investigator should immediately inform the sponsor. In the occurrence of any SAE, the sponsor must be contacted timely following the procedure for SAE reporting.

3.5 Early study termination/site closure

The sponsor has the right to terminate this study at any time. The sponsor and investigator have the right to close any study site at any time. This, however, may not be executed without mutual negotiation. When terminating the study, the Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB) must be reported to. In case of early study termination/site closure, all the study materials (except those files that are required to be retained at the site) must be returned to the sponsor. The investigator must retain other documents until being notified by the sponsor to destroy them. The reasons for early study termination/site closure include but are not limited to:

(1) Any new information that has led to a risk-benefit judgement that is unfavorable to the investigational product, e.g., due to:

- Lack of efficacy with the investigational product, either in this or other studies;
- Occurrence of any significant previously unknown adverse reaction, or any known adverse reaction with unexpectedly high severity/incidence ;
- Other untoward safety findings, including clinical findings and non-clinical manifestations.

(2) Where the sponsor considers it unreasonable to continue the study for medical, ethic or commercial reasons;

(3) Subject enrollment difficulty which make it unlikely that the study can be completed in an acceptable time frame;

(4) Termination required by the regulatory authorities.

3.6 Criteria for quarantine release and discharge of subjects

The criteria for quarantine release and discharge of subjects of Competent Authority and Italian Ministry of Health guidelines and the recommendations reported in Appendix 1 to the present protocol will be adopted, and any update of the criteria should prevail. For subjects who have been discharged, as much relevant data as possible should be collected at subsequent visits, unless relevant tests are not available as the subject has left the hospital.

The temporary criteria for quarantine release and discharge: body temperature normalized for over 3 days, respiratory symptoms significantly improved, chest imaging showing inflammations significantly absorbed, negativity in 2 consecutive respiratory tract pathogen nucleic acid tests (sampling at least 1 day apart), where the patient can be released from quarantine and discharged, or be transferred to the appropriate department for the treatment of other diseases.

3.7 Definition of end of study

End of study is defined as when the last subject completes the last visit as per the protocol.

4. Study design

4.1 Study type and design rationale

This is a multi-center, randomized, double-blind, placebo-controlled (1:1) clinical study to explore the efficacy and safety of Favipiravir in the treatment of adult subjects with COVID-19-Moderate type.

Subjects within 10 days of COVID-19 onset will be screened, and be randomized as early as possible within 24 hours following screen success.

It is planned to randomize 256 subjects in an 1:1 ratio. Subjects in the test group will receive supportive care recommended in the current guidelines+Favipiravir, and subjects in the control group will receive supportive care recommended in the current guidelines+placebo control; the efficacy and safety of Favipiravir versus the placebo in the treatment of COVID-19-Moderate type will be compared.

Note: Supportive care is to be selected by the local investigator according to the practice, referring to the recommendations of the Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol. Supportive care may not include any antiviral agents other than the study drug, e.g., α-interferon, lopinavir/ritonavir, and ribavirin.

Those subjects who have received treatment with antiviral agents can be screened and enrolled provided that these agents are discontinued after enrolment and supportive care is selected by the local investigator according to the practice.

4.2 Randomization and blinding

4.2.1 Randomization method

The subject will enter screening after signing ICF. Subjects meeting all the inclusion criteria and not meeting any exclusion criteria will be randomized 1:1 as early as possible within 24h after screen success. The randomization method and procedure are specified in other relevant documents.

4.2.2 Blinding level

This study will adopt a double-blind design, i.e., neither the investigators, subjects nor other study participants will be aware which medication the subject is receiving.

Normally, blinded state will remain until study completion and database lock. Emergency unblinding is allowed only in case the subject experiences any emergency and the investigator confirms that only by becoming aware of the treatment that the subject is receiving can the subject's interests be maximally protected. In such case, the investigator must contact the sponsor. If the investigator cannot contact the sponsor, the investigator may contact the randomization system to access information on the treatment that the subject is receiving, specifying the reason in the eCRF and retaining in the eCRF the copy of the fax the randomization system sends to permit unblinding or the email confirming unblinding. In case of emergency the investigator may also open the envelope containing the randomization of a single patient.

4.3 Study procedures and observational indicators

4.3.1 Observational indicators

4.3.1.1 General characteristics

(1) Demographics: age, sex and nationality/ethnic origin .

(2) Medical history: includes the date of diagnosis of adult COVID-19-Moderate type, prior treatment for adult COVID-19-Moderate type, as well as child-bearing status, smoking history and alcohol intake history.

4.3.1.2 Physical examinations and vital signs

(1) Physical examinations: include head, eye, ear, nose, and throat evaluations, as well as cardiovascular, skin, musculoskeletal, respiratory, gastrointestinal, urogenital, and nervous system evaluations.

(2) Vital signs: include body temperature, HR/PR, respiratory rate (as well as blood pressure and SaO_2 monitoring, where possible).

Note: The body temperature measurement and site can be selected according to the local laboratory practice, and should remain consistent from screening to subsequent visits for the same subject.

4.3.1.3 Clinical laboratory tests

(1) Hematology: Complete Blood Count (CBC) with differential (including RBC count), hemoglobin, hematocrit, WBC with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils and others) and platelet count.

(2) Biochemistry: glucose, blood urea nitrogen (BUN) or urea, uric acid, creatinine, sodium, potassium, magnesium, chlorine, bicarbonates or total carbon dioxide (depending on local practice), calcium, phosphorus, total bilirubin (TBIL), ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum creatinine kinase-MB (CK-MB), myoglobin, troponin, total protein, albumin.

(3) Coagulation function: activated partial thromboplastin time (aPTT) and prothrombin time (PT) or International Normalized Ratio (INR), D-dimer.

(4) Urinalysis: specific gravity, pH, glucose, protein, ketone bodies and occult blood.

(5) C-reactive protein (CRP).

(6) Cytokines: interferon (IFN) -γ, tumor necrosis factor (TNF), interleukin -1(IL-1β), IL-6 and IL-18 (where possible).

(7) Arterial blood gas analysis (when necessary at the discretion of the investigator).

(8) Serum pregnancy test is preferred for pregnancy test for women of child-bearing potential; or urine pregnancy test can be used depending on the local laboratory practice:

Women of child-bearing potential refer to any women who:

- have experienced menarche;
- have not undergone successful surgical sterilization (including hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
- are not postmenopausal [menopause is defined as amenorrhea ≥ 12 consecutive

months without another cause; or serum follicle stimulating hormone (FSH) level≥ 35 mIU/ml for women with irregular menstrual periods or receiving hormone replacement therapy (HRT)].

4.3.1.4 ECG

(1) 12-lead ECG (where possible): Unscheduled ECG can be examined when clinically indicated, including PR interval, QRS interval, RR interval, QT interval, mean corrected QT interval [QTc, corrected using Fridericia formula (QTcF)] and HR.

Fridericia formula: QTcF = QT/(RR^0.33)]

4.3.2 Screening and Baseline Visit

- Signing ICF;
- Eligibility criteria assessment;
- Demographics;
- Prior medical history and treatment history;
- 12-lead ECG;
- Chest imaging (CT or X-ray)-documented pneumonia; if CT cannot be performed, Pneumonia confirmed by X-ray may be used. The method of chest imaging pneumonia diagnosis must be consistent all through the study period.
- Vital signs;
- Physical examinations;
- Clinical symptoms;
- Laboratory assessments：hematology, urinalysis, coagulation function, biochemistry, CRP, cytokines, pregnancy;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract

secretions);

- Concomitant medications;
- AEs.

4.3.3 Treatment period (d1)

- Vital signs;
- Clinical symptoms;
- Type and conditions of breath support;
- ICU admission status;
- Survival status;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Randomization;
- Test drug/placebo administration;
- Concomitant medications;
- AEs.

4.3.4 Treatment period (d3)

- Vital signs;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;
- ICU admission status;

- Survival status;
- Laboratory assessments：hematology, urinalysis, coagulation function, biochemistry;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Test drug/placebo administration;
- Concomitant medications;
- AEs.

4.3.4 Treatment period (d5)

- Vital signs;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;
- ICU admission status;
- Survival status;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Test drug/placebo administration;
- Concomitant medications;
- AEs.

4.3.5 Treatment period (d7)

- Vital signs;
- Physical examinations;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;
- ICU admission status;
- Survival status;
- Laboratory assessments：hematology, urinalysis, coagulation function, biochemistry, CRP, cytokines;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Test drug/placebo administration;
- Concomitant medications;
- AEs.

4.3.6 Treatment period (d10)

- Vital signs;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;
- ICU admission status;

- Survival status;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Test drug/placebo administration;
- Concomitant medications;
- AEs.

4.3.7 Treatment period (d14)

- 12-lead ECG;
- Chest imaging (CT or X-ray)-documented pneumonia; if CT cannot be performed, Pneumonia confirmed by X-ray may be used. The method of chest imaging pneumonia diagnosis must be consistent all through the study period.
- Vital signs;
- Physical examinations;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;
- ICU admission status;
- Survival status;
- Laboratory assessments：hematology, urinalysis, coagulation function, biochemistry, CRP, cytokines;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by

the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);

- Test drug/placebo administration;
- Concomitant medications;
- AEs.

4.3.8 Follow-up period (d21)

- Vital signs;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;
- ICU admission status;
- Survival status;
- Laboratory assessments：hematology, urinalysis, coagulation function, biochemistry;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Concomitant medications;
- AEs.

4.3.9 Follow-up period (d28)

- Chest imaging (CT or X-ray)-documented pneumonia; if CT cannot be performed, Pneumonia confirmed by X-ray may be used. The method of chest imaging pneumonia diagnosis must be consistent all through the study period.
- Vital signs;

- Physical examinations;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;
- ICU admission status;
- Survival status;
- Laboratory assessments：hematology, urinalysis, coagulation function, biochemistry, CRP, cytokines;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Concomitant medications;
- AEs.

4.3.10 Premature discontinuation/EOT visit

- 12-lead ECG;
- Chest imaging (CT or X-ray)-documented pneumonia; if CT cannot be performed, Pneumonia confirmed by X-ray may be used. The method of chest imaging pneumonia diagnosis must be consistent all through the study period.
- Vital signs;
- Physical examinations;
- Clinical symptoms;
- Primary endpoint evaluation;
- Type and conditions of breath support;

- ICU admission status;
- Survival status;
- Laboratory assessments：hematology, urinalysis, coagulation function, biochemistry, CRP, cytokines;
- Arterial blood gas analysis (when necessary);
- Virus sampling：respiratory tract specimens (type of specimen to be determined by the investigator, e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions);
- Concomitant medications;
- AEs.

4.4 Sample handling and shipping

The respiratory tract specimens (e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions) will be labeled with a unique study code before being immediately sent, according to the local laboratory requirements, to the local laboratory for virus nucleic acid test. Samples will be stored and handled according to the local laboratory practice. In general, collected specimens should be stored under 4℃ before testing and be tested within 24h. Where it is not possible to test immediately, the specimen should be stored frozen under-70℃ or above. Samples will eventually be handled and stored according to the local laboratory practice.

Note: Sputum specimen is preferred for RT-PCR test of 2019-nCov nucleic acid; the specific type of respiratory tract specimen (e.g., nasopharyngeal swabs, sputum, lower respiratory tract secretions) is to be selected based on the conditions of the local laboratory. In case any new etiologically detection methods/criteria or any new detectable specimens become available afterwards, the new methods or new specimens may or may not be used at the discretion of the investigator.

The type of specimen and detection method should remain consistent for the same subject receiving study treatment;

5. Investigational products

5.1 Drug name and dosage form

5.1.1 Test drug:

Generic name: Favipiravir Tablets

Brand name: Not available

Chemical name: 6-fluoro-3-hydroxypyrazine-2-carboxamide

Strength: 200 mg/tablet

Dosage form: Tablet

Storage conditions: Store at room temperature

Manufacturer: Zhejiang Hisun Pharmaceutical Co. Ltd.

5.1.2 Control drug:

Strength: 200 mg/tablet

Dosage form: Tablet

Storage conditions: Store at room temperature

Manufacturer: Zhejiang Hisun Pharmaceutical Co. Ltd.

5.2 Method of administration

Route of administration： Oral

Test group: Favipiravir combined with supportive care. **Favipiravir dosage and method of administration:** Day 1: 1800mg, BID; Day 2 and thereafter: 600mg, TID, for a maximum of 14 days.

Placebo control group： placebo combined with supportive care. **Placebo dosage and method of administration:** Day 1: 1800mg, BID; Day 2 and thereafter: 600mg, TID, for a maximum of 14 days.

Where the subject has experienced an adverse event related to liver injury of grade≥3 (NCI CTCAE v5.0), the dose is to be reduced to 600mg BID. It is at the discretion of the investigator

whether or not to perform dose reduction based on how the subject is benefiting from study treatment. The subject should be discontinued from treatment if he/she re-experiences any adverse event related to liver injury of grade≥3 after dose reduction.

Supportive care： Supportive care is to be selected by the local investigator according to the practice, referring to Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol, to which any update should prevail. Supportive care may not include any antiviral agents other than the study drug, e.g., α-interferon, lopinavir/ritonavir, and ribavirin.

Note: During the treatment period, if the subject has met the clinical symptoms recovery criteria for the primary efficacy variable/has been negative for 2 consecutive pathogen nucleic acid tests (sampling at least 1 day apart; in case the criteria for quarantine release or discharge have been updated, the updated version should prevail) / has voluntarily discontinued, the treatment can be discontinued if at the discretion of the investigator this decision would not affect the subject's benefits. The treatment period may not exceed 14 days. Subjects will no longer have access to the study medication beyond the maximum of 14 days of treatment period.

5.3 Drug packaging and labeling

For all the study medications, the labeling will be designed, and the drugs will be packaged and labeled reporting ASST FATEBENEFRATELLI SACCO as Sponsor in accordance with the GCP provisions as well as the applicable national regulations and labelling requirements.

The placebo will be consistent with Favipiravir in terms of appearance, package and strength, etc.

5.4 Drug dispensing and accountability

The Drug Manager must keep accurate records of the amounts of the study medications. In this study, study medications must only be dispensed by 1 qualified person. Medications will be used by the subjects as required in the Protocol under the supervision of the investigator.

5.5 Drug return and destruction

The Drug Manager should keep appropriate records of all the study medications dispensed, including the date, amount and the subject using the medication. Unused study medications must be returned to the sponsor, or be destroyed at the study site according to relevant

regulations.

5.6 Subjects management

Foods that may affect liver enzyme activity such as grapefruit and Sevilla orange are prohibited.

6. Concomitant therapies and compliance

6.1 Allowed concomitant medications

The investigator may give the subject the treatments appropriate for the subject's medical history and AE profile, etc.

The investigator may give appropriate supportive care and concomitant therapies, such as antibiotics and non-steroidal anti-inflammatory and analgesic drugs as per the Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol..

Note: If any disconcordance, the Competent Authority and Italian Ministry of Health guidelines should prevail in front of the recommendations reported in Appendix 1 to the present protocol.

6.2 Prohibited concomitant medications

1. As a general rule, concomitant use of non-steroidal anti-inflammatory drugs is to be avoided whenever possible. If the subject has severe symptoms such as pyrexia (axillary temperature exceeding 38.5 °C), non-steroidal anti-inflammatory drugs or physical hypothermia can be used as appropriate, but detailed records must be kept.

2. Glucocorticoids should be avoided for subjects with COVID-19-Moderate type, unless indicated for the subject's disease progression or the subject is complicated with other indications, where the recommended dose is not to exceed the equivalent of 1-2 mg / kg / day of methylprednisolone.

3. No other antiviral drugs than those specified in the Protocol are allowed to be added during the study.

4. Concomitant use of herbal therapies is prohibited during the course of the study, as the potential drug-drug interactions have not be fully established.

Note: If any disconcordance, the Competent Authority and Italian Ministry of Health guidelines should prevail in front of the recommendations reported in Appendix 1 to the present protocol.6.3 Rescue treatment

If during the treatment period the subject experiences severe respiratory failure or aggravation

of condition, rescue medications and mechanical ventilation may be used as per the Competent Authority and Italian Ministry of Health guidelines and to the recommendations reported in Appendix 1 to the present protocol.Note: : If any disconcordance, the Competent Authority and Italian Ministry of Health guidelines should prevail in front of the recommendations reported in Appendix 1 to the present protocol.6.4 Measures to secure subject compliance

Before commencement of the study, it should be ensured that the subject is fully informed of the investigational product and treatment process, so as to increase the subject's confidence in completing the study. The subject should also be fully informed of the precautions and possible adverse drug reactions to gain as much understanding and cooperation of the subject as possible. In addition, compliance education for the subjects and their relatives should be emphasized, making them aware of the importance of following the study instructions, as well as the disease-related knowledge and potential benefits and risks associated with the study treatment. Before initiating the study, the sponsor or the Contract Research Organization (CRO) should develop a detailed Monitoring Plan in strict compliance with the Protocol requirements. The subject should be reminded via telephone before any visit.

7. Efficacy evaluation

7.1 Primary efficacy variable

1. Time from randomization to clinical recovery

   Defined as: The duration from start of treatment (Favipiravir or placebo) to normalization of pyrexia, respiratory rate and SPO_2 and relief of cough (where there are relevant abnormal symptoms at enrolment) that is maintained for at least 72h.

   Criteria for normalization or relief:

   - Pyrexia (body temperature):axillary≤36.9℃， or oral≤37.4℃， or rectal or axillary≤37.9℃;
   - Respiratory rate:≤24/min without oxygen inhalation;
   - SPO2:>94% without oxygen inhalation;
   - Cough: Subject-perceived improvement or resolution of cough.

7.2 Secondary efficacy variables

1. Time from randomization to negativity in RT-PCR nucleic acid test for 2019-nCov within 28 days of randomization;
2. Incidence of deterioration/aggravation of pneumonia (defined as SPO2≤93% or PaO2/FiO2 ≤300 mmHg or distressed RR≥30/min without oxygen inhalation and requiring oxygen therapy or more advanced breath support) within 28 days of randomization;
3. Time from randomization to resolution of pyrexia (defined the same as for the primary efficacy variable; applicable to subjects with pyrexia at enrolment) within 28 days of randomization;
4. Time from randomization to relief of cough (defined the same as for the primary efficacy variable; applicable to subjects with cough at enrolment) within 28 days of randomization;

   It is recommended that the severity of cough be graded as per NCI-CTCAE v5.0:

   - Mild: Requires non-prescription treatment;

- Moderate: Requires medication treatment; limits instrumental activities of daily living;
- Severe: Limits self-care activities of daily living;

5. Time from randomization to relief of dyspnoea (defined as subject-perceived improvement or resolution of dyspnoea; applicable to subjects with dyspnoea at enrolment) within 28 days of randomization;
6. Rate of auxiliary oxygen therapy or non-invasive ventilation within 28 days of randomization;
7. ICU admission rate within 28 days of randomization;
8. All-cause mortality within 28 days of randomization.

8. Safety evaluation

Post-treatment safety evaluation indicators include laboratory tests, vital signs, physical examinations, 12-lead ECG and AE evaluation, etc. Frequency and severity of AEs will be determined as per NCI-CTCAE v5.0.

8.1 Adverse events (AE)

An AE refers to any untoward medical occurrence in a clinical study subject after singing ICF, which does not necessarily have to have a causal relationship with the study treatment or procedure. An AE can therefore be any unfavorable or unintended symptoms, signs or conditions, including adverse drug reactions, significant laboratory abnormalities and any disorders developing during the study. The investigator must report all the AEs in the eCRF.

8.2 Adverse Drug Reactions (ADRs)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs.

8.3 Assessment of causality

The relatedness of an AE to the study treatment can be assessed as either Definitely related, Possibly related, Unlikely related, Unrelated or Uncertain

Definitely related： The AE follows a reasonable temporal sequence from the time of investigational product administration; follows a known response pattern to the investigational product; improves upon dose reduction or interruption of the investigational product and reappears when the investigational product is resumed.

Possibly related： The AE follows a reasonable temporal sequence from the time of investigational product administration; follows a known response pattern to the investigational product; but can also be attributable to the subject’s clinical state or other therapeutic options.

Unlikely related：The AE does not follow a reasonable temporal sequence from the time of investigational product administration; does not follow a known response pattern to the

investigational product; can also be attributable to the subject's clinical state or other therapeutic options. The possibility of relatedness to the treatment cannot be ruled out.

Unrelated： The AE does not follow a reasonable temporal sequence from the time of investigational product administration; follow a known response pattern to an non-investigational product; can also be attributable to the subject's clinical state or other therapeutic options. The response would resolve when the disease condition has improved or the other therapeutic option is discontinued, and would reappear when the other therapeutic option is resumed, and is closely related to other risk factors.

Uncertain: The AE does not follow a clear temporal sequence from the time of investigational product administration; follows a similar response pattern to the investigational product; can also be induced by the use of other medications, and no sufficient evidence is available to make the assessment.

8.4 Assessment of AE severity

The severity of an AE should be recorded according to NCI-CTCAE v5.0. The following criteria can be followed for adverse reactions not listed.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.5 Observation, recording and reporting of AEs

All the AEs occurring from signing ICF to 14 days after last treatment (±3d) must be completely recorded in the subject's eCRF.

All the document entries must be supported by source data. Each AE must be described in detail, including the AE diagnosis/description, start and end dates, severity, duration, causality with test drug, actions taken, and outcome.

8.5.1 Methods of identifying AEs

At each visit, efforts can be made to identify AEs through the following approaches:

- Subject- or caregiver-provided information
- Asking the subject open, non-directive questions: How have you been feeling? Since your last visit, have you had any (other) medical problem?
- Abnormalities observed by the investigator, other medical staff or the subject's relatives.

8.5.2 Description of AE outcome

The outcome of an AE can be described as one of the followings：

- Recovered/Resolved: "(S)AE end date" should be provided.
- Recovering/Resolving: The subject is known to be recovering from the symptoms. Event is not resolved yet, and the subject requires follow-up.
- Not recovered/not resolved: Event is ongoing.
- Recovered/Resolved with sequelae: To be used only with persistent incapacity/life-long sequelae, e.g. blindness induced by diabetes mellitus, hemiparesis induced by stroke. "(S)AE end date" should be provided.
- Fatal: "(S)AE end date" should be provided. Date of death should be provided only for

events leading to death.

- Unknown: Unknown to investigator, e.g. when the patient is lost to follow-up.

If the outcome is assessed as “not recovered/not resolved” or “recovering/resolving” or “unknown”, the AE end date can be temporarily left blank.

If the outcome is assessed as “recovered/resolved” or “recovered with sequelae/resolved with sequelae”, the AE end date must be provided.

All the AEs must be followed up to determine the outcome or until the AE stabilizes.

Once the subject has completed the study, the investigator should follow up for outcomes of all adverse events assessed with possible or uncertain relationship with the IP until stabilization.

8.5.3 Assessment and handling of laboratory abnormalities

The investigator should first compare the laboratory abnormality with baseline and assess whether it is clinically significant; those laboratory abnormalities assessed as clinically significant and having worsened from baseline will be reported as an AE and be followed up until normalization or recovery to baseline; those laboratory abnormalities assessed as not clinically significant or clinically significant but having not worsened from baseline will not be reported as an AE. Clinically significant laboratory abnormalities or other abnormalities related to the study disease will not be included as an AE or SAE, unless the investigator determines that they are more severe than expected with the subject’s condition. All the abnormal laboratory tests/vital signs should be accurately recorded in the relevant eCRF.

The investigator is responsible for reviewing all the abnormal laboratory tests/vital signs and determining whether or not they should be reported as an AE.

If a clinically significant abnormal laboratory test/vital sign is the sign of a syndrome or disease (e.g, ALP and bilirubin elevated to >5×ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) will be recorded in the eCRF AE Form; otherwise the abnormal laboratory test/vital sign should be recorded in the eCRF AE Form, indicating if the test value is higher or lower than the reference range (e.g., elevated blood potassium, instead of abnormal blood potassium). If a corresponding standard clinical term is available for an abnormal laboratory

test/vital sign, the clinical term should be recorded in the eCRF. For example, blood potassium elevated to 7.0mEg/L should be recorded as “hyperkalemia”.

For the same clinically significant abnormal laboratory tests/vital signs identified at multiple visits, only one AE or SAE should be recorded in the eCRF, unless there is any change in severity or etiology.

8.5.4 Diagnosis versus symptoms and signs

If the diagnosis has been available, the diagnosis, instead of the individual symptoms and signs should be recorded in the eCRF (e.g., hepatic failure, instead of jaundice, elevated aminotransferase and asterixis, should be recorded). However, if at the time of reporting the symptoms and signs are not attributable to any single diagnosis, each individual event should be recorded in the AE or SAE eCRF.

