Clinical trial results:
A Randomised Controlled Trial of plasma exchange with standard of care compared to standard of care alone in the treatment of severe COVID-19 infection (COVIPLEX)

Summary

EudraCT number	2020-002668-29
Trial protocol	GB
Global end of trial date	31 January 2022

Results information

Result version number	v1 (current)
This version publication date	21 October 2023
First version publication date	21 October 2023

Trial information

Trial identification

Sponsor protocol code	132796

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Joint Research Office, University College London, ctimps@ucl.ac.uk
Scientific contact	Professor Marie Scully, University College London, m.scully@ucl.ac.uk

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	25 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2022
Global end of trial reached?	Yes
Global end of trial date	31 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the reduction in inflammatory markers between Plasma Exchange (PEX) and control group in patients with severe COVID.

Protection of trial subjects:

1.Central vascath insertion:
There is a risk of pain, infection and bleeding or thrombosis with central vascath insertion. All the central lines are put in by a defined trained group within the trust i.e. ICU/anaesthetics or interventional radiology. Patients with severe COVID-19 infection are likely to need central line access e.g. PICC/Central line. While these lines are not suitable for PEX, central venous access is common in COVID-19 patients in ICU. Patients will be monitored frequently for infections, bleeding or thrombosis

2: PEX
A. Reaction to plasma: There is a risk of infusional and allergic reactions and rarely anaphylaxis with the use of Octaplas. This is considerably reduced with the use of Octaplas compared to standard fresh frozen plasma (FFP) Reactions grade 1-3 are amenable to standard therapy including antihistamine, hydrocortisone and paracetamol. If a patient experiences symptoms of anaphylaxis, treatment would be stopped immediately.

B. Citrate reactions: Some patients treated with PEX present with features of hypocalcaemia (fatigue, paraesthesia, tremor, and hypocalcemia). This is treated with calcium boluses, but offset by a calcium infusion throughout PEX.

C. Risk of viral transmission: Standard measures to prevent infections resulting from the use of medical products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pool for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. However Octaplas LG undergoes a number of additional pathogen inactivation steps and is considered very safe.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 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	United Kingdom: 22
Worldwide total number of subjects	22
EEA total number of subjects	0

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)	16
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

23 patients with severe COVID-19 were randomised. One patient withdrew from the study 1 day after randomisation and their data has been excluded from the analysis. 11 were randomised to the treatment group receiving at least one course of Plasma Exchange (PEX). 11 were assigned to the control group receiving only standard of care treatment (SOC).

Pre-assignment

Screening details:

Patients will be recruited following admission to hospital for supportive care relating to presumed or confirmed COVID19. Those deemed appropriate for inclusion, meeting the inclusion criteria in the protocol, will be discussed by 2 senior clinicians and approached about the study. In conjunction, this will be discussed with the next of kin.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm - PEX

Arm description:

Treatment group receiving at least one course of Plasma Exchange (PEX) treatment. Among the treatment group, 5 patients received 2 or more courses of treatment, and 3 patients received 3 courses of treatment.

Arm type	Experimental
Investigational medicinal product name	OctaplasLG (human plasma proteins)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Plasma exchange (PEX) of 3 litres if <100Kg and 4 litres if >100Kg, for a minimum of once a day for 5 days.
Option for a further 5 day block of PEX if clinical and biochemical improvement following initial 5-day block but persistent pro-thrombotic phenotype.

Arm title	Control Arm - Standard of Care

Arm description:

Control group, receiving only standard of care treatment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Treatment Arm - PEX	Control Arm - Standard of Care
Started	11	11
Completed	11	11

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Arm - PEX
Reporting group description:	
Treatment group receiving at least one course of Plasma Exchange (PEX) treatment. Among the treatment group, 5 patients received 2 or more courses of treatment, and 3 patients received 3 courses of treatment.	
Reporting group title	Control Arm - Standard of Care
Reporting group description:	
Control group, receiving only standard of care treatment.	

Reporting group values	Treatment Arm - PEX	Control Arm - Standard of Care	Total
Number of subjects	11	11	22
Age categorical 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)	9	7	16
From 65-84 years	2	4	6
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	2	4
Male	9	9	18

End points

End points reporting groups

Reporting group title	Treatment Arm - PEX

Reporting group description:

Treatment group receiving at least one course of Plasma Exchange (PEX) treatment. Among the treatment group, 5 patients received 2 or more courses of treatment, and 3 patients received 3 courses of treatment.

Reporting group title	Control Arm - Standard of Care

Reporting group description:

Control group, receiving only standard of care treatment.

Primary: Inflammatory marker reduction of at least 50% at any efficacy time point

End point title	Inflammatory marker reduction of at least 50% at any efficacy time point

End point description:

The primary outcome in this study is a binary outcome indicating whether there was a reduction of at least 50% (compared to baseline) in two or more inflammatory markers [CRP, LDH, D-Dimer] during a "comparable duration of treatment" with either PEX or Standard of Care after study initiation.

End point type	Primary

End point timeframe:

The inflammatory markers recorded in this study are C reactive protein (CRP), lactate dehydrogenase (LDH) and D-Dimer, and we consider whether there is a reduction during the designated follow-up period (i.e. follow-up days 6, 7, 14, 21 and 28)

End point values	Treatment Arm - PEX	Control Arm - Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: %	80	50		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis

Statistical analysis description:

The primary analysis will involve a comparison of the binary outcome '50% reduction in at least two inflammation markers' between the PEX and Standard of Care (control) trial arms using a chi-squared test. The risk difference (and ratio) will be estimated with a 95% confidence interval.

Comparison groups	Treatment Arm - PEX v Control Arm - Standard of Care

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16 [1]
Method	Chi-squared

Notes:

[1] - 8/10 (80%) PEX patients have two or more markers that achieve this compared to 5/10 (50%) Standard of Care patients. This is not statistically significant at the 5% level.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events will be recorded from consent to the end of trial.

Adverse event reporting additional description:

Serious Adverse Events associated with COVID-19 infection were not reported to Sponsor for this trial, however they were recorded in the database and are included in this report.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Treatment Arm - PEX

Reporting group description:

Treatment group receiving at least one course of Plasma Exchange (PEX) treatment. Among the treatment group, 5 patients received 2 or more courses of treatment, and 3 patients received 3 courses of treatment.

Reporting group title	Control Arm - Standard of Care

Reporting group description:

Control group, receiving only standard of care treatment.

Serious adverse events	Treatment Arm - PEX	Control Arm - Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 11 (54.55%)	4 / 11 (36.36%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood pressure decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oxygen saturation decreased			
subjects affected / exposed	2 / 11 (18.18%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Oxygen therapy			
subjects affected / exposed	2 / 11 (18.18%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug therapy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation			
subjects affected / exposed	4 / 11 (36.36%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung assist device therapy			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
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			
Lung disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system infection			

subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment Arm - PEX	Control Arm - Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	11 / 11 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 11 (18.18%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Thrombosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Surgical and medical procedures			
Oxygen therapy			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Intensive care			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Tracheostomy			

subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Endotracheal intubation complication			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Wound secretion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Complication associated with device			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Mass			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lung disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pleural effusion			

subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	5 / 11 (45.45%)	2 / 11 (18.18%)	
occurrences (all)	5	2	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Mood altered			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Agitation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood glucose decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	1 / 11 (9.09%)	2 / 11 (18.18%)	
occurrences (all)	2	2	
Blood pressure increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Body temperature abnormal			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Body temperature increased			

subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Coma scale abnormal			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Computerised tomogram thorax			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Troponin T increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Drug monitoring procedure incorrectly performed			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Endotracheal intubation complication			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Tooth loss			

subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Bradycardia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Extrasystoles			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 11 (27.27%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Paraesthesia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Orchitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Asymptomatic COVID-19			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Bacterial infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hepatitis B			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2020	• Clarify of the respiratory parameters of the inclusion criteria. • Minor changes to the wording in the IMP section. • Interim analysis once 20 patients have completed the study. • Inclusion of a central laboratory . • Amendments to the protocol appendices.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported