Clinical trial results:
Plasma Exchange Therapy for Post- COVID-19 Condition: A Pilot, Randomized Double-Blind Study

Summary

EudraCT number	2022-000641-33
Trial protocol	ES
Global end of trial date	15 June 2023

Results information

Result version number	v1 (current)
This version publication date	07 September 2024
First version publication date	07 September 2024
Summary attachment (see zip file)	Quality of life and laboratory Endpoints (PAX_SUMMARY EFFICACY ENDPOINTS ATTACHEMENT.pdf)

Trial information

Trial identification

Sponsor protocol code	PAX

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05445674
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundació Lluita contra les Infeccions
Sponsor organisation address	Carretera de Canyet s/n, Badalona, Spain, 08916
Public contact	ScienHub Research Support, Fundació Lluita contra les Infeccions, 34 934978414, info@scienhub.org
Scientific contact	ScienHub Research Support, Fundació Lluita contra les Infeccions, 34 934978414, info@scienhub.org

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	06 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2023
Global end of trial reached?	Yes
Global end of trial date	15 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and tolerability of PE in patients with Post-Acute Covid-19 Syndrome (PCC) compared to sham plasma exchange (placebo).

Protection of trial subjects:

Patients will discontinue participation in the study at the time they deem necessary. All study participants have the right to withdraw their consent at any time during the study. This event will be notified to the study monitor and duly documented both in the medical records and in the eCRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants have been recruited from the LONG COVID-19 unit at Hospital Universitari Germans Trias i Pujol.

Pre-assignment

Screening details:

Adult men and women with confirmed Post-Acute COVID-19 syndrome (PCC) diagnosis (Symptoms of persistent COVID-19 after 90 days of infection, not explainable by other causes and previous diagnosis of SARS-CoV-2 infection (WHO criteria), determined by PCR, validated antigen rapid diagnostic test and or positive serology test for COVID-19 (>90 days).

Period 1

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

Blinding implementation details:

Masking of investigational products ensured that the investigator and the participant were blinded to the type of exchange procedure. Patients could not distinguish true from sham procedures at the end of the study. Each procedure will take approximately 2 hours to complete. In the sham procedure, the patients will also underwear 6 procedures lasting approximately 2 hours each. Blinding will be maintained throughout the study until after 3-month follow-up assessment of the last

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental Arm

Arm description:

6 sessions of PE (Plasma Exchange) with human serum albumin. Plasma exchange sessions will occur on days 1, 3, 8, 10, 15 and 17.

Arm type	Experimental
Investigational medicinal product name	Plasma Exchange with human serum album
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Plasma exchanges will be performed with 5% albumin as the replacement fluid. The typical schedule prescribed will be an exchange of 1 volemia. Blood will be separated into cells and plasma; the cells will be combined with reconstituted 5% human serum albumin and reinfused into the patient with normal saline. Conventional fresh-frozen plasma will be used as replacement fluid (1/3 of the exchanged plasma volume) only in patients with a baseline coagulopathy (PT <50%). The fresh-frozen plasma to be used will be provided by the Blood and Tissues Bank from Hospital Universitari Germans Trias i Pujol.

Investigational medicinal product name	Human albumin 5%
Investigational medicinal product code	
Other name	Albutein 5% ®
Pharmaceutical forms	Infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Human albumin 5% (Albutein 5% ®), solution for intravenous infusion. It will be used in bottles of 250mL or 500mL depending on availability. The administration volume will be adapted for each participant. Solution for infusion, clear, slightly viscous. Storage conditions: Keep at 25ºC maximum. Refrigeration is not necessary under these conditions. Protect from light. Do not freeze.

Arm title	Placebo Arm

Arm description:

6 sessions with placebo (infusion of 200 to 250ml of sterile saline solution 0.9%) on days 1, 3, 8, 10, 15 and 17.

Arm type	Placebo
Investigational medicinal product name	Sterile saline solution 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

For sham plasma exchange procedures, a sound behind the curtain was performed imitating the sound of the cell processing platform, the participant wore headphones connected to a tablet with music. In these cases, only one infusion of 200 to 250ml of sterile saline solution 0.9% will be performed during the time established for all procedures. Albumin will not be necessary for those patients in the Sham plasma exchange arm.

Number of subjects in period 1	Experimental Arm	Placebo Arm
Started	25	25
Completed	24	25
Not completed	1	0
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Experimental Arm
Reporting group description:	
6 sessions of PE (Plasma Exchange) with human serum albumin. Plasma exchange sessions will occur on days 1, 3, 8, 10, 15 and 17.	
Reporting group title	Placebo Arm
Reporting group description:	
6 sessions with placebo (infusion of 200 to 250ml of sterile saline solution 0.9%) on days 1, 3, 8, 10, 15 and 17.	

Reporting group values	Experimental Arm	Placebo Arm	Total
Number of subjects	25	25	50
Age categorical			
Demographic, clinical profiles at baseline of all subjects analyzed are described in tables by study group. All categorical variables are described by the number of observations in each category and the percentage by study group. All continuous variables are described by number of cases, mean, median, 1st and 4th quartiles, standard deviation, and number of missing values.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	25	25	50
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Demographic, clinical profile at baseline of all subjects analyzed are described in tables by study group. All categorical variables are described by the number of observations in each category and the percentage by study group. All continuous variables are described by number of cases, mean, median, 1st and 4th quartiles, standard deviation, and number of missing values.			
Units: years			
median	48.88	48.40	
inter-quartile range (Q1-Q3)	45.00 to 53.00	40.00 to 57.00	-
Gender categorical			
Demographic, clinical profile at baseline of all subjects analyzed are described in tables by study group. All categorical variables are described by the number of observations in each category and the percentage by study group. All continuous variables are described by number of cases, mean, median, 1st and 4th quartiles, standard deviation, and number of missing values.			
Units: Subjects			
Female	16	17	33
Male	9	8	17

End points

End points reporting groups

Reporting group title	Experimental Arm
Reporting group description:	
6 sessions of PE (Plasma Exchange) with human serum albumin. Plasma exchange sessions will occur on days 1, 3, 8, 10, 15 and 17.	
Reporting group title	Placebo Arm
Reporting group description:	
6 sessions with placebo (infusion of 200 to 250ml of sterile saline solution 0.9%) on days 1, 3, 8, 10, 15 and 17.	

Primary: Proportion of adverse events (AEs) through day 90: all AEs

End point title	Proportion of adverse events (AEs) through day 90: all AEs
End point description:	
In the primary analysis, the proportions of adverse events up to day 90 were described and compared between treatment arms using a Fisher’s exact test. The proportions of adverse events were also described graphically. This analysis was performed considering: all AEs, grade 3 and 4 AEs and AEs leading to study treatment discontinuation or study withdrawal. The causal relationships with the treatment were also described in this section.	
End point type	Primary
End point timeframe:	
At 90 days	

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[1]	25[2]		
Units: %				
number (not applicable)	100	100		

Notes:

[1] - Per Protocol

[2] - Per Protocol

Statistical analyses

Statistical analysis title	Fisher's exact test
Statistical analysis description:	
In the primary analysis, the proportions of adverse events up to day 90 were described and compared between treatment arms using a Fisher’s exact test.	
Comparison groups	Placebo Arm v Experimental Arm
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	> 0.9
Method	Fisher exact

Primary: Proportion of adverse events (AEs) through day 90, considering: Grade 3 and 4 AEs

End point title	Proportion of adverse events (AEs) through day 90, considering: Grade 3 and 4 AEs

End point description:

In the primary analysis, the proportions of adverse events up to day 90 were described and compared between treatment arms using a Fisher’s exact test.

End point type	Primary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[3]	25[4]		
Units: Percentatge				
number (not applicable)	4.2	0		

Notes:

[3] - Per Protocol

[4] - Per Protocol

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Experimental Arm v Placebo Arm
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.5
Method	Fisher exact

Primary: Proportion of adverse events (AEs) through day 90: AEs leading to study withdrawal

End point title	Proportion of adverse events (AEs) through day 90: AEs leading to study withdrawal

End point description:

In the primary analysis, the proportions of adverse events up to day 90 were described and compared between treatment arms using a Fisher’s exact test.

End point type	Primary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[5]	25[6]		
Units: Percentatge				
number (not applicable)	13	4		

Notes:

[5] - Per Protocol

[6] - Per Protocol

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Experimental Arm v Placebo Arm
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence[7]
P-value	= 0.3
Method	Fisher exact

Notes:

[7] - In the primary analysis, the proportions of adverse events up to day 90 were described and compared between treatment arms using a Fisher’s exact test.

Secondary: Proportion of participants with an improvement in PCFS score to grades 1-2

End point title	Proportion of participants with an improvement in PCFS score to grades 1-2

End point description:

In the secondary analysis, the secondary endpoints were described through a table and graphically represented to evaluate its evolution over time. For the categorical endpoints sankey plots were used to describe the evolution of each category over time.

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[8]	25[9]		
Units: Percentatge				
number (not applicable)	24	40		

Notes:

[8] - Per Protocol

[9] - Per Protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation fatigue severity scale (FSS)

End point title	Evaluation fatigue severity scale (FSS)

End point description:

No changes were observed in the fatigue severity scale between the two groups during the study period.

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[10]	25[11]		
Units: Average score				
number (not applicable)	57.16	56.92		

Notes:

[10] - Per Protocol

[11] - Per protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the mean score of the Can Ruti PCC symptoms scale in the two groups over time

End point title	Evolution of the mean score of the Can Ruti PCC symptoms scale in the two groups over time

End point description:

Symptom Assessment (Can Ruti Scale): No significant changes were found in the progression of the Can Ruti Symptom Assessment Scale throughout the trial in both groups.

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: Mean score				
number (not applicable)	49.76	49.76		

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the mean score of EuroQol-5D in the two groups over time - PP population

End point title	Evolution of the mean score of EuroQol-5D in the two groups

	over time - PP population

End point description:

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[12]	25[13]		
Units: Mean				
number (not applicable)	0.37	0.42		

Notes:

[12] - Per Protocol

[13] - Per Protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the physical health component of MOS-HIV in the two groups over time (Really good))

End point title	Evolution of the physical health component of MOS-HIV in the two groups over time (Really good))

End point description:

% of participants indicated "really good" in the health component of MOS-HIV at 90 days.

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[14]	25[15]		
Units: Percentatge				
number (not applicable)	0	4.2		

Notes:

[14] - Per Protocol

[15] - Per Protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the mean score of Neu Screen in the two groups over time - PP population

End point title	Evolution of the mean score of Neu Screen in the two groups

	over time - PP population

End point description:

Evolution of the mean score of Neu Screen in the two groups over time - PP population (TMT-F+A+S)

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[16]	25[17]		
Units: score				
arithmetic mean (standard deviation)	33.04 (± 11.75)	29.52 (± 8.85)		

Notes:

[16] - PP population

[17] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the mean score of the semantic fluency test in the two groups over time - PP population

End point title	Evolution of the mean score of the semantic fluency test in the two groups over time - PP population

End point description:

Evolution of the mean score of the semantic fluency test in the two groups over time - PP population

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[18]	25[19]		
Units: Mean				
arithmetic mean (standard deviation)	18.71 (± 4.86)	16.88 (± 4.24)		

Notes:

[18] - PP population

[19] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the mean score of MEF-30 in the two groups over time - PP population

End point title	Evolution of the mean score of MEF-30 in the two groups over time - PP population

End point description:

Evolution of the mean score of MEF-30 in the two groups over time - PP population

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[20]	25[21]		
Units: Mean				
arithmetic mean (standard deviation)	66.83 (± 25.54)	67.92 (± 22.20)		

Notes:

[20] - Per Protocol

[21] - Evolution of the mean score of MEF-30 in the two groups over time - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the laboratory analysis profile of the two groups over time: FIBRINOGEN

End point title	Evolution of the laboratory analysis profile of the two groups over time: FIBRINOGEN

End point description:

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))	361.50 (321.00 to 466.00)	382.00 (343.00 to 410.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the laboratory analysis profile of the two groups over time: D-Dimer

End point title	Evolution of the laboratory analysis profile of the two groups over time: D-Dimer

End point description:

End point type	Secondary

End point timeframe:

At 90 days

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[22]	25[23]		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	240.50 (215.00 to 360.25)	265.00 (231.00 to 358.00)		

Notes:

[22] - Per Protocol

[23] - Per Protocol

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At 90 days

Adverse event reporting additional description:

A safety analysis was also conducted, considering adverse events on both a per-subject basis and a per-event basis.

Statistical analyses were performed with R software version 4.3.0 or higher and the most commonly used packages were gtsummary, ggplot2 and lme4.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Experimental Group

Reporting group description:

6 sessions of PE (Plasma Exchange) with human serum albumin. Plasma exchange sessions will occur on days 1, 3, 8, 10, 15 and 17.

Reporting group title	Control Group

Reporting group description:

6 sessions with placebo (infusion of 200 to 250ml of sterile saline solution 0.9%) on days 1, 3, 8, 10, 15 and 17.

Serious adverse events	Experimental Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Experimental Group	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	22 / 25 (88.00%)	
General disorders and administration site conditions			
Site administration discomfort			
subjects affected / exposed	25 / 25 (100.00%)	22 / 25 (88.00%)	
occurrences (all)	41	37	
Immune system disorders			

Allergic cough			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Reproductive tract disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	12 / 25 (48.00%)	6 / 25 (24.00%)	
occurrences (all)	12	6	
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Cardiac disorders			
Cardiac dysfunction			
subjects affected / exposed	5 / 25 (20.00%)	3 / 25 (12.00%)	
occurrences (all)	5	3	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	25 / 25 (100.00%)	22 / 25 (88.00%)	
occurrences (all)	45	31	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemias nonhaemolytic and marrow depression		
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			

Gastrointestinal disorder subjects affected / exposed occurrences (all)	25 / 25 (100.00%) 39	22 / 25 (88.00%) 29	
Hepatobiliary disorders Hepatobiliary disease subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 25 (0.00%) 0	
Skin and subcutaneous tissue disorders Skin disorders subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	7 / 25 (28.00%) 7	
Renal and urinary disorders Renal disorder subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	2 / 25 (8.00%) 2	
Musculoskeletal and connective tissue disorders Muscle discomfort subjects affected / exposed occurrences (all)	25 / 25 (100.00%) 31	13 / 25 (52.00%) 13	
Infections and infestations infections subjects affected / exposed occurrences (all)	14 / 25 (56.00%) 14	17 / 25 (68.00%) 17	
Metabolism and nutrition disorders Metabolism disorders subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	4 / 25 (16.00%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2022	To obtain the maximum information from participants diagnosed with Post-COVID-19 Syndrome (SPC), it is decided to add more parameters to be analyzed during the study, so the following documents are modified: - Protocol: New version 3.0, 06/22/2022 - Protocol Summary: New version 3.0, 06/22/2022 - HIP/CI: New version 4.0, 06/22/2022 - Annex IV: MOS-VIH (Annex IV (SF-36) is replaced by the MOS-VIH questionnaire. - Annex III: The version of the symptomatology questionnaire is updated. - Annex VI: The neurocognitive evaluation is added, based on the completion of 3 "Neuropsychological Assessment" questionnaires
19 December 2022	To obtain the maximum information from participants diagnosed with Post-COVID-19 Syndrome (PCS), it is decided to add an extra visit in case the participant presents re-infection by COVID-19, and it will be considered appropriate to carry out all the visits established by protocol, in case the participant has to prematurely discontinue the study treatment. Due to these changes, the following documentation is generated: - Protocol: New version 4.0, 12/19/2022 - Protocol Summary: New version 4.0, 12/19/2022 - HIP/CI: New version 5.0, 12/19/2022

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported