Clinical trial results:
A Phase 3 Open-label, Randomized, Controlled Study to Evaluate the Efficacy and Safety of Intravenously Administered Ravulizumab Compared with Best Supportive Care in Patients with COVID-19 Severe Pneumonia, Acute Lung Injury, or Acute Respiratory Distress Syndrome

Summary

EudraCT number	2020-001497-30
Trial protocol	GB FR DE ES IT
Global end of trial date	08 April 2021

Results information

Result version number	v1
This version publication date	22 April 2022
First version publication date	22 April 2022

Trial information

Trial identification

Sponsor protocol code	ALXN1210-COV-305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04369469
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals, Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Europe SAS, +33 1 47 10 06 15, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +33 1 47 10 06 15, clinicaltrials.eu@alexion.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	08 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2021
Global end of trial reached?	Yes
Global end of trial date	08 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of ravulizumab + best supportive care (BSC) compared with BSC alone on the survival of participants with acute respiratory distress syndrome due to coronavirus disease 2019 (COVID-19).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonized Tripartite Guideline, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

Best supportive care

Evidence for comparator: -

Actual start date of recruitment	10 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 152
Worldwide total number of subjects	202
EEA total number of subjects	37

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)	95
From 65 to 84 years	104
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 210 participants screened, 8 (3.8%) participants were screen failures. A total of 202 participants were randomized and treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 - Ravulizumab + BSC

Arm description:

Ravulizumab: Weight-based doses of ravulizumab were administered intravenously on Days 1, 5, 10, and 15. BSC: Participants received medications, therapies, and interventions per standard hospital treatment protocols.

Arm type	Experimental
Investigational medicinal product name	ALXN1210
Investigational medicinal product code	
Other name	Ultomiris, Ravulizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants randomized to ravulizumab + BSC received a weight-based dose of ravulizumab on Day 1, followed by weight-based doses of 600 milligrams (mg) or 900 mg ravulizumab on Days 5 and 10, and thereafter a single dose of 900 mg ravulizumab on Day 15. No additional doses were allowed during the Primary Evaluation Period (Day 1 through Day 29).

Arm title	Group 2 - BSC alone

Arm description:

Participants received medications, therapies, and interventions per standard hospital treatment protocols.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Group 1 - Ravulizumab + BSC	Group 2 - BSC alone
Started	135	67
Intent to Treat (ITT) Population	135	66
Pharmacokinetic (PK)	127	52 [1]
Safety Population	127	67
Completed	125	58
Not completed	10	9

Not qualified due to anaphylaxis	1	-
Physician decision	2	1
Consent withdrawn by subject	2	3
Adverse event	1	-
Unable to provide consent	-	1
Did not meet inclusion/exclusion criteria	2	-
Lost to follow-up	2	4

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The data reported in the intermediate milestones is applicable to the number of participants in the respective populations. The PK population is smaller than the number of subjects in the arm because fewer patients contributed samples.

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 - Ravulizumab + BSC
Reporting group description:	
Ravulizumab: Weight-based doses of ravulizumab were administered intravenously on Days 1, 5, 10, and 15. BSC: Participants received medications, therapies, and interventions per standard hospital treatment protocols.	
Reporting group title	Group 2 - BSC alone
Reporting group description:	
Participants received medications, therapies, and interventions per standard hospital treatment protocols.	

Reporting group values	Group 1 - Ravulizumab + BSC	Group 2 - BSC alone	Total
Number of subjects	135	67	202
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)	63	32	95
From 65-84 years	71	33	104
85 years and over	1	2	3
Age continuous Units: years			
arithmetic mean	63.2	63.0	
standard deviation	± 13.23	± 12.79	-
Gender categorical Units: Subjects			
Female	39	23	62
Male	96	44	140
Ethnicity Units: Subjects			
Not Hispanic or Latino	100	47	147
Hispanic or Latino	27	11	38
Missing/Unknown	7	5	12
Not reported	1	4	5
Race Units: Subjects			
White	72	40	112
Black or African American	20	7	27
Missing/Unknown	17	5	22
Other	12	5	17
Asian	9	7	16
Not Reported	4	2	6

American Indian or Alaska Native	1	0	1
Native Hawaiian or Other Pacific Islander	0	1	1

Subject analysis sets

Subject analysis set title	Group 1 - Ravulizumab + BSC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Ravulizumab: Weight-based doses of ravulizumab were administered intravenously on Days 1, 5, 10, and 15. BSC: Participants received medications, therapies, and interventions per standard hospital treatment protocols.

Subject analysis set title	Group 2 - BSC Alone
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received medications, therapies, and interventions per standard hospital treatment protocols.

Reporting group values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone	
Number of subjects	135	66	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	63	31	
From 65-84 years	71	33	
85 years and over	1	2	
Age continuous Units: years			
arithmetic mean	63.2	63.5	
standard deviation	± 13.23	± 12.40	
Gender categorical Units: Subjects			
Female	39	23	
Male	96	43	
Ethnicity Units: Subjects			
Not Hispanic or Latino	100	46	
Hispanic or Latino	27	11	
Missing/Unknown	7	5	
Not reported	1	4	
Race Units: Subjects			
White	72	40	
Black or African American	20	7	
Missing/Unknown	17	5	

Other	12	5	
Asian	9	6	
Not Reported	4	2	
American Indian or Alaska Native	1	0	
Native Hawaiian or Other Pacific Islander	0	1	

End points

End points reporting groups

Reporting group title	Group 1 - Ravulizumab + BSC
Reporting group description:	
Ravulizumab: Weight-based doses of ravulizumab were administered intravenously on Days 1, 5, 10, and 15. BSC: Participants received medications, therapies, and interventions per standard hospital treatment protocols.	
Reporting group title	Group 2 - BSC alone
Reporting group description:	
Participants received medications, therapies, and interventions per standard hospital treatment protocols.	
Subject analysis set title	Group 1 - Ravulizumab + BSC
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Ravulizumab: Weight-based doses of ravulizumab were administered intravenously on Days 1, 5, 10, and 15. BSC: Participants received medications, therapies, and interventions per standard hospital treatment protocols.	
Subject analysis set title	Group 2 - BSC Alone
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received medications, therapies, and interventions per standard hospital treatment protocols.	

Primary: Survival (Based On All-Cause Mortality) in Participants in the ITT Population At Day 29

End point title	Survival (Based On All-Cause Mortality) in Participants in the ITT Population At Day 29
End point description:	
Survival (based on all-cause mortality) in Participants in the ITT Population at Day 29 was analyzed. The result for the survival was estimated survival combined over all imputations. The ITT Population consisted of all randomized participants. Participants were analyzed as randomized.	
End point type	Primary
End point timeframe:	
Day 29	

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	135	66		
Units: Percentage of participants				
number (not applicable)	57.6	59.7		

Statistical analyses

Statistical analysis title	Survival (Based On All-Cause Mortality) At Day 29
Comparison groups	Group 1 - Ravulizumab + BSC v Group 2 - BSC Alone

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6059 [1]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.0205
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1703
upper limit	0.1293

Notes:

[1] - One-sided Mantel-Haenszel test of the difference in two proportions stratified by intubated or not intubated on Day 1 and a family-wise Type I error of 0.025.

Secondary: Number Of Days Free Of Mechanical Ventilation At Day 29

End point title	Number Of Days Free Of Mechanical Ventilation At Day 29

End point description:

The number of days free of mechanical ventilation was defined as the total number of days from Day 1 to Day 29 without invasive or non-invasive mechanical ventilation. The ITT Population consisted of all randomized participants. Participants were analyzed as randomized. Here, 'Number of Participants Analyzed' signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Day 29

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	62		
Units: Days				
least squares mean (confidence interval 95%)				
Overall	6.79 (4.79 to 8.80)	6.81 (4.19 to 9.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days the Participants were Alive and Not in ICU

End point title	Number of Days the Participants were Alive and Not in ICU

End point description:

The number of days that the participants were alive and not in the ICU from Day 1 through Day 29 are presented. The ITT Population consisted of all randomized participants. Participants were analyzed as randomized. Here, 'Number of Participants Analyzed' signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	62		
Units: Days				
least squares mean (confidence interval 95%)				
Overall	6.09 (4.31 to 7.87)	6.71 (4.38 to 9.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Sequential Organ Failure Assessment (SOFA) At Day 29

End point title	Change From Baseline In Sequential Organ Failure Assessment (SOFA) At Day 29

End point description:

Baseline was defined as the last available assessment on or before Day 1 for all participants. Participants were evaluated using the SOFA score, an assessment tool that included a review of 6 organ systems: respiratory, renal, hepatic, cardiac, coagulation, and central nervous system. Each organ system was scored from 0 to 4 points using the worst value observed within the previous 24 hours. The total score ranged from 0 to 24, with a higher score indicating a worse condition. The ITT Population consisted of all randomized participants. Participants were analyzed as randomized. Here, 'Number of Participants Analyzed' signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Day 29

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	17		
Units: Units on a scale				
arithmetic mean (standard deviation)	-2.0 (± 6.25)	-4.5 (± 4.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Peripheral Capillary Oxygen Saturation/Fraction Of Inspired Oxygen (SpO2/FiO2) At Day 29

End point title	Change From Baseline In Peripheral Capillary Oxygen Saturation/Fraction Of Inspired Oxygen (SpO2/FiO2) At Day 29

End point description:

Oxygenation was measured using the SpO2 and the amount of supplemental oxygen as measured by the FiO2 received by taking the ratio of these 2 measures at the same time point. The ITT Population consisted of all randomized participants. Participants were analyzed as randomized. Here, 'Number of Participants Analyzed' signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Day 29

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	17		
Units: ratio				
arithmetic mean (standard deviation)	62.5 (± 112.43)	134.0 (± 104.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days the Participants were Alive and Not in the Hospital

End point title	Number of Days the Participants were Alive and Not in the Hospital

End point description:

The number of days that the participants were alive and not in the hospital from Day 1 through Day 29 are presented. The ITT Population consisted of all randomized participants. Participants were analyzed as randomized. Here, ‘Number of Participants Analyzed’ signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	62		
Units: Days				
least squares mean (confidence interval	3.02 (1.76 to	3.47 (1.83 to		

95%)	4.29)	5.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Alive At Up To Day 60 and At Up To Day 90

End point title	Number of Participants Alive At Up To Day 60 and At Up To Day 90

End point description:

For this analysis, 2 participants in Group 1 (Ravulizumab + BSC) and 1 participant in Group 2 (BSC Alone) were censored at Day 90. The number of participants alive for this this analysis was calculated using the method of Kaplan and Meier (KM) and compared using a log-rank test stratified by intubated or not intubated on Day 1 as a sensitivity analysis. The ITT Population consisted of all randomized participants. Participants were analyzed as randomized. Here, "Number Analyzed" signifies those participants who were evaluable for the assessment at the specified time frame.

End point type	Secondary

End point timeframe:

Up to Day 60 and Up to Day 90

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	135	66		
Units: participants				
Day 60 (n=135, 66)	60	29		
Day 90 (n=133, 65)	49	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Ravulizumab Concentrations Prior to Dosing on Day 1 and Day 29

End point title	Serum Ravulizumab Concentrations Prior to Dosing on Day 1 and Day 29

End point description:

Results are reported in micrograms/milliliter (µg/mL). Pharmacokinetics/Pharmacodynamics (PK/PD) Population: participants in the ITT population with at least 1 postdose PK or PD result.

End point type	Secondary

End point timeframe:

Day 1 and Day 29

End point values	Group 1 - Ravulizumab + BSC			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1 (predose) (n=116) Day 29 (predose) (n=44)	0.00 (± 0.00) 231.35 (± 149.741)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Serum Free Complement Component 5 Concentrations At Day 29

End point title	Change From Baseline In Serum Free Complement Component 5 Concentrations At Day 29

End point description:

PK/PD Population: participants in the ITT population with at least 1 postdose PK or PD result. Here, 'Number of Participants Analyzed' signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Day 29

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	14		
Units: µg/mL				
arithmetic mean (standard deviation)	-156.31 (± 61.599)	21.79 (± 67.918)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Terminal Complement Complex C5b-9 At Day 29

End point title	Change From Baseline In Terminal Complement Complex C5b-

	9 At Day 29

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 29

End point values	Group 1 - Ravulizumab + BSC	Group 2 - BSC Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	14		
Units: ug/L				
arithmetic mean (standard deviation)	-133.23 (± 202.070)	-277.21 (± 604.742)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Day 90

Adverse event reporting additional description:

Data for All-Cause Mortality was collected for ITT Population (randomized participants; participants analyzed as randomized [N=135, 66]). Serious and Other (Not Including Serious) Adverse Events were collected for Safety Population (randomized participants who received at least 1 dose of study drug; participants analyzed as treated [N=127, 67]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Group 1 - Ravulizumab + BSC

Reporting group description:

Ravulizumab: Weight-based doses of ravulizumab were administered intravenously on Days 1, 5, 10, and 15. BSC: Participants received medications, therapies, and interventions per standard hospital treatment protocols.

Reporting group title	Group 2 - BSC alone

Reporting group description:

Participants received medications, therapies, and interventions per standard hospital treatment protocols.

Serious adverse events	Group 1 - Ravulizumab + BSC	Group 2 - BSC alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 127 (62.20%)	38 / 67 (56.72%)	
number of deaths (all causes)	55	66	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 127 (2.36%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	1 / 127 (0.79%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	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	14 / 127 (11.02%)	6 / 67 (8.96%)	
occurrences causally related to treatment / all	0 / 14	0 / 6	
deaths causally related to treatment / all	0 / 11	0 / 6	
Condition aggravated			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	12 / 127 (9.45%)	5 / 67 (7.46%)	
occurrences causally related to treatment / all	0 / 12	0 / 5	
deaths causally related to treatment / all	0 / 10	0 / 4	
Acute respiratory failure			
subjects affected / exposed	6 / 127 (4.72%)	4 / 67 (5.97%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 4	

Respiratory failure			
subjects affected / exposed	5 / 127 (3.94%)	5 / 67 (7.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 4	
Hypoxia			
subjects affected / exposed	4 / 127 (3.15%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pneumothorax			
subjects affected / exposed	4 / 127 (3.15%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	3 / 127 (2.36%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	2 / 127 (1.57%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumomediastinum			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			

subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal stenosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood beta-D-glucan positive			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactic acid increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrin D dimer increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (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	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transaminases increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	4 / 127 (3.15%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Atrial fibrillation			
subjects affected / exposed	1 / 127 (0.79%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 127 (0.79%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Cardio-respiratory arrest			
subjects affected / exposed	0 / 127 (0.00%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Ventricular tachycardia			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain injury			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			

subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ischaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Ischaemic hepatitis			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 127 (1.57%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 127 (1.57%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haematoma muscle			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	13 / 127 (10.24%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	0 / 15	0 / 5	
deaths causally related to treatment / all	0 / 8	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	7 / 127 (5.51%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 7	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 127 (3.15%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	2 / 127 (1.57%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 127 (2.36%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	2 / 127 (1.57%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (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 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptococcosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter pneumonia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Herpes simplex pneumonia			

subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Group 1 - Ravulizumab + BSC	Group 2 - BSC alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 127 (76.38%)	49 / 67 (73.13%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	16 / 127 (12.60%)	8 / 67 (11.94%)	
occurrences (all)	18	10	

Deep vein thrombosis			
subjects affected / exposed	14 / 127 (11.02%)	2 / 67 (2.99%)	
occurrences (all)	14	2	
Hypertension			
subjects affected / exposed	9 / 127 (7.09%)	3 / 67 (4.48%)	
occurrences (all)	9	3	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	12 / 127 (9.45%)	5 / 67 (7.46%)	
occurrences (all)	12	5	
Bradycardia			
subjects affected / exposed	6 / 127 (4.72%)	4 / 67 (5.97%)	
occurrences (all)	6	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 127 (10.24%)	4 / 67 (5.97%)	
occurrences (all)	15	5	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 127 (7.87%)	6 / 67 (8.96%)	
occurrences (all)	12	6	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 127 (3.94%)	5 / 67 (7.46%)	
occurrences (all)	5	6	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	1 / 127 (0.79%)	4 / 67 (5.97%)	
occurrences (all)	1	6	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	8 / 127 (6.30%)	4 / 67 (5.97%)	
occurrences (all)	9	4	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 127 (7.09%)	5 / 67 (7.46%)	
occurrences (all)	10	5	

Infections and infestations Pneumonia bacterial subjects affected / exposed occurrences (all)	 7 / 127 (5.51%) 7	 4 / 67 (5.97%) 4	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all) Hypernatraemia subjects affected / exposed occurrences (all)	 8 / 127 (6.30%) 9 11 / 127 (8.66%) 11	 6 / 67 (8.96%) 6 3 / 67 (4.48%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2020	- Clarified the informed consent process for participants who were unconscious and whose legally acceptable representative was not immediately available. - Appended Investigator guidance regarding the management of potential drug infusion reactions during ravulizumab administration.
17 April 2020	- Relocated "Survival (based on all-cause mortality) at Day 60 and Day 90" from the list of exploratory endpoints to the list of secondary endpoints. - Clarified that participants discharged from the hospital before the end of the Primary Evaluation Period would be contacted via telephone on Day 29 to determine health status (for example, survival, mechanical ventilation, hospitalization, intensive care unit, and dialysis). - Removed the definition of Full Analysis Set and added definition of Intent to Treat. - Revised analyses of selected endpoints.
09 June 2020	- Updated the inclusion and exclusion criteria, study endpoints and objectives, and the schedule of activities. Participant reported outcomes (Short Form 12 and EuroQol 5 Dimension 5 Level) were added and implemented change to align content in Section 9 (Statistical Considerations) with version 1 and version 2 of the statistical analysis plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 January 2021	Enrollment of participants was paused on 13-Jan-2021. At that time, 202 participants had been randomized. An interim analysis for efficacy and futility was conducted on data from the first 122 participants who completed the Primary Evaluation Period. The analysis showed that the study met the prespecified stopping criteria for futility. After review of all participant data, Alexion terminated the study on 01-Sep-2021.	-

Notes:

Limitations and caveats

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

Enrollment of participants was paused on 13-Jan-2021. Subsequent analysis showed that the study met the prespecified stopping criteria for futility. After review of all participant data, Alexion terminated the study on 01-Sep-2021.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33826106

http://www.ncbi.nlm.nih.gov/pubmed/32660611