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

Summary

EudraCT number	2020-002753-22
Trial protocol	ES
Global end of trial date	05 October 2021

Results information

Result version number	v1 (current)
This version publication date	15 September 2022
First version publication date	15 September 2022
Summary attachment (see zip file)	Sinopsis (FAVID_sinopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	FAVID-01-20-SP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferrer Internacional, S.A.
Sponsor organisation address	Diagonal 549, Barcelona, Spain, 08029
Public contact	Rebeca Aldonza Aguayo, Ferrer Internacional, S.A., +34 662 213 660, raldonza@ferrer.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 October 2021
Global end of trial reached?	Yes
Global end of trial date	05 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was conducted in compliance with the protocol, regulatory requirements, data protection laws, good clinical practice (GCP) and the ethical principles of the Declaration of Helsinki as adopted by the World Medical Assembly, 1964 (and subsequent revisions). Before the first patient was enrolled in the study, all ethical, regulatory, and legal requirements were met. The study was not started until approval by the ethics committee and other pertinent authorities has been obtained. By signing the protocol, the investigator agreed to adhere to the instructions and procedures described in the protocol and by so doing to follow the principles of good clinical practice they entail.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	43

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Forty-six patients signed the ICF and were assessed for eligibility. There were no screening failures. The included patients (n=46) were randomized 1:1 in the study as follows: 24 patients were randomized to favipiravir and 22 to placebo. A total of 8 patients discontinued the study prematurely: 5 patients from favipiravir group and 3 from placebo.

Pre-assignment

Screening details:

All patients provided written informed consent to participate in the study prior to being screened. The planned target of patients was 100 patients. Finally, 46 patients were screened and 44 included.

Period 1

Period 1 title	Observation/Examination Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The randomization list was not available to the investigator, study staff, patients, sponsor, or monitor. CRO made randomization envelopes. Treatment codes had not to be broken except in emergency situations and, if possible, the sponsor had to be contacted before the emergency code was opened. At the end of the study, the unused emergency code labels were checked and a statement to the effect that all were intact (or not as the case may be) was made on the database lock form.

Arms

Are arms mutually exclusive?	Yes
Arm title	Favipiravir

Arm description:

1800 mg (9 pills) × 2 times/day × 1 day + 800 mg (4 pills) × 2 times/day × 9 days (10 days). And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol; Symptomatic treatment including tocilizumab and corticosteroids according to the clinical assessment by the investigator.

Arm type	Experimental
Investigational medicinal product name	Favipiravir
Investigational medicinal product code	T-705a
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage form: tablet (one tablet contains 200mg of favipiravir). Orally administered twice on Day 1, and then 800 mg daily on Day 2 and thereafter for up to 9 days

Arm title	Placebo

Arm description:

Favipiravir matching placebo. And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol. Symptomatic treatment including Tocilizumab and corticosteroids according to the clinical assessment by the investigator

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1800 mg (9 pills) × 2 times/day × 1 day + 800 mg (4 pills) × 2 times/day × 9 days (10 days)

Number of subjects in period 1	Favipiravir	Placebo
Started	23	21
Completed	19	19
Not completed	4	2
Adverse event, serious fatal	2	-
Consent withdrawn by subject	-	2
Lost to follow-up	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Favipiravir

Reporting group description:

1800 mg (9 pills) × 2 times/day × 1 day + 800 mg (4 pills) × 2 times/day × 9 days (10 days). And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol; Symptomatic treatment including tocilizumab and corticosteroids according to the clinical assessment by the investigator.

Reporting group title	Placebo

Reporting group description:

Favipiravir matching placebo. And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol. Symptomatic treatment including Tocilizumab and corticosteroids according to the clinical assessment by the investigator

Reporting group values	Favipiravir	Placebo	Total
Number of subjects	23	21	44
Age categorical Units: Subjects			
Adults (18 years or older)	23	21	44
Age continuous Units: years			
arithmetic mean	51.43	50.86	
standard deviation	± 11.43	± 9.92	-
Gender categorical Units: Subjects			
Female	6	7	13
Male	17	14	31

End points

End points reporting groups

Reporting group title	Favipiravir

Reporting group description:

1800 mg (9 pills) × 2 times/day × 1 day + 800 mg (4 pills) × 2 times/day × 9 days (10 days). And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol; Symptomatic treatment including tocilizumab and corticosteroids according to the clinical assessment by the investigator.

Reporting group title	Placebo

Reporting group description:

Favipiravir matching placebo. And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol. Symptomatic treatment including Tocilizumab and corticosteroids according to the clinical assessment by the investigator

Primary: Primary endpoint: Time to clinical improvement

End point title	Primary endpoint: Time to clinical improvement

End point description:

End point type	Primary

End point timeframe:

28 days

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: day				
median (full range (min-max))	10 (10 to 12)	10 (5 to 11)		

Statistical analyses

Statistical analysis title	Time to clinical improvement by treatment group

Statistical analysis description:

The primary treatment comparison has been evaluated using a two-sided significance level of 0.05. The functions used for the hypothesis contrast and plotting the survival curves were the survfit() and ggsurvplot() functions from the {survival} and {survminer} packages respectively from the R statistical software

Comparison groups	Favipiravir v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Logrank

Secondary: Secondary endpoint: WHO ordinal scale displacement analysis

End point title	Secondary endpoint: WHO ordinal scale displacement analysis
End point description: WHO score mean change	
End point type	Secondary
End point timeframe: from baseline to Day 28	

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: score mean change				
arithmetic mean (standard deviation)	-2.5 (± 0)	-2.6 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Time to fever resolution

End point title	Secondary: Time to fever resolution
End point description:	
End point type	Secondary
End point timeframe: from baseline to Day 28	

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: event of fever resolution	12	13		

Statistical analyses

No statistical analyses for this end point

Secondary: secondary: National Early Warning Score (NEWS)

End point title	secondary: National Early Warning Score (NEWS)

End point description:

End point type	Secondary

End point timeframe:
from baseline to Day 28

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: patients	14	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: time to weaning from mechanical ventilation

End point title	Secondary: time to weaning from mechanical ventilation

End point description:

End point type	Secondary

End point timeframe:
from baseline to Day 28

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: patients	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Time to hospital discharge

End point title	Secondary: Time to hospital discharge

End point description:

End point type	Secondary

End point timeframe:
from baseline to Day 28

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: hospital discharges	19	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Mortality up to 28 (incidence)

End point title	Secondary: Mortality up to 28 (incidence)

End point description:

End point type	Secondary

End point timeframe:
from baseline to Day 28

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: patients	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Time until weaning from oxygen therapy

End point title	Secondary: Time until weaning from oxygen therapy

End point description:

End point type	Secondary

End point timeframe:
from baseline to Day 28

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: patients	17	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded beginning immediately after the ICF was signed. The investigator (and/or designee) documented all AEs reported by the subject from the ICF signing to completion of the final follow-up.

Adverse event reporting additional description:

Any subject who is withdrawn from the study due to an AE shall be followed until the outcome of the event is determined, and the investigator will document available follow-up information on the subject's database.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Favipiravir

Reporting group description:

1800 mg (9 pills) × 2 times/day × 1 day + 800 mg (4 pills) × 2 times/day × 9 days (10 days). And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol; Symptomatic treatment including tocilizumab and corticosteroids according to the clinical assessment by the investigator.

Reporting group title	Placebo

Reporting group description:

Favipiravir matching placebo. And existing treatment for COVID-19 according to the current clinical practice for each participating site, except for prohibited medications in this protocol. Symptomatic treatment including Tocilizumab and corticosteroids according to the clinical assessment by the investigator

Serious adverse events	Favipiravir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 23 (21.74%)	4 / 21 (19.05%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Nervous system disorders			
Cerebral venous thrombosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seizure			

subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	3 / 23 (13.04%)	3 / 21 (14.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.1 %

Non-serious adverse events	Favipiravir	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 23 (78.26%)	7 / 21 (33.33%)	
Investigations			
Hepatitis B virus test positive			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Nervous system disorders			
Cerebral venous thrombosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Headache			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
subjects affected / exposed	1 / 23 (4.35%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Hypotension			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 23 (17.39%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	1 / 23 (4.35%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	

Dyspepsia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Anxiety			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Superinfection bacterial			
subjects affected / exposed	2 / 23 (8.70%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Clostridium difficile infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Haematoma infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 21 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2020	Include an inclusion criterion (influenza test) and an exclusion criterion (patients on the current treatment with remdesevir or who have been treated with remdesevir during last 7 days before inclusion) and their rationales, change the evaluation of clinical findings from twice daily to once daily, update the study period, update key contacts and add a footnote with the protocol version.
08 February 2021	The person responsible for signing the protocol from the sponsor side has been changed. Some inclusion and exclusion criteria have been modified, some secondary and additional endpoints have been changed to be adapted to the current clinical practice, study period has been updated, study schedule has been modified and the section of statistical methods has been changed to be better defined and to include the estimands

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported