Clinical trial results:
Randomized clinical trial to evaluate the efficacy of different treatments in patients with COVID-19 who require hospitalization

Summary

EudraCT number	2020-001156-18
Trial protocol	ES
Global end of trial date	17 July 2023

Results information

Result version number	v1 (current)
This version publication date	01 November 2023
First version publication date	01 November 2023
Summary attachment (see zip file)	Informe Final PANCOVID (PANCOVID_publicación_informe final.pdf)

Trial information

Trial identification

Sponsor protocol code	PanCOVID19

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fundación para la investigación Biomedica Hospital Universitario La Paz
Sponsor organisation address	Paseo de la Castellana, 261, Madrid, Spain, 28046
Public contact	Alberto Borobia, Servicio de Farmacología Clínica. Unidad de Ensayos Clínicos (UCICEC), +34 912071466, a.borobia@gmail.com
Scientific contact	Alberto Borobia, Servicio de Farmacología Clínica. Unidad de Ensayos Clínicos (UCICEC), +34 912071466, a.borobia@gmail.com

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	30 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Provide reliable estimates of the effects of these antiviral treatments on hospital mortality.

Protection of trial subjects:

The cumulative incidence of adverse effects attributed to therapy in the study will be evaluated

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 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: 355
Worldwide total number of subjects	355
EEA total number of subjects	355

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)	355
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Principal inclusion criteria
• Signing the informed consent.
• Men and women aged ≥18 years
• Patients admitted with a diagnosis of severe pneumonia due to SARS-CoV-2.
• Diagnosis of SARS-CoV-2 infection confirmed by PCR carried out ≤ 4 days prior to randomization.
• Onset of symptoms ≤ 4 days.
• Using of contraceptive methods

Pre-assignment

Screening details:

Diagnosis of SARS-CoV-2 infection confirmed by PCR carried out ≤ 4 days prior to randomization.

Period 1

Period 1 title	First Randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded study

Arms

Are arms mutually exclusive?	Yes
Arm title	Emtricitabine/Tenofovir disoproxil fumarate

Arm description:

Emtricitabine/Tenofovir disoproxil fumarate (200/245 mg): 2 tablets the first day, and 1 tablet per day administered for a total of 14 days, orally.

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

Dosage and administration details:

200mg: 2 tablets on the first day, and 1 tablet daily for a total of 14 days, orally.

Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250mg: 2 tablets on the first day, and 1 tablet daily for a total of 14 days, orally.

Arm title	No treatment with Emtricitabine/Tenofovir

Arm description:

No treatment with Emtricitabine/Tenofovir disoproxil fumarate

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Emtricitabine/Tenofovir disoproxil fumarate	No treatment with Emtricitabine/Tenofovir
Started	177	178
Completed	167	171
Not completed	10	7
Death	7	4
Discontinued	3	3

Period 2

Period 2 title	Second randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded study

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexamethasone + Baricitinib

Arm description:

Dexamethasone: 6 mg once daily for 7-10 days orally or i.v. + Baricitinib: 4 mg once daily for 10-14 days at the investigator's discretion, orally.

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

Dosage and administration details:

4 mg once daily for 10-14 days at the investigator's discretion, orally

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Dexamethasone: 6 mg once daily for 7-10 days oral or i.v. at investigator's discretion.

Arm title	Dexamethasone

Arm description:

Dexamethasone: 6 mg once daily for 7-10 days oral or i.v. at investigator's discretion.

Arm type	Active comparator

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Injection/infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Dexamethasone: 6 mg once daily for 7-10 days oral or i.v. at investigator's discretion.

Number of subjects in period 2[1]	Dexamethasone + Baricitinib	Dexamethasone
Started	145	142
Completed	137	135
Not completed	8	7
Death	3	7
Discontinued	5	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 355 patients were enrolled in the trial and underwent the first randomization. In the first randomization, 177 and 178 patients were respectively assigned to receive or not TDF/FTC. Of these 355 patients, 287 underwent the second randomization to receive baricitinib plus dexamethasone or dexamethasone alone.

Baseline characteristics

Reporting groups

Reporting group title	First Randomization

Reporting group description: -

Reporting group values	First Randomization	Total	
Number of subjects	355	355	
Age categorical			
Adults (18-64)			
Units: Subjects			
Adults (18-64 years)	355	355	
Age continuous			
Adults (18-78)			
Units: years			
median	0		
full range (min-max)	0 to 0	-	
Gender categorical			
Units: Subjects			
Female	126	126	
Male	229	229	

Subject analysis sets

Subject analysis set title	Patients treated
Subject analysis set type	Intention-to-treat

Subject analysis set description:
Patients treated

Reporting group values	Patients treated		
Number of subjects	177		
Age categorical			
Adults (18-64)			
Units: Subjects			
Adults (18-64 years)	177		
Age continuous			
Adults (18-78)			
Units: years			
median	0		
full range (min-max)	0 to 0		
Gender categorical			
Units: Subjects			
Female	64		
Male	113		

End points

End points reporting groups

Reporting group title	Emtricitabine/Tenofovir disoproxil fumarate
Reporting group description:	
Emtricitabine/Tenofovir disoproxil fumarate (200/245 mg): 2 tablets the first day, and 1 tablet per day administered for a total of 14 days, orally.	

Reporting group title	No treatment with Emtricitabine/Tenofovir
Reporting group description:	
No treatment with Emtricitabine/Tenofovir disoproxil fumarate	

Reporting group title	Dexamethasone + Baricitinib
Reporting group description:	
Dexamethasone: 6 mg once daily for 7-10 days orally or i.v. + Baricitinib: 4 mg once daily for 10-14 days at the investigator's discretion, orally.	

Reporting group title	Dexamethasone
Reporting group description:	
Dexamethasone: 6 mg once daily for 7-10 days oral or i.v. at investigator's discretion.	
Subject analysis set title	Patients treated
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients treated	

Primary: Death

End point title	Death[1]
End point description:	
Number of deaths from first randomization to 28 days of treatment.	
End point type	Primary
End point timeframe:	
During 28 days after the start of treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Based on mortality data during the first COVID-19 wave in Spain, sample size calculations assumed a 20% mortality in this mixed population. We also assumed an α error of .025, β error of .2, and a 0.7 risk reduction in mortality. resulting in a predefined sample of 1482 patients for each group (TDF/FTC vs no TDF/FTC). The trial was stopped before reaching the planned sample size due to the decrease in the number of cases during the recruitment period and the much lower global mortality observed

End point values	Emtricitabine/Tenofovir disoproxil fumarate	Dexamethasone + Baricitinib	No treatment with Emtricitabine/Tenofovir	Dexamethasone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	177	145	178	142
Units: Number of deaths	167	137	171	135

End point values	Patients treated			
Subject group type	Subject analysis set			
Number of subjects analysed	177			

Units: Number of deaths	167			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease progression and length of hospital stay

End point title	Disease progression and length of hospital stay

End point description:

Number of patients with disease progression and critical care unit admission (oxygen support, steroid dose, new medication...)
Number of days since first randomization until death/discharge

End point type	Secondary

End point timeframe:

During 28 days after the start of treatment

End point values	Emtricitabine/Tenofovir disoproxil fumarate	Dexamethasone + Baricitinib	No treatment with Emtricitabine/Tenofovir	Dexamethasone
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	177	145	178	142
Units: Number				
Disease progression	39	36	42	39
Critical care unit admission	39	36	42	39
28-d mortality	7	3	4	7

End point values	Patients treated			
Subject group type	Subject analysis set			
Number of subjects analysed	177			
Units: Number				
Disease progression	39			
Critical care unit admission	39			
28-d mortality	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded continuously throughout the entire duration of the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	Randomized patients
Reporting group description:	
Randomized patients	

Serious adverse events	Randomized patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 355 (3.66%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	0		
Vascular disorders			
Acute arterial ischemia			
subjects affected / exposed	1 / 355 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart failure			
subjects affected / exposed	2 / 355 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ischiorectal abscess			
subjects affected / exposed	1 / 355 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary thromboembolism			

subjects affected / exposed	3 / 355 (0.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Acute respiratory insufficiency			
subjects affected / exposed	3 / 355 (0.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 355 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchial aspiration			
subjects affected / exposed	1 / 355 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Randomized patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 355 (22.54%)		
Blood and lymphatic system disorders			
Hyperglycaemia	Additional description: High blood sugar		
subjects affected / exposed	17 / 355 (4.79%)		
occurrences (all)	17		
Hypertransaminasaemia	Additional description: Increase in serum transaminase values above normal levels		
subjects affected / exposed	13 / 355 (3.66%)		
occurrences (all)	13		
Hyperglycemia steroid-induced	Additional description: Steroids cause high blood sugar levels in people with pre-existing diabetes.		
subjects affected / exposed	9 / 355 (2.54%)		
occurrences (all)	9		
Arterial hypertension			
subjects affected / exposed	3 / 355 (0.85%)		
occurrences (all)	3		

General disorders and administration site conditions			
Insomnia			
subjects affected / exposed	8 / 355 (2.25%)		
occurrences (all)	8		
Asthenia			
subjects affected / exposed	5 / 355 (1.41%)		
occurrences (all)	5		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	9 / 355 (2.54%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	9 / 355 (2.54%)		
occurrences (all)	9		
Nausea and vomiting			
subjects affected / exposed	4 / 355 (1.13%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Pulmonary thromboembolism			
subjects affected / exposed	6 / 355 (1.69%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2020	Substantial modification: Modified documents: Part I: · Protocol, version 3.1, dated April 2nd 2020 Part II: · Information sheet for the legal representative of the minor patient and an informed consent document, version 3.0, dated March 31st 2020. · Information sheet for the mature minor (12 to 17 years old) and informed consent document, version 3.0, dated March 31st 2020 · Information sheet for the adult patient and an informed consent document, version 3.0, dated March 31st 2020
08 October 2020	Modified documents: Part I: - Protocol V5.1 of September 13, 2020. Part II: - Mature Minor Patient Information Sheet and Informed Consent Document (addressed to the mature minor 12-17 years), V5.1 of September 13, 2020. Mature Minor 12-17 years old), V5.1 of September 13, 2020 - Minor patient guardian information sheet and informed consent document, V5.1 of September 13, 2020 - Information sheet for patient of legal age and informed consent document, V5.1 dated September 13, 2020 September 13, 2020 - Information sheet for the patient's legal representative/family member, version: 1.0 of July 4, 2020. 2020.
05 November 2020	Modified documents: Part II: - Expansion of centers (see Annex II)
03 December 2020	Modified documents: Part II: - A new center is included.
11 March 2021	Part II: - The principal investigator of the Hospital Universitario de Fuenlabrada is changed, Dr. Callejas will not be able to continue in charge of the study and is replaced by Dr. Lourdes Muñoz.
11 March 2021	Part II: - Expansion of a center: Hospital de Emergencias Enfermera Isabel: Zendal Dra. Cristina Marcelo Calvo Hospital Universitario de Badajoz: Dr. Francisco Félix Rodríguez Vidigal
24 June 2021	Part II: - Change of Principal Investigator at the Centro Hospital de Emergencias Enfermera Isabel Zendal: Dr. Sara Castro González replaces Dr. Cristina Marcelo Calvo.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 June 2020	In view of new evidence from clinical trials demonstrating the lack of efficacy of two of the treatment arms, the scientific committee has decided to withdraw the treatment arm involving hydroxychloroquine and to redesign the clinical trial.	13 October 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/93846