Clinical trial results:
A prospective, randomized, open-label, interventional study to investigate the efficacy of complement C5 inhibition with Zilucoplan® in improving oxygenation and short- and long-term outcome of COVID-19 patients with acute hypoxic respiratory failure.

Summary

EudraCT number	2020-002130-33
Trial protocol	BE
Global end of trial date	09 April 2021

Results information

Result version number	v1 (current)
This version publication date	04 June 2022
First version publication date	04 June 2022

Trial information

Trial identification

Sponsor protocol code	ZILU-COV

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04382755
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZ Gent
Sponsor organisation address	C. Heymanlaan 10, Ghent, Belgium, 9000
Public contact	HIRUZ CTU, University Hospital Ghent, +32 93320500, hiruz.ctu@uzgent.be
Scientific contact	HIRUZ CTU, University Hospital Ghent, 093322352 93320500, hiruz.ctu@uzgent.be

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	12 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 December 2020
Global end of trial reached?	Yes
Global end of trial date	09 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this intervention is to study if Zilucoplan® affects the the median and/or mean change in oxygenation between enrolment (baseline) and at predose day 6 and day 15 (or discharge, whichever comes first) through assessment of the PaO2/FiO2 ratio and through measurement of the P(A-a)O2 gradient, which can easily be performed in the setting of clinical observation of patients admitted to the COVID-19 ward or ICU COVID-19 unit. For patients on ECMO the PaO2/FiO2 ratio and Aa-gradient cannot be calculated as in this case the FiO2 will be missing. Therefore, the last available value of PaO2/FiO2 ratio and Aa gradient prior to ECMO can be used at that timepoint.

Protection of trial subjects:

Ethics review and approval, informed consent, supportive care and routine monitoring, data protection in accordance with law on General Data Protection Regulation (GDPR) and institutional rules [Belgian law dated on 30 July 2018 and 22 Aug. 2002], insurance.

Background therapy:

All patients will receive standard of Care (SoC). Due to the rapidly evolving scientific insights, SoC for Covid-19 was not further defined a priori.

Prophylaxis against meningococcal disease will be given in the active group A receiving zilucoplan, in the form of antibiotic prophylaxis with a third generation cephalosporin or alternative covering N. menigitidis and S. pneumoniae in case of allergies or clinical indication. A antibiotic is administered until at least 14 days after the last dose of zilucoplan in group A.

Group B patients will receive a daily injection of 2g ceftriaxone IV or appropriate alternative in case of allergies or on clinical indication, during one week or until hospital discharge, whichever comes first.

Evidence for comparator:

Treatment with the approved C5 inhibitors eculizumab and ravulizumab, as well as rare genetic deficiencies in C5, are associated with a markedly increased risk for infection with encapsulated bacteria, most notably Neisseria meningitidis and H. influenzae, but not for viral infections generally, or for coronavirus infections in particular. To prevent the risk of meningococcal disease and prevent other infections with encapsulated bacteria, patients in the active group A will receive prophylactic antibiotics.

To control for the effects of antibiotic prophylaxis against menigococcal disease on clinical course of COVID-19, the control group B will also receive 1 week (or until hospital discharge whichever comes first) of IV 3rd generation cephalosporin. In case of allergies to these antibiotics, or on clinical indication, these antibiotics may be switched to antibiotics that also cover Neisseria meningitidis.

Actual start date of recruitment	22 May 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 81
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	42
From 65 to 84 years	38
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

84 patients were assessed for eligibility and 81 patients were randomized in the period from 15-aug-2020 till 16-dec-2021. 78 patients were included in the safety and primary analysis. End of trial notification was dated 27-may-2021 (last patient last visit) and submitted to EC and CA 30-jul-2021.

Pre-assignment

Screening details:

Confirmed COVID-19 patients between the age of 18 and 80 years were screened for acute hypoxic respiratory failure (saturation <93% on minimal 2 L/min O2 or PaO2/FiO2 <350). Invasive mechanical ventilation >24h, history of severe allergic reactions and unlikely to servive beyond 48h were the most important exclusion criteria.

Period 1

Period 1 title	Randomized Set
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N.A.

Arms

Are arms mutually exclusive?	Yes
Arm title	arm A (Zilucoplan + SoC)

Arm description:

standard of care + 32.4 mg Zilucoplan SC once daily for 14 days or until discharge, whichever comes first + daily prophylactic 3d generation cephalosporin IV for 14 days or untill discharge whichever comes first.
After last Zilucoplan dose :
- Patient still hospitalized: continue daily prophylactic 3d generation cephalosporin IV until 14 days after last Zilucoplan dose.
- Patient discharged: prophylactic oral ciprofloxacin 500mg daily until 14 days after last Zilucoplan dose.

Arm type	Experimental
Investigational medicinal product name	Zilucoplan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigational drug product will be provided in prefilled syringes containing 32.4 mg of Zilucoplan® for subcutaneous injection in the abdomen (preferred site), thigh, or upper arm. This dose is equivalent to that administered to the highest weight bracket in prior weight-based dosing regimens and is expected to achieve rapid, profound, and sustained complement inhibition with acceptable safety and tolerability. Subjects who present with very low body weight (<54kg) are excluded from enrolment. Subjects with very high body weight (>150 kg) are also excluded.

Investigational medicinal product name	ceftriaxone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for emulsion for injection
Routes of administration	Intravenous use

Dosage and administration details:

daily IV infusion of 2g of ceftriaxone until hospital discharge (or until 28 days after randomization when still in hospital, whichever comes first). If patient is discharged before day 28 after randomization, patient will switch to oral ciprofloxacin 1x500 mg per day until at least 14 days after the last

Zilucoplan® administration.

Arm title	Arm B (SoC)

Arm description:

Group B patients will receive daily IV infusion of 2g of ceftriaxone daily IV during one week or until hospital discharge, whichever comes first. In case of unavailability, ceftriaxone can be replaced by cefotaxime 1g every 8 hours.

Arm type	prophylactic antibiotics
Investigational medicinal product name	ceftriaxone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for emulsion for injection
Routes of administration	Intravenous use

Dosage and administration details:

Daily IV infusion of 2g of ceftriaxone daily IV during one week or until hospital discharge, whichever comes first. In case of allergies or on clinical grounds, prophylaxis with ceftriaxone could be changed to another antibiotic also providing coverage for N. meningitidis and S. pneumoniae.

Number of subjects in period 1	arm A (Zilucoplan + SoC)	Arm B (SoC)
Started	55	26
Completed	54	24
Not completed	1	2
Consent withdrawn by subject	1	-
Protocol deviation	-	2

Period 2

Period 2 title	Full Analysis Set
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Zilucoplan + Soc)

Arm description:

standard of care + 32.4 mg Zilucoplan SC once daily for 14 days or until discharge, whichever comes first + daily prophylactic 3rd generation cephalosporin IV for 14 days or until discharge whichever comes first.
After kast Zilucoplan dose:
- Patients still hospitalized: continue daily prophylactic 3rd generation cephalosporin IV until 14 days after last Zilucoplan dose.
- Patient discharged: prophylactic oral ciprofloxacin 500 mg daily until 14 days after last Zilucoplan dose.

Arm type	Experimental
Investigational medicinal product name	Zilucoplan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigational drug product will be provided in prefilled syringes containing 32.4 mg of Zilucoplan® for subcutaneous injection in the abdomen (preferred site), thigh, or upper arm. This dose is equivalent to that administered to the highest weight bracket in prior weight-based dosing regimens and is expected to achieve rapid, profound, and sustained complement inhibition with acceptable safety and tolerability. Subjects who present with very low body weight (<54kg) are excluded from enrolment. Subjects with very high body weight (>150 kg) are also excluded.

Investigational medicinal product name	ceftriaxone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for emulsion for injection
Routes of administration	Intravenous use

Dosage and administration details:

daily IV infusion of 2g of ceftriaxone until hospital discharge (or until 28 days after randomization when still in hospital, whichever comes first). If patient is discharged before day 28 after randomization, patient will switch to oral ciprofloxacin 1x500 mg per day until at least 14 days after the last Zilucoplan® administration.

Arm title	Arm B (SoC)

Arm description:

Group B patients will receive daily IV infusion of 2g of ceftriaxone daily IV during one week or until hospital discharge, whichever comes first. In case of unavailability, ceftriaxone can be replaced by cefotaxime 1 g every 8 hours.

Arm type	prophylactic antibiotics
Investigational medicinal product name	ceftriaxone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for emulsion for injection
Routes of administration	Intravenous use

Dosage and administration details:

Daily IV infusion of 2g of ceftriaxone daily IV during one week or until hospital discharge, whichever comes first. In case of allergies or on clinical grounds, prophylaxis with ceftriaxone could be changed to another antibiotic also providing coverage for N. meningitidis and S. pneumoniae.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the Randomized Set. This set includes 3 patients of whom we did not collect any data, but who were randomized.
Period 2 is the Full Analysis Set (without the aforementioned 3 patients). Therefore, this set is used as baseline period.

Number of subjects in period 2[2]	Arm A (Zilucoplan + Soc)	Arm B (SoC)
Started	54	24
Completed	54	24

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Three patients were randomized, but did not meet inclusion criteria or withdrew consent prior to first drug administration. Hence, no data of these patients are collected.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Zilucoplan + Soc)
Reporting group description:	
standard of care + 32.4 mg Zilucoplan SC once daily for 14 days or until discharge, whichever comes first + daily prophylactic 3rd generation cephalosporin IV for 14 days or until discharge whichever comes first. After kast Zilucoplan dose: - Patients still hospitalized: continue daily prophylactic 3rd generation cephalosporin IV until 14 days after last Zilucoplan dose. - Patient discharged: prophylactic oral ciprofloxacin 500 mg daily until 14 days after last Zilucoplan dose.	
Reporting group title	Arm B (SoC)
Reporting group description:	
Group B patients will receive daily IV infusion of 2g of ceftriaxone daily IV during one week or until hospital discharge, whichever comes first. In case of unavailability, ceftriaxone can be replaced by cefotaxime 1 g every 8 hours.	

Reporting group values	Arm A (Zilucoplan + Soc)	Arm B (SoC)	Total
Number of subjects	54	24	78
Age categorical Units: Subjects			
Adults (18-64 years)	29	12	41
From 65-84 years	25	11	36
85 years and over	0	1	1
Age continuous			
The median age was 63 years (range 35-85) .			
Units: years			
median	62	64.8	
full range (min-max)	35 to 83	50 to 85	-
Gender categorical Units: Subjects			
Female	5	5	10
Male	49	19	68
Ordinal scale			
6-point ordinal scale: 1 death, 2 on invasive mechanical ventilation or ECMO; 3 on non-invasive ventilation or high flow oxygen devices; 4 hospitalized, requiring supplemental oxygen; 5 hospitalized, not requiring supplemental oxygen, 6 not hospitalized.			
Units: Subjects			
2.	8	2	10
3.	19	8	27
4.	26	14	40
5.	1	0	1
Ethnicity Units: Subjects			
African	4	0	4
Arabian	3	1	4
Asian	1	0	1
Caucasian	46	22	68
Other	0	1	1

SOFA score			
SOFA, severity of organ failure assessment			
Units: Subjects			
1-2	29	14	43
3-4	14	7	21
5-6	1	2	3
7-8	7	0	7
Not done	3	1	4
Arterial hypertension Units: Subjects			
Yes	26	10	36
No	28	14	42
Diabetes mellitus Units: Subjects			
Yes	14	4	18
No	40	20	60
Cardiovascular disease Units: Subjects			
Yes	9	10	19
No	45	14	59
Chronic kidney disease Units: Subjects			
Yes	4	0	4
No	50	24	74
Glucocorticoids at randomisation Units: Subjects			
Yes	49	18	67
No	5	6	11
Glucocorticoid use during first 28 days Units: Subjects			
Yes	52	21	73
No	2	3	5
Anticoagulants at randomisation Units: Subjects			
Yes	49	21	70
No	5	3	8
Antibiotics at randomisation Units: Subjects			
Yes	16	2	18
No	38	22	60
Remdesivir at randomisation Units: Subjects			
Yes	7	2	9
No	47	22	69
PaO2/FiO2 ratio at baseline			
The ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2; PaO2/FiO2)			
Units: mmHg			
arithmetic mean	169	175	
standard deviation	± 94	± 93	-

End points

End points reporting groups

Reporting group title	arm A (Zilucoplan + SoC)

Reporting group description:

standard of care + 32.4 mg Zilucoplan SC once daily for 14 days or until discharge, whichever comes first + daily prophylactic 3d generation cephalosporin IV for 14 days or untill discharge whichever comes first.
After last Zilucoplan dose :
- Patient still hospitalized: continue daily prophylactic 3d generation cephalosporin IV until 14 days after last Zilucoplan dose.
- Patient discharged: prophylactic oral ciprofloxacin 500mg daily until 14 days after last Zilucoplan dose.

Reporting group title	Arm B (SoC)

Reporting group description:

Group B patients will receive daily IV infusion of 2g of ceftriaxone daily IV during one week or until hospital discharge, whichever comes first. In case of unavailability, ceftriaxone can be replaced by cefotaxime 1g every 8 hours.

Reporting group title	Arm A (Zilucoplan + Soc)

Reporting group description:

standard of care + 32.4 mg Zilucoplan SC once daily for 14 days or until discharge, whichever comes first + daily prophylactic 3rd generation cephalosporin IV for 14 days or until discharge whichever comes first.
After kast Zilucoplan dose:
- Patients still hospitalized: continue daily prophylactic 3rd generation cephalosporin IV until 14 days after last Zilucoplan dose.
- Patient discharged: prophylactic oral ciprofloxacin 500 mg daily until 14 days after last Zilucoplan dose.

Reporting group title	Arm B (SoC)

Reporting group description:

Group B patients will receive daily IV infusion of 2g of ceftriaxone daily IV during one week or until hospital discharge, whichever comes first. In case of unavailability, ceftriaxone can be replaced by cefotaxime 1 g every 8 hours.

Primary: LSMean change from baseline in PaO2/FiO2

End point title	LSMean change from baseline in PaO2/FiO2

End point description:

End point type	Primary

End point timeframe:

Day 6

End point values	arm A (Zilucoplan + SoC)	Arm B (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	20		
Units: mmHg				
least squares mean (confidence interval 95%)	56.4 (31.9 to 80.9)	20.6 (-17.3 to 58.5)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	arm A (Zilucoplan + SoC) v Arm B (SoC)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Mixed models analysis

Primary: LSMean change from baseline in PaO2/FiO2

End point title	LSMean change from baseline in PaO2/FiO2
End point description:	
End point type	Primary
End point timeframe:	
Day 15	

End point values	arm A (Zilucoplan + SoC)	Arm B (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	17		
Units: mmHg				
least squares mean (confidence interval 95%)	123.5 (94.3 to 152.7)	83.7 (39.0 to 128.4)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	arm A (Zilucoplan + SoC) v Arm B (SoC)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Mixed models analysis

Primary: LSMean change from baseline in a/A PO2	
End point title	LSMean change from baseline in a/A PO2
End point description:	

End point type	Primary
End point timeframe:	
Day 6	

End point values	arm A (Zilucoplan + SoC)	Arm B (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	20		
Units: mmHg				
least squares mean (confidence interval 95%)	0.1 (0.06 to 0.15)	0.04 (-0.04 to 0.11)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	arm A (Zilucoplan + SoC) v Arm B (SoC)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Mixed models analysis

Primary: LSMean change from baseline in a/A PO2	
End point title	LSMean change from baseline in a/A PO2
End point description:	

End point type	Primary
End point timeframe:	
Day 15	

End point values	arm A (Zilucoplan + SoC)	Arm B (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	17		
Units: mmHg				
least squares mean (confidence interval 95%)	0.25 (0.19 to 0.31)	0.17 (0.08 to 0.26)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	arm A (Zilucoplan + SoC) v Arm B (SoC)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Mixed models analysis

Primary: Geometric LSMean (A-a) gradient

End point title	Geometric LSMean (A-a) gradient
End point description: Geometric LSMean	
End point type	Primary
End point timeframe: Day 6	

End point values	arm A (Zilucoplan + SoC)	Arm B (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	20		
Units: mmHg				
geometric mean (confidence interval 95%)	114.6 (92.6 to 141.9)	146.7 (105.4 to 204.3)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	arm A (Zilucoplan + SoC) v Arm B (SoC)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Mixed models analysis

Primary: Geometric LSMean (A-a) gradient	
End point title	Geometric LSMean (A-a) gradient
End point description: Geometric LSMean	
End point type	Primary
End point timeframe: Day 15	

End point values	arm A (Zilucoplan + SoC)	Arm B (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	17		
Units: mmHg				
geometric mean (confidence interval 95%)	58.6 (44.9 to 76.5)	86.9 (57.9 to 130.6)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	arm A (Zilucoplan + SoC) v Arm B (SoC)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: screening and during 28 day assessment period.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	Arm A (Zilucoplan + SoC)

Reporting group description:

standard of care + 32.4mg Zilucoplan SC once daily for 14 days or until discharge, whichever comes first + daily prophylactic 3d generation cephalosporin IV for 14 days or until dicharge, wichever comes first.
After last Zilucoplan dose:
- patient still hospitalized:
  Continue daily prophylactic 3d generation cephalosporin IV untill 14 days after last Zilucoplan dose.
- patient discharged:
  prophylactic oral ciprofloxacin 500mg daily until 14 days after last Zilucoplan dose.

Reporting group title	Arm B (SoC)

Reporting group description:

standard of care + daily prophylactic 3d generation cephalosporin IV for 7 days or until discharge, whichever comes first.

Serious adverse events	Arm A (Zilucoplan + SoC)	Arm B (SoC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 54 (18.52%)	5 / 24 (20.83%)	
number of deaths (all causes)	5	5	
number of deaths resulting from adverse events	5	5	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoxic-sichaemic encephalopathy			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Death			

subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Aspergillus infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypercapnia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 54 (3.70%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillus			

subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic shock			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Thrombosis in device			

subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	
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	Arm A (Zilucoplan + SoC)	Arm B (SoC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 54 (72.22%)	17 / 24 (70.83%)	
Investigations			
Alanine animontransferase increased			
subjects affected / exposed	4 / 54 (7.41%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Aspartate animontransferase increased			
subjects affected / exposed	3 / 54 (5.56%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 54 (14.81%)	2 / 24 (8.33%)	
occurrences (all)	8	2	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	4 / 54 (7.41%)	2 / 24 (8.33%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 54 (12.96%)	5 / 24 (20.83%)	
occurrences (all)	7	5	
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	2 / 54 (3.70%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Pneumonia pseudomonal			

subjects affected / exposed	0 / 54 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 54 (11.11%)	1 / 24 (4.17%)	
occurrences (all)	6	1	
Delirium			
subjects affected / exposed	3 / 54 (5.56%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	5 / 54 (9.26%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 54 (7.41%)	3 / 24 (12.50%)	
occurrences (all)	4	3	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 54 (9.26%)	1 / 24 (4.17%)	
occurrences (all)	5	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 54 (1.85%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Hyperglycemia			
subjects affected / exposed	1 / 54 (1.85%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Hypoalbuminia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 24 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2020	Section 2.1: study design added. Section 7.1.2: wording changed to "An Investigator must discontinue or withdraw a subject from the study for the following reason." Clarification added on prophylaxis for meningococcal disease Section 9.2, 9.4: Follow up visit week 12-22 after randomization: additional assessments were added: WHO performance scale, 6 minutes walk test (per standard of care), HRCT scan to evaluate HRCT fibrosis score Section 9.4: assessment of vital signs: values to be collected at morning assessment, between 7-10 AM for all parameters. 6-point ordinal scale: scoring updated to "1=Death". HRCT fibrosis score: instructions on how to score HRCT findings. Section 13.5: text added: A careful assessment will be performed in cases where disease related events appear to be enhanced by the IMP. In accordance with CT-3 guidance, a causality assessment will be performed for each SAE, and if the investigator considers disease related event to be IMP-related and the event is serious,related and unexpected, then it will be reported as a SUSAR. Section 13.6: Additional information on DSMB Charter Section 9.3, 9.4, 10: details on samples to be collected updated, cfr. updated lab manual provided by central lab, Covance Section 12.1.2 information added that no data will be collected directly into the eCRF. Section 11.1: primary endpoint changed to day 6, day 15 (or discharge). Section 6.1: information added on anti-conception requirements for male subjects. Section 4.2: definition of ARDS changed according to the Berlin criteria according to Jason Chertoff. Section 1., 5.1: definition of Hypoxic respiratory failure changed.
10 June 2020	Section 1., 3.2, 4.2: secondary objectives changed. Section 3.1 and 4.1 Clarification for ECMO patients added. Section 4.2: Definition of ARDS: bullet point 4 changed. Section 6.1: Definition hypoxia changed. Section 9.2, 9.4: - laboratory assessments removed (fibrinogen and triglycerides at Day 6, 15 and FU) - Score assessments removed: Clinical Sign Score, Glasgow Come Scale and NEWS2. HScore only at Day 1. - Information added on timing of evaluation of 6 point ordinal scale and HScore.6 minute walk test: protocol requirement, not following SOC. Section 9.3: - Listing of lab assessments removed. - Day 4 was changed into day 6 Timepoint of analysis of cytokines changed from Day 14 to Day 15. General: typo's corrected. Section 10: D1: samples of 5ml for PK was changed into 6 ml. One 6 ml EDTA tube was added for complement (according to flowchart). Section 13.4: in flowchart reporting , 'HIRUZ CTU will inform all participating sites' was added for SUSARs Section 9.2: clinical exam and ECG added to section "at screening", to correspond with 9.4.
10 July 2020	Section 3.1 and 5.1 and 7.1 and 9.4: statement/clarification on use of alternative antibiotics in case of allergy to cephalosporin or ciprofloxacin Section 6.2: Exclusion Criteria added: patient on ECMO at screening Section 8.1.4: clarification added on administration of IMP during 24 hours dialysis. Section 9.4: Physical Examination: to be assessed on clinical grounds, as per standard of care. Clarification for ECMO patients added

09 April 2021	Section 4.2: Typo "≥60" corrected to "≥ 50". Section 4.2: Secondary endpoints updated according to SAP Section 4.3 has been added and describes the pharmacodynamics and pharmacokinetic endpoints Section 7.3, 9.4: information added on assessment of arterial blood gas: if an arterial blood gas value is available of less than 24 hours before randomization, there's no need to have a new ABG done on Day 0/1. Section 9.4: correction in footnote: time window of assessment of vital signs is not applicable for the follow-up visit. Section 13.3: Reporting address for SAEs changed to DS_ICT@ucb.com Section 13.7: clarification added on timelines of submission of DSUR. Section 10.3, 10.4: clarification added on analysis and storage by selected centres of optional samples. Section 10.5: identification of FAGG certified biobank to store remaining samples for future use. Section 9.2: volume of DNA EDTA changed from 5 ml to 4 ml (typo). Section 11.0: Update of statistical analysis team Section 5.1: "Group B" removed from sentence about prophylactic antibiotic treatment for patient randomized to Group A. *Amendment was approved by the regulatory authority on 27-Apr-2021*
09 April 2021	Section 4.2 : All secondary endpoints not related to secondary objectives have been moved to new section 4.3 "exploratory endpoints" section. Duplicates within secondary endpoint section have been removed. Removal of analytical language e.g. 'means' has been updated to reflect the endpoint itself not the analytical approach Section 4.3 Exploratory Endpoints was added. The content of this section concerns endpoints previously listed under section 4.2 which have been moved to the current section 4.3. For some of the endpoints, analytical language e.g. 'means' has been updated to reflect the endpoint itself not the analytical approach Section 4.4: clarification was added related to the exploratory nature of pharmacodynamic and pharmacokinetic endpoints Section 4.4: aPTT and PT have been removed from Pharmacodynamic endpoints Section 11.1 : name of individual UCB statistician Trevor Smart replaced by UCB Section 11.2: Clarification was added regarding the endpoints to be summarized. Section 11.2: the sentence "Data from SOC in another study with a very similar protocol will be incorporated into the analysis using a Bayesian frame work. This will be described more fully in the statistical analysis plan (SAP)." Has been replaced by "Data from SOC in another study with a very similar protocol may be incorporated into the analysis using a Bayesian frame work. This will be described more fully in the statistical analysis plan (SAP)." Section 12.4: The sentence "Pseudonymized biological analyses and study results will also be shared with the provider of Zilucoplan® (UCB Pharma)" has been replaced by "Pseudonymized biological analyses, study data and study results will also be shared with the provider of Zilucoplan® (UCB Pharma) " *Amendment was approved by the regulatory authority on 09-June-2021*

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1) open label design
2) 14 days of prophylactic antibiotics in Zilucoplan group vs 7 days in SoC
3) population predominantly composed of white men
4) FiO2 based on the method of oxygen delivery and flow
5) differences in baseline characteristics

Notes: