



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 Health 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:
 - o Acetaminophen 500 mg 1-4 times daily for control of fever and as an analgesic.
 - o Non-steroidal anti-inflammatory drugs in the doses indicated as per their fact sheet.
 - o Symptomatic treatment.
 - o Adequate hydration.
 - In moderate clinical conditions:
 - o Only in the case of suspected bacterial co-infection/superinfection antibiotic treatment will be introduced with:
 - o Azithromycin 500 mg/24h oral for 3 days plus amoxicillin 1 g/12 hours for 7 days
 - o OR Amoxicillin/Clavulanic Acid 875 mg/125 mg every 8 hours for 7 days.
 - o Alternatively, levofloxacin 500 mg every 12 hours on the first day and 500 mg every 24 hours for 4 days [thereafter].
 - o Symptomatic treatment.
 - o Adequate hydration.
 - o 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.
 - o 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.
 - o 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: °C 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 occurrences (all) | 2 / 98 (2.04%) 2 | 0 / 93 (0.00%) 0 | |
| Blood and lymphatic system disorders Leucocytosis subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Transaminases increased subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Mouth ulceration subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |
| Tooth abscess subjects affected / exposed occurrences (all) | 0 / 98 (0.00%) 0 | 1 / 93 (1.08%) 1 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 93 (0.00%) 0 | |

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