8.5.5 AEs secondary to other events

In general, for AEs secondary to other events (e.g., cascading event or clinical sequelae), the primary cause should first be identified, with the exception of severe or serious secondary events. If the secondary AE is clinically significant, and the two events are temporally independent, the secondary event should be recorded in the AE eCRF as a separate event. For example:

- If in a healthy adult vomiting has led to mild dehydration not requiring other treatment, only “vomiting” should be recorded in the eCRF.
- If vomiting has led to serious hydration, two events should be separated reported in the eCRF.
- If serious gastrointestinal hemorrhage has led to renal failure, two events should be separated reported in the eCRF.
- If dizziness has led to falling which further caused fracture, three events should be separated reported in the eCRF.
- If reduced neutrophils has led to infection, two events should be separated reported in

the eCRF.

- If the association between events is not clear, all the relevant events should be separately recorded in the AE eCRF.

8.5.6 Persisting or recurrent AEs

Persisting AEs refer to those AEs that have not resolved and are persisting over the interval between two evaluation time points. The initial intensity of the event should be recorded, and, in case the event has worsened in intensity, the worst intensity of the same event should be recorded as updated.

8.5.7 Preexisting medical states

After the subject has entered the study, those symptoms/signs existing at screening should be recorded and reported as an AE only when the severity, intensity, frequency or nature of the symptom/sign has worsened (except for worsening of the disease studied). The change from the previous state, e.g., “increased frequency of headache”, should be reflected in the record.

8.6 Serious Adverse Event (SAE)

8.6.1 Definition of SAE

An SAE refers to any AE occurring when using the study drug or placebo at any dose during any study period (screening/baseline, treatment period , follow-up period) which：

- Results in death
- Is life-threatening (posing an immediate risk of death to the subject)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires medical or surgical intervention to permanent injury or impairment

Other important medical events: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important

medical events that may not be immediately life-threatening or result in death or hospitalization but may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious.

8.6.2 SAE reporting

For any SAE occurring in the study, whether or not related to the study drug, the investigator should immediately give rescue treatment, and, within 24 hours of becoming aware of the SAE, complete, sign, date and send the SAE form to the CA, the Sponsor, the sponsor-designated CRO, and the Ethics Committee according to national requirements.

For any SAE, the symptoms, severity, duration, time of treatment, actions taken, follow-up duration and method and outcome should be recorded in detail.

The investigator must provide his/her assessment of causality when reporting the SAE. Where the investigator's assessment of causality is lost or not accessible, the sponsor's assessment should apply until the investigator's assessment eventually becomes available.

If the investigator cannot determine whether an AE constitutes an SAE, the AE would be regarded as an SAE before its nature is established. Such events should be communicated in written to the local authorities and investigators concerned according to the local requirements.

The investigator should follow up any SAEs (including those ongoing after end of study and occurring within 28 days following end of study) until a clear outcome is available to ensure that all the issues have been resolved. The specific follow-up information (e.g., whether occurring after end of study, whether special treatment is required, whether hospitalization is required) should be provided.

The investigator should provide Follow-up Report to the Sponsor and Sponsor-designated CRO until event resolution. Where the SAE has caused permanent impairment, the event should be followed up until considered stabilized.

If a female subject becomes pregnant during the study, the Pregnancy Report Form should be completed and expeditiously reported to the Sponsor and Sponsor-designated CRO in the same time frame as for SAE reporting, and this should be recorded in the eCRF so that the subject

can be followed up for the pregnancy outcome.

Any abortion, whether it is accidental, therapeutic or spontaneous, should also be reported in the Pregnancy Report Form.

Once a female subject becomes pregnant during the study, the study treatment should be immediately discontinued, and the investigator and sponsor should be notified. The investigator should provide advice to the subject, and discuss the risk and potential impact on the fetus if she insists to continue pregnancy. The subject must be discontinued from study, and be further monitored until termination of pregnancy.

8.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

8.7.1 Definition of SUSAR

A SUSAR refers to an adverse reaction to an investigational product of which the nature and severity are inconsistent with the existing clinical study information, including Investigator’s Brochure and Package Insert in pre-approval experience and Package Insert and/or Summary of Product Characteristics (SPC) in post-approval experience.

8.7.2 Assessment of expectedness

An AE is considered unexpected if its nature, severity and/or frequency is inconsistent with the information in the Reference Safety Information (e.g., the documents including the Investigator’s Brochure).It will be left to the discretion of the sponsor or sponsor-designated CRO whether an AE is expected or unexpected.

The following documents or circumstances will be used to determine whether an adverse reaction is expected:

(1) For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document.

(2) Reports which add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected".

Specific examples would be ① acute renal failure as a listed adverse reaction with a subsequent new report of interstitial nephritis and ② hepatitis with a first report of fulminant hepatitis.

8.7.3 Reporting of SUSARs

Any suspected, unexpected, serious adverse reactions should be reported expeditiously in the form of Individual Case Safety Reports （ICSRs） in accordance with the Criteria and Procedure for Expedited Reporting of Safety Data during Drug Clinical Trials (Center for Drug Evaluation, April 27, 2018). Expedited reporting also applies when the applicant and investigator cannot reach consensus on the causality and either the applicant or investigator cannot exclude the causality. Expedited reporting does not apply to:

（1）non-serious adverse events;

（2）serious adverse events unrelated to the investigational product;

（3）serious but expected adverse reactions.

With regard to serious adverse reactions related to the positive control, it is the responsibility of the sponsor or sponsor-designated CRO to decide whether or not to report to other drug manufacturers and/or directly to the national drug administration. The Sponsor or Sponsor-designated CRO must report these events to the drug manufacturer and, in any case, according to national requirements.

The Sponsor or the designated CRO should report any fatal or life-threatening, unexpected serious adverse reactions as early as possible but no later than 7 after first knowledge, followed by as complete a report as possible within 8 additional days. The application should report any non-fatal and non-life-threatening, unexpected serious adverse reactions as early as possible but no later than 15 after first knowledge. Within the prescribed time, initial report must meet the following minimum criteria:

(1) an identifiable patient;

(2) the name of the suspect medicinal product;

(3) an identifiable reporting source; and

(4) an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship.

After initial reporting, the sponsor or sponsor-designated CRO should continue tracking serious adverse reactions, and timely report any relevant new information or information on changes to the previous report in the form of follow-up reports, within 15 days after the new information becomes available.

The start date of expedited reporting is the date of obtaining clinical trial approval/implied approval from the national drug evaluation institution, and the end date of expedited reporting is the date when the last subject completes follow-up. Serious adverse events emerging after end of study or follow-up until the review conclusion is available should be reported by the investigator to the sponsor or sponsor-designated CRO, and should also be subject to expedited reporting if an unexpected serious adverse reaction is constituted.

In addition to ICSRs for unexpected serious adverse reactions, the Sponsor or Sponsor-designated CRO should also report other potential serious safety risk information to the national drug evaluation institution as early as possible while applying medical and scientific judgment for each situation. Unexpected serious adverse reactions and other potential serious safety risk information related to the investigational product that become available to the Sponsor or Sponsor-designated CRO from other sources should also be reported in an expedited fashion to the national drug evaluation institution.

Refer to the Criteria and Procedure for Expedited Reporting of Safety Data during Drug Clinical Trials for the electronic transmission method for individual case adverse reactions. For expedited reporting of other potential serious safety risk information, send emails to the CRO safety department at: safety@operacro.com

Note: The day of first knowledge by the applicant is defined as Day 0.

8.8 Significant adverse event

An significant adverse event refers to any AE or significant hematological or other laboratory

abnormality other than a serious adverse event for which specific medical actions (e.g., drug withdrawal, dose reduction and symptomatic treatment) have been taken.

8.9 Adverse event of special interest (AESI)

8.9.1 Potential drug-induced liver injury

This includes elevated ALT or AST with increased bilirubin or jaundice. Refer to the Hy's Law for the specific definition

ALT or AST elevation (>3.0×baseline) with total bilirubin elevation (>2.0×ULN) or jaundice and without cholestasis or other etiology of hyperbilirubinemia would indicate the presence of severe liver injury (according to the Hy's Law). Therefore the occurrence of any of the followings should be reported as an AE;

- Treatment-emergent ALT or AST >3.0×baseline with total bilirubin > 2.0×ULN (of which ≥35% is direct bilirubin)
- Treatment-emergent ALT or AST >3.0×baseline with jaundice

The most appropriate diagnosis or abnormal laboratory test result (where the diagnosis cannot be established) will be recorded in the AE eCRF as an AESI and be immediately reported to the sponsor within 24h of first knowledge.

8.9.2 Anaphylactoid reactions

Suspected allergic reactions include oropharyngeal edema, severe rash, and immediate hypersensitivity. If a suspected allergic reaction occurs during the study, antihistamines, epinephrine or other drugs should be given under the guidance of the investigator as needed for the subject's condition.

In the occurrence of a suspected allergic reaction, the subject will immediately discontinue study treatment, and the suspected allergic reaction will be recorded in the AE eCRF as an AESI and be immediately reported to the sponsor within 24h of first knowledge.

8.9.3 Acute kidney injury

The staging criteria for acute kidney injury are provided in Appendix 2. In the occurrence of a grade 3 acute kidney injury, the investigator will give the subject appropriate treatment as per

the clinical practice, and the acute kidney injury will be recorded in the AE eCRF as an AESI and be immediately reported to the sponsor within 24h of first knowledge.

8.10 Death

Any death occurring during the study must be reported to the sponsor or sponsor-designated CRO within 24h of first knowledge.

In case a subject is discontinued from study due to death, the event will be reported as a disease progression or an AE, and the cause of death will be recorded in the appropriate eCRF field. If the death is caused by both disease progression and other reason(s), the investigator must identify the primary cause of death and classify the reason for discontinuation appropriately.

The information to be included in the report includes the status of disease progression and the primary or second cause of death (if any).

Where there is an AE leading to death when recording the death event, a single medical term should be used to record this fatal AE, and this event should be reported expeditiously in an SAE term; if the cause of death remains unclear at the time of reporting, this is to be recorded as “death of unknown cause”, and “death of unknown cause” will first be reported expeditiously in an SAE term before further investigating the exact cause of death.

8.11 Definition of hospitalization

An AE requiring hospitalized treatment is considered to be serious. In general, an AE for which admission procedure is completed and treatment is given should be considered serious.

Hospitalization for elective surgery, routine clinical procedures, annual physical examination, in-hospital observation or as required in the Protocol, instead of being due to an AE, should not be considered as an AE but should be entered into the Clinical Evaluation Form and added to the eCRF. If any unexpected event occurs during this process, this should be reported as a “serious” or “non-serious” AE according to the general requirements.

Note: Hospitalization or prolongation of existing hospitalization for non-medical reasons, convenience or other reasons, or for the sole purpose of the clinical study does not fulfill a medical event, and therefore should not be regarded as an SAE.

8.12 Overdose

Overdose is defined as where the dose of the investigational product used by the subject exceeds the protocol-specified dose by at least 20% for any reason (intentionally or accidentally).

If the investigator considers that an overdose has occured during the clinical study, the investigator should report it to the sponsor in the same time frame as for SAE reporting, even though the circumstances of the occurrence are not included in the definition described above. Overdose should be recorded in the AE page of the eCRF and be indicated in the source record as underlined.

In the event of overdose and the symptoms associated with overdose, an AE should be reported. If the symptoms meet the criteria for an SAE, the event should be reported as per the procedure and time frame for SAE reporting. In the event of overdose alone without any associated clinical symptoms or laboratory abnormalities, the event should be reported to the sponsor within 24h after the investigator becomes aware of it, using the term “accident without AE or intentional overdose” (overdose itself should not be reported as an AE or SAE).

9 Data management

9.1 Completion and transfer of eCRF

Data management for this study will be the responsibility of the CRO and its designated data department, so as to ensure the authenticity, completeness, secrecy and traceability of the study data.

All data to be entered into the eCRF will originate from the source documents, and will be entered by the investigator or investigator-designated personnel, where the completeness and accuracy of information should be ensured. In case of any entry error requiring correction, revisions can be made in a formal manner as per the Instructions for eCRF Completion, and the eCRF system will automatically capture the name of person and date of making the revision.

Completed eCRFs should be timely submitted online to the eCRF system, in which the data will undergo source data verification (SDV), Data Manager (DM) review and queries, etc., to make sure that no issues remain, and the investigator will need to e-sign to confirm before database lock.

9.2 Design and establishment of database

The database will be established by the sponsor or its designated data department, and should comply with the requirements of FDA 21 CFR Part 11. The database should allow management of system login and the data traces such as data entry, revision and deletion. Whenever possible, the Clinical Data Interchange Standards Consortium (CDISC) standard should be adopted to establish the database.

9.3 Data entry

Data will be entered into the Electronic Data Collection (EDC) database by authorized personnel. After completion of data entry, the EDC system will perform data verification using pre-programmed, study-specific logic check to ensure data completeness and accuracy.

9.4 Data verification and query

After data are entered and saved in EDC system, system checks will run and queries will be

kicked which require the investigator to review and respond. Data management staff will review answered queries and close the queries if the responses are acceptable. Data Manager will also conduct manual review on the entered data to ensure the logic, consistency, and accuracy of the data.

Subject data listings/reports will be programmed to support manual data review during the study progress. Manual queries will be added in the EDC system when there is a need for the site staff to clarify/verify/confirm the data. Data Manager should make sure that all queries are resolved before database lock.

10. Statistical analysis

The specific statistical analysis methods will be specified in and subject to the final Statistical Analysis Plan (SAP).

10.1 Sample size estimation

This study is concerned with a public health emergency. Taking into account the observed clinical recovery status of adults patients with COVID-19-Moderate type treated with the antiviral therapies recommended in the current guidelines, it is estimated that the median time to clinical recovery in the control group would be approximately 14 days, and the addition of test drug could reduce this time to within 9 days (i.e., HR≥1.56); at the two-sided significance level of 0.05 and with an over 80% power, approximately 226 subjects (randomized 1:1 to the test or control group) will be required; considering the size of randomization block and the 10% dropout rate, a total of 256 subjects will actually be required to be enrolled. At least 100 subjects will be enrolled in Italy. This number can be increased in case of elevated monthly recruitment rate in Italy, because the study will use competitive enrolment

10.2 Statistical analysis sets

Full Analysis Set: A set consisting of as many randomized subjects meeting the Intent-to-Treat (ITT) principle as possible. Only the randomized subject who have violated any key inclusion/exclusion criteria, have not received any study treatment and for whom no safety, efficacy or 2019-nCov nucleic acid test data are available after randomization will be removed.

Per-protocol Set (PPS): A set consisting of subjects in the FAS who have not had any protocol violation that may interfere with efficacy evaluation.

Safety Set (SS): A set consisting of all the subjects who have received at least 1 dose of study treatment.

10.3 General rules

Statistical analyses will be performed using SAS 9.4 (or above) software. Continuous variables will be described by mean, standard deviation, median, minimum, and maximum. Categorical variables will be described by number and percentage of subjects in each category. t-test or

Wilcoxon rank-sum test (depending on the data distribution pattern) will be used for inter-group comparison of continuous variables; chi-square test or Fisher exact test (where chi-square test does not apply) will be used for inter-group comparison of categorical variables; Wilcoxon rank-sum test or CMH test will be used for rank data. Unless otherwise specified, all the statistical analyses will be two-sided, and $p<0.05$ (two-sided) would indicate a statistically significant difference in the variable tested.

10.4 Subjects disposition

Subjects disposition will be described for all the subjects who have received screening. Subjects screening, enrolment, discontinuation from study, completion of treatment and follow-up, and inclusion in different analysis sets will be described. Subjects screen failures, screen successes failing to be enrolled, completion of treatment, discontinuation from study and reasons for excluding subjects from each analysis set will be summarized.

10.5 Demographics and baseline characteristics

Subjects demographics and baseline characteristics will be described by descriptive statistics and be listed, using the analysis methods provided in General Rules.

10.6 Safety analysis

Safety analysis will be based on SS. AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) (the latest version at the time of analysis), and will be summarized descriptively by System Organ Class (SOC)/ Preferred Term (PT). The overall incidence and incidences by SOC/PT will be summarized for AEs, adverse reactions, treatment-emergent AEs (TEAEs), study treatment-related AEs, significant AEs, and SAEs. The number of subjects experiencing AEs and number of AE occurrences during the treatment period will be summarized by SOC and severity. AEs, adverse reactions, TEAEs, study treatment-related AEs, significant AEs, and SAEs, etc., will be listed.

Changes in laboratory tests will be presented by a cross table specifying the changes from abnormal/normal to abnormal/normal before and after treatment. The laboratory test results will be listed.

Changes in ECG will be presented by a cross table specifying the changes from abnormal/normal to abnormal/normal before and after treatment. QTc measurements will be described by >450 ms, >480 ms, and >500 ms， and by changes from baseline >30 ms and >60 ms. The ECG results will be listed.

Vital signs and physical examinations at each visit will be analyzed and listed, using the analysis methods provided in General Rules.

10.7 Efficacy analysis

Efficacy analyses will be primarily based on FAS, and also be based on PPS.

Log-rank test will be used for inter-group comparison of the primary endpoint “time from randomization to clinical recovery”, and the hazard ratio (HR) (with its 95% CI) of clinical improvement will be calculated by univariate Cox regression. Intent-to-treat analysis will be used for the primary endpoint. With regard to the secondary efficacy endpoints, log-rank test will be used for inter-group comparison of time from randomization to symptom improvement or seroconversion, and the hazard ratio (HR) (with its 95% CI) of clinical improvement will be calculated by univariate Cox regression. The corresponding statistical methods appropriate for the variable type will be used for comparison of other secondary efficacy endpoints and safety endpoints. t-test or Wilcoxon rank-sum test (depending on the data distribution pattern) will be used for continuous variables; chi-square test or Fisher exact test (where chi-square test does not apply) will be used for categorical variables. Wilcoxon rank-sum test or CMH test will be used for rank data. The efficacy data will be listed.

11 Administrative issues

11.1 Statement

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Seventh revision, 2013), the Convention of Oviedo, April 4th, 1997 and additional Protocol January 12th1998 and will be consistent with GCP. In addition, the study will follow international laws and regulations and national laws of Italy, as well as any applicable guidelines. If there are conflicts between local laws and regulations, the more stringent requirements will be adopted.

The study will be conducted in compliance to the present protocol: all its revisions must be discussed with and prepared by the Sponsor. The Investigator should not implement any deviation or change to the study protocol without prior review and documented approval/favorable opinion from the Ethical Committee of an Amendment. Any significant deviation must be documented in the CRF.

11.2 Ethical considerations

According to the regulatory requirements of the country, the investigator will submit the study documentation to the relevant Ethics Committee.

A copy of the letter of approval from the Ethics Committee, which contains a list of the names and occupations of the members of the Ethics Committee having participated at the session, as well as a list of documents reviewed, must be received by the sponsor prior to shipment of drug supplies to the investigator.

Approval of the Ethics Committee and drug regulatory authorities must have been obtained before study commencement.

All protocol amendments must be submitted to the Ethics Committee for approval.

The investigator must also inform the Ethics Committee of any serious or unexpected adverse events occurring during the study which are likely to affect the safety of the subjects or the conduct of the trial.

11.3 Insurance

An additional insurance for the patients enrolled, specifically designed to cover the clinical trial, has been taken out (HDI Global SE, number 390-76217803-30016).

11.4 Source data verification

Investigators should make the best of source data of this study to safeguard the subjects' rights and confidentiality. The investigator must allow the monitor/auditor/inspector to inspect and review all relevant source documents to confirm that the accuracy of source data and study progression can be authenticated. If source documents authentication is not possible, investigators should agree to assist the monitor/auditor/inspector in further confirming data quality control

11.5 Quality Assurance/Audit

Quality assurance audits of this study could be conducted by the sponsor or its designee. GCP audits can also be performed by the drug regulatory authorities. The quality assurance auditor should have access to all medical records, the trial related files and correspondence, and the informed consent documentation that is relevant to this study.

11.6 Informed Consent

The investigator is responsible for explaining the purpose, methods, benefits and potential risks associated with participating in this study. An Informed Consent Form (ICF) signed by the subject must be obtained before starting any study-related procedures. The informed consent should be given both orally and in a written form. The ICF must be dated and signed personally by the subject (or parent/legal guardian for any subjects who for any reason are not able to sign ICF personally). A copy of the signed ICF and information sheet should be retained by the subject.

The subject must accept by signing the ICF that the source study data may be examined by the sponsor, the drug regulatory authorities, a mandated auditor and/or the study monitor in compliance with the statement of confidentiality.

11.7 Rules for amending the protocol

Any amendment to the Protocol, once the final version has been issued, has to be detailed in a protocol amendment history. All protocol amendments must be signed, numbered and dated at least by the investigator and the sponsor.

All protocol amendments must be formally approved by the Ethics Committee, and, if required, be submitted to the local drug regulatory authorities. Purely administrative amendments can be sent to the ECs for information only. All the relevant documents should be provided to the sponsor.

11.8 Electronic Case Report Form (eCRF)

eCRFs will be setup in the EDC system by the Sponsor-designated CRO Data Manager. Patients are identified on the eCRF only by appropriate coded identifier (e.g. subject number) and subject initials. eCRFs are used to record clinical trial data and are an integral part of the study and subsequent reports. The entries, therefore, must be accurate and complete. The eCRF will be completed by the investigator/authorized persons (mentioned in the Study Authorization Form) in EDC system. All required data fields must be completed and saved. The investigators are required to declare the accuracy of all data recorded in the eCRF via electronic signature.

eCRFs must be completed after each visit to reflect subject status during the course of the study.

Documented medical histories and narrative statements relative to the subject's progress during the study will be maintained by the investigator. These records should include the following: originals or copies of laboratory, other medical test results (e.g, ECG), which must be kept at the site along with the patient’s medical file.

11.9 Monitoring

The sponsor assigns monitors for on-site monitoring. These monitors belong to the Sponsor-authorized CRO, and have to work according to the applicable SOPs. Monitoring visits will be performed by monitors at regular intervals throughout the course of the study.

The monitor ensures data completeness, accuracy, and consistency with source data by accessing and reviewing the study-related source data and eCRF entries according to SOPs.

eCRFs, copies of laboratory and medical test results must be available at all times for inspection

by the monitors, auditors and health authorities. The monitor will review all eCRFs and written informed consents.

11.10 Secrecy Agreement and patient privacy

The investigator commits himself/herself to keep secret from third parties any confidential information obtained from the Sponsor or from the manufacture of the tested drug, which in connection with the present contractual relationship are made available or disclosed, and to use this knowledge only as agreed upon.

This commitment is valid and independent of the existence and the duration of the present actual relationship, but only so far and so long as the sponsor is reasonably and justly interested in the investigator's maintaining this secrecy undertaking.

The investigator also commits him/her to protect the subjects' privacy. In all documents submitted to the sponsor, the identity of a subject can only be determined with the subject number, rather than with the subject's name, inpatient number or other documents or numbers that may reveal the subject's identity. The investigator must take good care of the names and addresses of subjects and enrollment lists corresponding to subject numbers. These enrollment lists should be strictly kept confidential by the investigator, and cannot be submitted to the sponsor. The Sponsor, the Sponsor-designated CRO and regulatory authorities have direct access to subject records; for the protection of the enrolled subjects, this study will be conducted respecting the actual general data protection regulations (GDPR). According to local Legislation regarding the protection of personal data, the responsible of the data treatment/intervention of the subject in each clinical site is the medical doctor responsible of the site.

12 Publication

ASST FATEBENEFRATELLI SACCO as the Sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and ASST FATEBENEFRATELLI SACCO personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple sites, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.

ASST FATEBENEFRATELLI SACCO will have the final decision regarding the manuscript and publication.

The Sponsor is committed to publication of results after study conclusion through scientific journals, ministerial bulletins, direct communications to the EC, etc., also in the case of negative results; in addition, the Sponsor agree to notice all the Investigators (Italian Law DM 12/5/06, art.5) and to comply with the prescriptions of the Italian Ministry of Health (n. 6 dated 2/9/2002) regarding the rules for the transparency of data and their publication. The Sponsor is aware of its specific communication obligations placed by the Italian Law D.Lgs. 211/2003 as modified by DL 269/2003 and into law n. 326/2003.

13 Archiving of documents

The investigator at each investigational site must appropriately store the essential trial documents, including the Investigator Trial File according to related regulations. All essential documents should be retained until at least 5 years after completion of study. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

14. Appendices

Appendix I: Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia

Note: if the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* is updated, the latest version shall prevail.

Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia

(Trial Version 5)

Since December 2019, multiple cases of novel coronavirus pneumonia (NCP) have been identified in Wuhan, Hubei. With the spread of the epidemic, such cases have also been found in other parts of China and abroad. As an acute respiratory infectious disease, NCP has been included in class B infectious diseases prescribed in the *Law of the People's Republic of China on Prevention and Treatment of Infectious Diseases*, and managed as an infectious disease of class A.

With a better understanding of the epidemic and accumulation of diagnosis and treatment experience, we now revise the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 4)* and release the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 5).*

I. Etiological Characteristics

The novel coronaviruses belong to the β genus. They have envelopes, and the particles are round or oval, often polymorphic, with diameter being 60 to 140 nm. Their genetic characteristics are significantly different from SARSr-CoV and MERSr-CoV. Current research shows that they share more than 85% homology with bat SARS-like coronaviruses (bat-SL-CoVZC45). When isolated and cultured in vitro, the 2019-nCoV can be found in human respiratory epithelial cells in about 96 hours, however it takes about 6 days for the virus to be found if isolated and cultured in Vero E6 and Huh-7 cell lines.

Most of the know-how about the physical and chemical properties of coronavirus comes from the research on SARS-CoV and MERS-CoV. The virus is sensitive to ultraviolet and heat. Exposure to 56℃ for 30 minutes and lipid solvents such as ether, 75% ethanol, chlorine-

containing disinfectant, peracetic acid, and chloroform can effectively inactivate the virus. Chlorhexidine has not been effective in inactivating the virus.

II. Epidemiological Characteristics

(I) Source of infection

Now, the patients infected by the novel coronavirus are the main source of infection. *Asymptomatic infected people can also be an infectious source.*

(II) Transmission

Transmission of the virus happens mainly through respiratory droplets and close contact. *The transmission through aerosol and gastrointestinal tract remains to be confirmed.*

(III) Susceptible groups

People are generally susceptible.

III. Clinical Characteristics

(I) Clinical manifestations

Based on the current epidemiological investigation, the incubation period is one to fourteen days, mostly three to seven days.

Main manifestations include fever, fatigue and dry cough. Nasal congestion, runny nose, sore throat and diarrhea are found in a few cases. Severe cases mostly developed dyspnea and/or hypoxemia after one week. In severe cases, patients progress rapidly to acute respiratory distress syndrome, septic shock, metabolic acidosis that is difficult to correct, and blood coagulation dysfunction. It is worth noting that for severe and critically ill patients, their fever could be moderate to low, or even barely noticeable.

The patients with mild symptoms did not develop pneumonia but only low fever and mild fatigue.

From current situations, most patients have good prognosis and a small number of patients are critically ill. The prognosis for the elderly and patients with chronic underlying diseases is poor. Children’s symptoms are relatively mild.

(II) Laboratory Tests

In the early stages of the disease, peripheral WBC count is normal or decreased and the lymphocyte count decreases. Some patients see an increase in liver enzymes, lactate dehydrogenase (LDH), muscle enzymes and myoglobin. Elevated troponin is seen in some critically ill patients while most patients have elevated C-reactive protein and erythrocyte sedimentation rate and normal procalcitonin. In severe cases, D-dimer increases and peripheral blood lymphocytes progressively decrease.

Novel coronavirus nucleic acid can be detected in *nasopharyngeal swabs*, sputum, lower respiratory tract secretions, blood, feces and other specimens.

(III) Chest imaging

In the early stage, imaging shows multiple small patchy shadows and interstitial changes, apparent in the outer lateral zone of lungs. As the disease progresses, imaging then shows multiple ground glass opacities and infiltration in both lungs. In severe cases, pulmonary consolidation may occur while pleural effusion is rare.

IV. Case Definitions

Provinces other than Hubei:

(I) Suspect cases

Considering both the following epidemiological history and clinical manifestations:

1. Epidemiological history

(1) History of travel to or residence in Wuhan and its surrounding areas, or in other communities where cases have been reported within 14 days prior to the onset of the disease;

(2) In contact with novel coronavirus infected people (with positive results for the nucleic acid test) within 14 days prior to the onset of the disease;

(3) In contact with patients who have fever or respiratory symptoms from Wuhan and its surrounding area, or from communities where confirmed cases have been reported within 14 days before the onset of the disease;

(4) A cluster of cases.

2. Clinical manifestations

(1) Fever and/or respiratory symptoms;

(2) The aforementioned imaging characteristics of NCP;

(3) Normal or decreased WBC count and decreased lymphocyte count in the early stage of onset.

A suspect case has any of the epidemiological history plus any two clinical manifestations or all three clinical manifestations if there is no clear epidemiological history.

(II) Confirmed cases

Suspect cases with one of the following etiological evidence:

1. Real-time fluorescent RT-PCR of respiratory tract or blood specimens indicates positive for new coronavirus nucleic acid;

2. Viral gene sequence of respiratory tract or blood specimens is highly homologous to known new coronaviruses.

Hubei:

(I) Suspect cases

Considering both the following epidemiological history and clinical manifestations:

1．Epidemiological history

(1) History of travel to or residence in Wuhan and its surrounding areas, or in other communities where cases have been reported within 14 days prior to the onset of the disease;

(2) In contact with novel coronavirus infected people (with positive results for the nucleic acid test) within 14 days prior to the onset of the disease;

(3) In contact with patients who have fever or respiratory symptoms from Wuhan and its surrounding area, or from communities where confirmed cases have been reported within 14 days before the onset of the disease;

(4) A cluster of cases.

2. Clinical manifestations

(1) Fever and/or respiratory symptoms;

(2) Normal or decreased WBC count and decreased lymphocyte count in the early stage of onset.

Has any of or no epidemiological history plus any two clinical manifestations;

(II) Clinical diagnosis cases

Suspect cases with imaging characteristics of NCP;

(III) Confirmed cases

Clinical diagnosis cases or suspect cases with one of the following etiological evidence:

1. Real-time fluorescent RT-PCR of respiratory tract or blood specimens indicates positive for new coronavirus nucleic acid;

2. Viral gene sequence of respiratory tract or blood specimens is highly homologous to known new coronaviruses.

V. Clinical Classification

(I) Mild cases

The clinical symptoms were mild, and there was no sign of pneumonia on imaging.

(II) Moderate cases

Showing fever and respiratory symptoms with radiological findings of pneumonia.

(III) Severe cases

Cases meeting any of the following criteria:

1. Respiratory distress, RR≥30 breaths/min;

2. Oxygen saturation≤93% at rest;

3. Arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2)≤300mmHg

(l mmHg=0.133kPa).

(IV) Critical cases

Cases meeting any of the following criteria:

1. Respiratory failure and requiring mechanical ventilation;

2. Shock

3. With other organ failure that requires ICU care.

VI. Differential Diagnosis

NCP is mainly distinguished from other known viral pneumonia infections such as influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, SARS-associated coronavirus. It should be also distinguished from mycoplasma pneumoniae, chlamydia pneumoniae and bacterial pneumonia. Moreover, it should also be distinguished from non-infectious diseases such as vasculitis, dermatomyositis and organizing pneumonia.

VII. Case Finding and Reporting

Provinces other than Hubei:

Health professionals in medical institutions of all types and at all levels, upon discovering suspect cases that meet the definition, should immediately put them in single room for isolation and treatment. If the cases are still considered as suspected after consultation made by hospital experts or attending physicians, it should be reported directly online within 2 hours; samples should be collected for new coronavirus nucleic acid testing and suspect cases should be safely transferred to the designated hospitals immediately. People who have been in close contact with patients who have been confirmed of new coronavirus infection are advised to perform new coronavirus pathogenic testing in a timely manner, even though common respiratory pathogens are tested positive.

Suspect cases who have nuclei acid tests negative for respiratory tract pathogen twice consecutively (sampling interval being at least one day) can be excluded.

Hubei:

Health professionals in medical institutions of all types and at all levels, upon discovering suspect cases and clinical diagnosis cases that meet the definition, should immediately put them in single room for isolation and treatment. A suspect case and clinical diagnosis case should be treated in isolation in a single room. Samples should be collected from suspect cases and clinical diagnosis cases in a timely manner for pathogenic testing.

VIII. Treatment

(I) Treatment venue determined by the severity of the disease

1. Suspected and confirmed cases should be isolated and treated at designated hospitals with effective isolation, protection and prevention conditions in place. A suspect case should be treated in isolation in a single room. Confirmed cases can be treated in the same room.

2. Critical cases should be admitted to ICU as soon as possible.

(II) General treatment

1. Letting patients rest in bed and strengthening support therapy; ensuring sufficient caloric intake for patients; monitoring their water and electrolyte balance to maintain internal environment stability; closely monitoring vital signs and oxygen saturation.

2. According to patients' conditions, monitoring blood routine result, urine routine result, c-reactive protein (CRP), biochemical indicators (liver enzyme, myocardial enzyme, renal function etc.), coagulation function, arterial blood gas analysis and chest imaging. The cytokines detection can be performed if necessary.

3. Timely providing effective oxygen therapy, including nasal catheter, mask oxygenation, and nasal high-flow oxygen therapy.

4. Antiviral therapy: currently, there is no confirmed effective antiviral therapy. Hospitals can try Alpha-interferon (5 million U or equivalent dose each time for adults, adding 2ml of sterilized water, atomization inhalation twice daily), lopinavir/ritonavir (200mg/50mg per pill), two pills each time, twice daily, or ribavirin which is suggested to be intravenously given jointly

with interferon or lopinavir/ritonavir (4g for the first dose for adults, once every 8 hours at the next day, 1.2g each time, or 8 mg/kg iv. once every 8 hours). *Be aware of such adverse reactions as lopinavir/ritonavir-related diarrhea, nausea, vomiting, liver damage, and pay attention to interactions with other drugs.*

5. Antibiotic drug treatment: Blind or inappropriate use of antibiotic drugs should be avoided, especially in combination with broad-spectrum antibiotics.

(III) Treatment of severe and critical cases

1. Treatment principle: On the basis of symptomatic treatment, complications should be proactively prevented, underlying diseases should be treated, secondary infections also be prevented, and organ function support should be provided timely.

2. Respiratory support:

(1) Oxygen therapy: Patients with severe symptoms should receive nasal cannulas or masks for oxygen inhalation and timely assessment of respiratory distress and/or hypoxemia should be performed.

(2) High-flow nasal-catheter oxygenation or noninvasive mechanical ventilation: When respiratory distress and/or hypoxemia of the patient cannot be alleviated after receiving standard oxygen therapy, high-flow nasal cannula oxygen therapy or non-invasive ventilation can be considered. If conditions do not improve or even get worse within a short time (1-2 hours), tracheal intubation and invasive mechanical ventilation should be used in a timely manner.

(3) Invasive mechanical ventilation: Lung protective ventilation strategy, namely low tidal volume (4-8ml/kg of ideal body weight) and low inspiratory pressure (platform pressure <30cmH_20) should be used to perform mechanical ventilation to reduce ventilator-related lung injury. There are many cases of human-machine asynchronization, therefore sedation and muscle relaxants should be used in a timely manner.

(4) Rescue therapy: Pulmonary re-tensioning is recommended for patients with severe ARDS. With sufficient human resources, prone position ventilation should be performed for more than

12 hours per day. If the outcome of prone position ventilation is poor, extracorporeal membrane oxygenation (ECMO) should be considered as soon as possible.

3. Circulatory support: On the basis of adequate fluid resuscitation, hospitals should improve microcirculation, use vasoactive drugs and perform hemodynamic monitoring when necessary.

4. Other therapeutic measures

The glucocorticoids can be used in a short period of time (three to five days) based on the degree of dyspnea, progress in chest imaging. It is recommended that dose should not exceed the equivalent of methylprednisolone 1-2 mg/kg/day. Note that a larger dose of glucocorticoid will delay the removal of coronavirus due to immunosuppressive effects. Xuebijing 100ml/time can be administered intravenously twice a day. Intestinal microecological regulators can be used to maintain intestinal microecological balance and prevent secondary bacterial infections. For critically ill patients with high inflammatory reactions, extracorporeal blood purification technology can be considered when conditions permit.

Patients often suffer from anxiety and fear and they should be supported by psychological counseling.

(IV) Traditional Chinese Medicine treatment

This disease belongs to the category of plague in traditional Chinese medicine (TCM), caused by the epidemic pathogenic factors. According to the different local climate characteristic and individual state of illness and physical conditions, the following treatment Protocol may vary.

1. During medical observation

Clinical manifestation 1: fatigue and gastrointestinal discomfort

Recommended Chinese patent medicine: Huoxiang Zhengqi capsules (pills, liquid, or oral solution)

Clinical manifestation 2: fatigue and fever

Recommended Chinese patent medicine: Jinhua Qinggan granules, Lianhua Qingwen capsules (granules), Shufeng Jiedu capsules (granules), Fangfeng Tongsheng pills (granules)

2. During clinical treatment

(1) Mild cases: cold dampness and stagnation lung syndrome

Clinical manifestations: fever with aversion to cold or no fever, dry cough, dry throat, tiredness and fatigue, chest tightness, abdominal distention and fullness, or vomiting, loose stool. Tongue is pale or faint red, the coating is white and greasy and the pulse is moisten.

Recommended prescription: Cangzhu 15g, Chenpi 10g, Houpo 10g, Huoxiang 10g, Caoguo 6g, Raw ephedra 6g, Qianghuo 10g, ginger 10g, Betel nut 10g

(2) Moderate cases: Plague poison and lung-closing syndrome

Clinical manifestations: fever or alternate attacks of chill and fever, cough with little sputum or yellowish phlegm, abdominal distention and constipation; Chest tightness and anhelation, cough and wheezing, asthma on exercise; Red tongue, yellow greasy coating, slippery pulses.

Recommended prescription: almond 10g, raw gypsum 30g, Gualou 30g, raw rhubarb 6g (later), raw ephedra 6g, lepidium seed 10g, peach seed 10g, Caoguo 6g, Betel nut 10g, Cangzhu 10g;

Recommended Chinese patent medicines: Xiyanping injection and Xuebijing injection

(3) Critical cases (syndrome of inner blocking causing collapse)

Clinical manifestations: dyspnea, asthma on exercise or need mechanical ventilation, fainting, irritability, cold sweating, dark purple tongue, thick or dry moss, large floating roots.

Recommended prescription: 15g of ginseng, 10g of Heishun tablets (decoct first), 15g of dogwood, delivered with Suhexiang Pill or Angong Niuhuang Pill.

Recommended Chinese patent medicines: Xuebijing injection, Shenfu injection and Shengmai injection

(4) Convalescent period: Lung and spleen qi deficiency syndrome

Clinical manifestations: shortness of breath, tiredness and fatigue, anorexia, nausea, distention and fullness, weak stool, loose stool and uneasiness; pale enlarged tongue, pale and greasy moss;

Recommended prescription: French Pinellia 9g, Chenpi 10g, Codonopsis 15g, Sunburn

Astragalus 30g, Poria 15g, Huoxiang 10g and Amomum villosum 6g (later)

IX. Isolation Removal and After-discharge Notice

Body temperature is back to normal for more than three days; Respiratory symptoms improve obviously; Nuclei acid tests negative for respiratory tract pathogen twice consecutively (sampling interval being at least one day). Those who meet the above conditions can be discharged from isolation or transferred to other corresponding department to receive treatment of other diseases.

X. Patients Transportation Principles

Patients should be transported in accordance with the *Work Protocol for Transfer of the Novel Coronavirus Pneumonia Patients (Trial Version)* issued by the National Health Commission.

XI. Nosocomial Infection Prevention and Control

Measures to prevent and control nosocomial infection should be implemented in accordance with the requirements of the *Technical Guidelines for the Prevention and Control of Infection by the Novel Coronavirus in Medical Institutions (First Edition)* and the *Guidelines on the Usage of Common Medical Protective Equipment against Novel Coronavirus Infection (Trial Version)* formulated by the National Health Commission.

Appendix II：Staging of Acute Kidney Injury (AKI)

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline，or ≥0.3 mg/dL(≥26.5 μmol/L) increase	<0.5mL/kg/h for 6-12hours
2	2.0-2.9 times baseline	<0.5 mL/kg/h≥12 hours
3	3.0 times baseline，or Increase in serum creatinine to≥4.0 mg/dL(≥353.6 μmol/L)，or Initiation of rental replacement therapy，or In patients<18 years, decrease in eGFR to f<35 ml/min/1.73 m^2	<0.3 ml/kg/h≥24 hours，or Anuria≥12 hours

Source：Khwaja, Arif. KDIGO Clinical Practice Guidelines for Acute Kidney Injury[J]. Nephron Clinical Practice, 120(4):179-184.

15 References

[1] Chen BC.A New Antiviral Agent——Baloxavir marboxil)[J].Herald of Medicine,2019.