CONFIDENTIAL

CLINICAL STUDY REPORT

Safety and Efficacy of Favipiravir in COVID-19 Patients with Pneumonia
A randomized, double blind, placebo-controlled study

Study code/Protocol:	FAVID-01-20-SP	Study development phase:	Phase II
EudraCT number:	2020-002753-22	Investigational medicinal product:	Favipiravir

Indication:	Novel or re-emerging influenza virus infection in patients for which other anti-influenza virus drugs are either ineffective or not sufficiently effective.
Sponsor:	Ferrer Internacional, S.A.

First patient enrolled:	November 3rd, 2020	Last patient last visit:	October 5th, 2021
Version:	Final 1.0	Date:	July 26th, 2022

Investigator coordinating:	Dr. Juan Pablo Horcajada
Sponsor signatory:	Rebeca Aldonza Aguayo

2 SYNOPSIS

Name of the Sponsor: Ferrer Internacional, S.A.		
Name of Finished Product: Favipiravir		
Name of Active Ingredient: T-705a		
STUDY CODE: FAVID-01-20-SP		
EUDRACT NUMBER: 2020-002753-22		
TITLE OF STUDY: Safety and Efficacy of Favipiravir in COVID-19 Patients with Pneumonia. A randomized, double blind, placebo-controlled study.		
COORDINATING INVESTIGATOR: Dr. Juan Pablo Horcajada		
STUDY CENTRES (enrolling patients): Hospital del Mar Hospital Universitari Joan XXIII de Tarragona Hospital de Sant Pau i Santa Tecla		
PUBLICATION (REFERENCE): Not applicable (N/A)		
STUDY PERIOD (YEARS): Date of first enrolment: November 3rd, 2020 Date of patient last visit: October 5th, 2021		
PHASE OF DEVELOPMENT: Phase II		
BACKGROUND AND RATIONALE: Favipiravir is an antiviral agent approved for novel or re-emerging influenza virus infection in patients for which other anti-influenza virus drugs are either ineffective or not sufficiently effective. Since its mechanism of action is selective inhibition of viral RNA polymerase, favipiravir may also be effective for RNA viruses other than influenza virus. In fact, it has been reported to be effective against the Ebola virus, Arenaviridae, and Bunyaviridae. SARS-COV2, reported for the first time at the end of 2019, belongs to the Coronaviridae family of viruses within the order Nidovirales. It has been reported that favipiravir's concentration that inhibits 50% (EC50) of SARS-COV2 virus, in Vero E6 cells, was 61.88 µM. This corresponds to a concentration of 9.72 µg/mL, which is almost equivalent to 10.5 µg/mL for EC50 of Ebola virus. In a clinical study in patients with Ebola virus infection, the currently approved dose (1600/600 mg twice daily) was administered for 3 to 11 days. The survival rate in these patients treated with existing treatment (historical control) was 35%, while the survival rate in patients treated with favipiravir was 56% with significant difference. In addition, when favipiravir was administered along with interferon to 26 COVID-19 patients, resolution of fever was observed on Day 2 after administration in 78% of the patients and lung image symptoms improved within 3 days in 38% and within 6 days in 70% of the patients. Thus, early improvement was reported as compared to Kaletra® (lopinavir 200 mg/ritonavir 50 mg). In a clinical pharmacology study in which 1800 mg of favipiravir was administered twice daily on Day 1 and 800 mg of favipiravir was administered twice daily on Day 2 and thereafter (1800/800 mg twice daily) for 22 days to healthy Japanese adult males aged 20 to 39 years, the peak plasma concentration of favipiravir remained at approximately 87 to 104 µg/mL on Day 5 and after, and C_{min} remained at approximately 56 to 75 µg/mL after the 2nd administration on Day 1. This value exceeds 9.72 µg/mL, the EC50 of favipiravir for		

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the SARS-COV2 virus mentioned above and is significant even when the human protein binding rate of favipiravir of approximately 50% is taken into consideration. Therefore, efficacy of favipiravir in COVID-19 patients is supported.

At the time of study initiation, no established treatment for COVID-19 was available and epidemiological studies suggested a risk of further increase in patient exposure in the future. Considering that this viral infection has such a relatively high infectivity, the development of effective treatments for COVID-19 was urgently needed. If the therapeutic effect of favipiravir on COVID-19 could be verified in humans, it could contribute to the improvement of public health. Therefore, Ferrer Internacional, S.A., in collaboration with Hospital del Mar (Barcelona) and FUJIFILM Toyama Chemical Co., Ltd., has planned this clinical trial.

OBJECTIVES:

The overall objective of the study was to evaluate the clinical safety and potential efficacy of favipiravir relative to the control arm in patients hospitalized with COVID-19.

METHODOLOGY:

Since the primary objective of this clinical trial was to verify the therapeutic effect of favipiravir on COVID-19, it was conducted as a randomized double-blind trial to reduce the effects of bias if possible. Moreover, the trial was conducted as a multicenter study to improve the universality of the study results. Since no treatment method was established for COVID-19 at the time of study initiation, the existing treatment (i.e., standard of care at the study site) plus placebo was selected as a control (except for prohibited medications detailed in the protocol) in addition to the symptomatic treatment. Thus, the trial was designed to confirm that better responses are obtained in the group treated with favipiravir in addition to the existing treatment compared to the group treated with the existing treatment alone plus placebo.

NUMBER OF PATIENTS (planned and analyzed):

	Favipiravir group	Control group	Total
No. planned:	50	50	100
No. screened:	24	22	46
No. randomised and treated:	24	22	46
Males/females:	17/6	14/7	31/13
Mean age (range):	51.4 (33,70)	50.9 (32,64)	51.2 (32,70)
No. analysed for efficacy:			
Modified intent-to-treat (mITT)	23	21	44
Per Protocol Set (PPS)	13	12	25
No. analysed for safety:			
Safety Set	23	21	44
No. completed the study:	19	19	38

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

Patients included were adults from 18 to 85 years of both genders, with categories 3 to 5 on the ordinal scale. At the time of enrolment patients had to be tested positive for SARS-COV2 on RT-PCR test from respiratory specimen(s), present new lung lesions on chest images (chest x-ray, CT scan, etc.), and SpO2 < 94%. Moreover, patients had to meet at least 2 of the following: fever of 37.5°C or higher, respiratory rate ≥ 24/min and cough. For premenopausal female patients, patients had to be confirmed to be negative on a pregnancy test before administration of the study drug. Patients had to understand the contents of this study and had to be able to provide written consent by themselves or by legally authorized representative. During the influenza virus season, if the incidence is above the epidemic threshold, patients with a negative test result

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Name of Active Ingredient: T-705a

Reasons for exclusions were increased procalcitonin levels (1 ng/ml or higher), concurrent bacterial infection, abnormal NT-pro BNP levels (400 pg/mL or higher), suspected concurrent congestive heart failure, severe hepatic or renal impairment, disturbed consciousness, pregnancy lactating or nursing patients, patients not using contraceptive methods, patients with hereditary xanthinuria, previously hypouricemia diagnosis (< 1 mg/dL) or xanthine urinary calculi, history of gout or on treatment for gout or hyperuricemia, patients receiving immunosuppressants, known allergy to any study medication and its excipients. Patients on the current treatment or who have been treated during last 7 days with remdesivir. Patients judged ineligible by the principal investigator.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Favipiravir tablets containing 200 mg (batch numbers XD516F200) for oral administration.

Doses regimen consisted of 1800 mg orally administered twice on Day 1, and then 800 mg orally administered twice daily on Day 2 and thereafter for up to 9 days.

On Day 1, the second dose was taken at least 4 hours apart

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Placebo (batch numbers QC603F100) was supplied as tablets identical to the favipiravir tablets

Regimen (number of tablets and administration) was the same as favipiravir.

DURATION OF TREATMENT:

The treatment period was 10 days.

ENDPOINTS FOR EVALUATION:

Primary Endpoint

Time to clinical improvement measured as improvement for ≥ two categories on a 7-point ordinal scale (Time frame: up to 28 days)

Secondary Efficacy Endpoints

Clinical Severity

1. Ordinal scale:
   - Patient clinical status on an ordinal scale at days 3, 5, 8, 11, and 28 (if the patient is still hospitalized) or up to hospital discharge (Time frame: up to 28 days).
   - Mean change in the ranking on an ordinal scale from baseline to days 3, 5, 8, 11, 15 and 28 (if the patient is still hospitalized) or up to hospital discharge (Time frame: up to 28 days)
2. Duration of pyrexia
   - Time to resolution of fever.
3. National Early Warning Score (NEWS):
   - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
   - Change from baseline to days 3, 5, 8, 11, 15, and 28 in NEWS (if the patient is still hospitalized) or up to hospital discharge (Time frame: up to 28 days).
4. Oxygenation:
   - Oxygenation free days in the first 28 days (if the patient is still hospitalized) or up to hospital discharge (Time frame: up to 28 days)
   - Incidence and duration of new oxygen use during the trial.
5. Mechanical Ventilation:

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Name of Finished Product: Favipiravir

Name of Active Ingredient: T-705a

- Ventilator free days in the first 28 days (if the patient is still hospitalized) or up to hospital discharge (Time frame: up to 28 days).
- Incidence and duration of new mechanical ventilation use during the trial.

6. Hospitalization
   - Duration of hospitalization (days).
7. Mortality up to 28 days

Safety endpoints:

Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:

1. Cumulative incidence of serious adverse events (SAEs)
2. Cumulative incidence of Grade 3 and 4 adverse events (AEs).
3. Discontinuation or temporary suspension of study treatment (for any reason).
4. Changes in white cell count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST over time

Additional endpoints:

1. Days up to negative SARS-COV2 PCR test.
2. Days up to positive SARS-COV2 antibody IgG test.

STATISTICAL METHODS:

Efficacy Analysis Set:

1. Modified intent-to-treat (mITT): A group of patients who have been confirmed to be positive for SARS-COV2 on the RT-PCR test, enrolled in this study and received the study drug at least once. The primary efficacy analysis set in this study.
2. Per protocol set (PPS): A group of patients who meet the selection criteria, have the measures of the primary endpoints and do not have major deviations from the protocol.

Safety Analysis Set:

Population of patients who received at least one interventional study drug administration.

Primary efficacy variable analysis

The estimand for the time to event endpoints was defined as follows:

Population: mITT population.

Variable: Continuous variable response (time) and binary response.

Intercurrent Event (IE): Include death, drop-out due to an AE, treatment unblinding and loss of follow up. For patients experiencing an IE, time was censored at the time of the IE occurrence, this is, the last recorded visit.

Population level summary: Hazard ratio between treatment groups.

All statistical tests were applied with 0.05 two-sided significance level

The primary efficacy analysis was performed on the time to response for all patients in the mITT set using a Mantel-Haenszel log-rank test and Kaplan-Meier survival curves by treatment group.

Safety variable analysis

Safety of the intervention through 28 days was evaluated. The treatment period was 10 days in principle, however, the treatment could be discontinued because of AEs, if required. The frequency of onset of AEs

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were tabulated by severity and causal relationship for each group, and the incidence was calculated. Summary statistics and changes over time were presented by measurement time point for each group. Deaths were listed and reason for death detailed. Deaths as an outcome of an AE were identified too. Mortality rate up to 28 days was assessed.

SUMMARY OF RESULTS AND CONCLUSIONS:

Overall, both groups were similar in the demographic characteristics, concomitant conditions, prior medications prescribed for COVID-19, and treatment compliance.

EFFICACY RESULTS:

Treatment with favipiravir was not associated with a statistical difference in time to clinical improvement (p=0.45). Median time to improvement for both groups was 10 days**.** This, result was corroborated with analysis in the per protocol (PP) population.

No differences were found between groups in any of the secondary efficacy analysis: WHO ordinal scale displacement (stable or improving clinical status not associated with being treated with favipiravir), duration of pyrexia (median time to fever solution for both groups was 1 day), NEWS (median time to discharge or to NEWS < 3 was 5 and 6 days for favipiravir and placebo, respectively), oxygenation (median time until weaning from oxygen therapy for both groups was 5 days) and hospitalization (median time to hospital discharge for both groups was 10 days).

Few patients needed mechanical ventilation or died during the study.

SAFETY RESULTS:

A total of 41 AEs was reported during the study: 29 non-SAEs (20 in favipiravir group and 9 in placebo group) and 12 SAEs (8 in favipiravir group and 4 in placebo group). Abdominal pain upper was the most frequent reported non-SAs whereas hypoxia was the most frequent reported SAE.

Most non-SAEs were mild and moderate in severity. Likewise, most of SAEs and non-SAEs were considered not related to treatment.

Only two deaths in favipiravir groups were reported during the study, with one of them considered related to the study drug.

Furthermore, laboratory values, vital signs, physical examination, and imaging tests did not reveal any major issues with respect to the safety of favipiravir.

OTHER RESULTS:

No differences were found between groups in any of the exploratory efficacy analysis: time to negative SARS-CoV-2 PCR Test and positive SARS-CoV-2 Antibody Test.

CONCLUSION(S):

The results of this study show a good safety profile of favipiravir although more evidence is needed to demonstrate efficacy in COVID-19 patients.