Clinical trial results:
A Randomized, Open-label, Standard-of-care comparative, Repositioning Clinical Trial to Evaluate the Efficacy and Safety of FDA-135 in combination with standard of care in the Treatment of Infection Caused by SARS-CoV-2, in Patients With early Stage COVID-19 Disease, in Primary Heatlh Care setting.

Summary

EudraCT number	2021-001227-41
Trial protocol	ES
Global end of trial date	28 July 2022

Results information

Result version number	v1 (current)
This version publication date	25 December 2022
First version publication date	25 December 2022
Summary attachment (see zip file)	Synopsis Annex _1 _ICH_ E3 (Synopsis-Clinical Study Report FINAL CSIC-FDA135-2021-01 version 1 15-9-2022.pdf)

Trial information

Trial identification

Sponsor protocol code	CSIC-FDA135-2021-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Agencia Estatal Consejo Superior de Investigaciones Científicas, M.P.
Sponsor organisation address	Calle Serrano, 117, Madrid, Spain, 28006
Public contact	Sponsor, Agencia Estatal Consejo Superior de Investigaciones Científicas, M.P., 34 918373112, ana.martinez@csic.es
Scientific contact	Sponsor, Agencia Estatal Consejo Superior de Investigaciones Científicas, M.P., 34 918373112, ana.martinez@csic.es

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	10 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2022
Global end of trial reached?	Yes
Global end of trial date	28 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of FDA-135 combined with standard of care on reducing the SARS-CoV-2 viral load.

Protection of trial subjects:

All patients could be treated for symptoms due to SARS-CoV-2 infection as per standard of care recommendation:

- In mild clinical conditions:
  - Acetaminophen 500 mg 1-4 times daily for control of fever and as an analgesic.
  - Non-steroidal anti-inflammatory drugs in the doses indicated as per their fact sheet.
  - Symptomatic treatment.
  - Adequate hydration.
- In moderate clinical conditions:
  - Only in the case of suspected bacterial co-infection/superinfection antibiotic treatment will be introduced with:
  - Azithromycin 500 mg/24h oral for 3 days plus amoxicillin 1 g/12 hours for 7 days
  - OR Amoxicillin/Clavulanic Acid 875 mg/125 mg every 8 hours for 7 days.
  - Alternatively, levofloxacin 500 mg every 12 hours on the first day and 500 mg every 24 hours for 4 days [thereafter].
  - Symptomatic treatment.
  - Adequate hydration.

  - BRONCHODILATORS: If required, they were preferably administered in pressurized cartridge with individual holding chamber (spacer), to avoid aerosol generation: salbutamol, 100 mcg/inhalation plus Ipratropium Bromide 20 mcg/inhalation: 2 inhalations every 4-6 hours; inhaled corticosteroids: only used in patients with bronchial asthma or COPD.
  - SYSTEMIC CORTICOSTEROIDS: Use in outpatients without the need for oxygen therapy is not recommended. Its use could be counterproductive in patients who do not require oxygen therapy. They were exclusively recommended at low doses in patients requiring oxygen therapy.
  - ANTITHROMBOTIC PROPHYLAXIS: Low molecular weight heparin at prophylactic doses for patients immobilized or with risk factors: Enoxaparin 4,000 IU (40 mg) subcutaneously once daily. If creatinine clearance is observed at 15-30 mL/min, enoxaparin 2000 IU (20 mg) could be administered subcutaneously once daily. Enoxaparin was not recommended if creatinine clearance was less than 15 mL/min. Bemiparin could be used as an alternative.

In all cases, home isolation was required, according to the rules applicable at the time of study

Background therapy:

Standard of care

Evidence for comparator:

Standard of care

Actual start date of recruitment	24 February 2022
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: 191
Worldwide total number of subjects	191
EEA total number of subjects	191

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)	1
Adults (18-64 years)	162
From 65 to 84 years	26
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The first patient was included in the study on February 24, 2022. The last patient was included on June 30, 2022. The last patient last visit was completed on July 28, 2022.

Pre-assignment

Screening details:

The patients must be diagnosed of active SARS-CoV-2 infection confirmed by compatible symptoms and a positive result in the detection tests for active infection (DTAI), rapid antigen detection test or in the PCR for viral RNA detection test.

Period 1

Period 1 title	Treatment and Follow-up period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bromhexine

Arm description:

Bromhexine 16 mg (10 mL) three times a day (48 mg/day) for 7 days, given before meals (breakfast, lunch, and dinner); Plus Standard of Care for SARS-CoV-2 disease.

Arm type	Experimental
Investigational medicinal product name	Bromhexine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Bromhexine 16 mg (10 mL) three times a day (48 mg/day) for 7 days

Arm title	Standard of care

Arm description:

Standard of care treatment (SOC) for SARS-CoV-2 disease: acetaminophen 500 mg 1-4 times daily, non-steroidal anti-inflammatory drugs, symptomatic treatment, and hydration for mild clinical conditions. Only if suspected bacterial co-infection/superinfection should be prescribed azithromycin 500 mg/24 h oral for 3 days plus amoxicillin 1g/12 hours for 7 days, or amoxicillin/clavulanic acid 875 mg/125 mg every 8 hour for 7 days; alternatively, levofloxacin 500 mg every 12 hours on the first day and 500 mg every 24 hour for 4 days.

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Bromhexine	Standard of care
Started	98	93
Completed	96	91
Not completed	2	2
Consent withdrawn by subject	2	1

Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment and Follow-up period

Reporting group description:

This analysis population consist of all patients included in the "all randomized patient population" who have not violated the protocol so that it may affect the assessment of the effect of the study drug on the primary endpoint, ie, without major protocol deviations. The criteria for identifying major protocol deviations were reviewed prior to the start of the analysis and unblinding of treatment and was described in the analysis plan.
Two patients were excluded from the data set due to protocol deviation. The set population was 191 patients.

Reporting group values	Treatment and Follow-up period	Total	
Number of subjects	191	191	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	162	162	
From 65-84 years	26	26	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	47.8		
standard deviation	± 1.1	-	
Gender categorical Units: Subjects			
Female	127	127	
Male	64	64	
SARS-CoV-2 infection severity			
Severity of SARS-CoV-2 infection at baseline			
Units: Subjects			
Asymptomatic	5	5	
Mild disease	179	179	
Moderate disease	7	7	
SARS-CoV-2 infection before the study			
Presence or absence of previous SARS-CoV-2 infection before the one for the selection for the study			
Units: Subjects			
No	154	154	
Yes	37	37	
SARS-CoV-2 complete vaccination Units: Subjects			
No	9	9	
Yes	182	182	

Systolic Blood Pressure Units: mmHg arithmetic mean standard deviation	 123 ± 1	 -	
Diastolic Blood Pressure Units: mmHg arithmetic mean standard deviation	 76 ± 1	 -	
Respiratory rate Units: Inspirations/minute arithmetic mean standard deviation	 16 ± 0.1	 -	
Oxygen saturation Units: Saturation % arithmetic mean standard deviation	 97 ± 0.1	 -	
Heart rate Units: Pulses/minute arithmetic mean standard deviation	 79 ± 1	 -	
Temperature			
Axillary temperature			
Units: ºC arithmetic mean standard deviation	 36.5 ± 0.1	 -	
Time from previous SARS-CoV-2 infection Units: Months arithmetic mean standard deviation	 16.3 ± 1.4	 -	
Time from last SRS-CoV-2 vaccination dose Units: Month arithmetic mean standard deviation	 5.3 ± 0.2	 -	

End points

End points reporting groups

Reporting group title	Bromhexine

Reporting group description:

Bromhexine 16 mg (10 mL) three times a day (48 mg/day) for 7 days, given before meals (breakfast, lunch, and dinner); Plus Standard of Care for SARS-CoV-2 disease.

Reporting group title	Standard of care

Reporting group description:

Standard of care treatment (SOC) for SARS-CoV-2 disease: acetaminophen 500 mg 1-4 times daily, non-steroidal anti-inflammatory drugs, symptomatic treatment, and hydration for mild clinical conditions. Only if suspected bacterial co-infection/superinfection should be prescribed azithromycin 500 mg/24 h oral for 3 days plus amoxicillin 1g/12 hours for 7 days, or amoxicillin/clavulanic acid 875 mg/125 mg every 8 hour for 7 days; alternatively, levofloxacin 500 mg every 12 hours on the first day and 500 mg every 24 hour for 4 days.

Primary: Change in ORF1ab viral load (Ct) Day4-Baseline

End point title	Change in ORF1ab viral load (Ct) Day4-Baseline

End point description:

Baseline – 4 days difference ORF1ab RT-PCR number of cycles.
The viral load was estimated by the number of cycles (Cts) until detection of three specific genes of the SARS-Cov-2 pathogenic viral strain, using the TaqPath COVID-19 CE-IVD RT-PCR Kit (Thermofisher, USA), which detects three highly conserved regions of the RNA SARS-CoV-2 virus along with an internal positive control (MS2-IPC) in a single PCR reaction: genes encoding ORF1ab, N Protein, S Protein, with a sensitivity of >99% and Specificity of 99.5%.
For the correct interpretation of data: an increase in the number of amplified cycles means a better result as a reduction in the viral load. So, the difference D4-D0 positive means an improvement, better as the figure is higher. If the difference D4-D0 is negative, it means a worsening.

End point type	Primary

End point timeframe:

Baseline - Day 4 of treatment

End point values	Bromhexine	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	93		
Units: Number of RT-PCR cycles				
arithmetic mean (standard error)	13.5 (± 2.6)	14.4 (± 2.8)		

Attachments (see zip file)	ORF1ab RT-PCR Ct Baseline-Day4/ORF1ab RT-PCR Ct Baseline-

Statistical analyses

Statistical analysis title	Student t test for independent groups

Statistical analysis description:

Student t test for independent groups

Comparison groups	Bromhexine v Standard of care
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.817
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	8.5
Variability estimate	Standard error of the mean
Dispersion value	3.8

Primary: Change in N Protein viral load (Ct) Day4-Baseline

End point title	Change in N Protein viral load (Ct) Day4-Baseline

End point description:

Baseline – 4 days difference ORF1ab RT-PCR number of cycles.
The viral load was estimated by the number of cycles (Cts) until detection of three specific genes of the SARS-Cov-2 pathogenic viral strain, using the TaqPath COVID-19 CE-IVD RT-PCR Kit (Thermofisher, USA), which detects three highly conserved regions of the RNA SARS-CoV-2 virus along with an internal positive control (MS2-IPC) in a single PCR reaction: genes encoding ORF1ab, N Protein, S Protein, with a sensitivity of >99% and Specificity of 99.5%.
For the correct interpretation of data: an increase in the number of amplified cycles means a better result as a reduction in the viral load. So, the difference D4-D0 positive means an improvement, better as the figure is higher. If the difference D4-D0 is negative, it means a worsening.

End point type	Primary

End point timeframe:

Baseline - Day 4 of treatment

End point values	Bromhexine	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	93		
Units: Number of RT-PCR cycles				
arithmetic mean (standard error)	7.7 (± 1.9)	6.4 (± 1.8)		

Attachments (see zip file)	N Protein RT-PCR Ct Baseline-Day4/N Protein RT-PCR Ct

Statistical analyses

Statistical analysis title	Student t test for independent groups
Comparison groups	Bromhexine v Standard of care

Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.603
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	2.6

Primary: Change in S Protein viral load (Ct) Day4-Baseline

End point title	Change in S Protein viral load (Ct) Day4-Baseline

End point description:

Baseline – 4 days difference ORF1ab RT-PCR number of cycles.
The viral load was estimated by the number of cycles (Cts) until detection of three specific genes of the SARS-Cov-2 pathogenic viral strain, using the TaqPath COVID-19 CE-IVD RT-PCR Kit (Thermofisher, USA), which detects three highly conserved regions of the RNA SARS-CoV-2 virus along with an internal positive control (MS2-IPC) in a single PCR reaction: genes encoding ORF1ab, N Protein, S Protein, with a sensitivity of >99% and Specificity of 99.5%.
For the correct interpretation of data: an increase in the number of amplified cycles means a better result as a reduction in the viral load. So, the difference D4-D0 positive means an improvement, better as the figure is higher. If the difference D4-D0 is negative, it means a worsening.

End point type	Primary

End point timeframe:

Baseline - Day 4 of treatment

End point values	Bromhexine	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	93		
Units: Number of RT-PCR cycles				
arithmetic mean (standard error)	9.7 (± 3)	13.8 (± 3)		

Attachments (see zip file)	S Protein RT-PCR Ct Baseline-Day4/S Protein RT-PCR Ct

Statistical analyses

Statistical analysis title	Student t test for independent groups
Comparison groups	Bromhexine v Standard of care

Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	12.4
Variability estimate	Standard error of the mean
Dispersion value	4.2

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe from Day 1 to Day 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Bromhexine plus standard of care
Reporting group description:	
Bromhexine 16 mg (10 mL) three times a day (48 mg/day) for 7 days, given before meals (breakfast, lunch, and dinner); Plus Standard of Care for SARS-CoV-2 disease.	
Reporting group title	Standard of care
Reporting group description:	
Standard of care treatment (SOC) for SARS-CoV-2 disease: acetaminophen 500 mg 1-4 times daily, non-steroidal anti-inflammatory drugs, symptomatic treatment, and hydration for mild clinical conditions. Only if suspected bacterial co-infection/superinfection should be prescribed azithromycin 500 mg/24 h oral for 3 days plus amoxicillin 1g/12 hours for 7 days, or amoxicillin/clavulanic acid 875 mg/125 mg every 8 hour for 7 days; alternatively, levofloxacin 500 mg every 12 hours on the first day and 500 mg every 24 hour for 4 days.	

Serious adverse events	Bromhexine plus standard of care	Standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 98 (0.00%)	1 / 93 (1.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Bromhexine plus standard of care	Standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 98 (8.16%)	4 / 93 (4.30%)	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 98 (2.04%)	0 / 93 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Leucocytosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	0 / 98 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	

Infections and infestations			
Mononucleosis syndrome			
subjects affected / exposed	1 / 98 (1.02%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported