Clinical trial results:
Safety and efficacy of inhaled pegylated adrenomedullin (PEG-ADM) in patients suffering from Acute Respiratory Distress Syndrome (ARDS): a double-blind, randomized, placebo-controlled, multicenter Phase 2a/b clinical trial

Summary

EudraCT number	2019-001078-27
Trial protocol	DE CZ AT IT GR NL BE DK IE FI HU SK
Global end of trial date	18 January 2023

Results information

Result version number	v1 (current)
This version publication date	19 January 2024
First version publication date	19 January 2024

Trial information

Trial identification

Sponsor protocol code	BAY1097761/19999

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04417036
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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	18 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety and efficacy of inhaled PEG-ADM in ARDS

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 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	Czechia: 10
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	90
EEA total number of subjects	86

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)	54
From 65 to 84 years	35
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study Part A was conducted at multiple sites in 7 countries between 07 JUL 2020 (first subject first visit) and 28 DEC 2022 (last subject last visit).

Pre-assignment

Screening details:

In total, 98 subjects were screened, of those 90 were randomized and treated. Of 8 subjects who failed screening, 6 were due to screen failures, 1 was withdrawal by subject/guardian, 1 was due to other reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A - BAY1097761 Active Dose 1

Arm description:

Subject received BAY1097761 dose 1 by inhalation for up to 14 days.

Arm type	Experimental
Investigational medicinal product name	Pegylated adrenomedullin
Investigational medicinal product code	BAY1097761
Other name	PEG-ADM
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

dose 1, inhalation

Arm title	Part A - BAY1097761 Active Dose 2

Arm description:

Subject received BAY1097761 dose 2 by inhalation for up to 14 days.

Arm type	Experimental
Investigational medicinal product name	Pegylated adrenomedullin
Investigational medicinal product code	BAY1097761
Other name	PEG-ADM
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

dose 2, inhalation

Arm title	Part A - Placebo

Arm description:

Subject received matching placebo for up to 14 days.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:
placebo, inhalation

Number of subjects in period 1	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo
Started	29	30	31
Completed	17	18	21
Not completed	12	12	10
Adverse event, serious fatal	11	7	7
Physician decision	1	-	-
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	-	1
Other reasons	-	1	1
Lost to follow-up	-	2	-
Protocol deviation	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A - BAY1097761 Active Dose 1
Reporting group description:	
Subject received BAY1097761 dose 1 by inhalation for up to 14 days.	
Reporting group title	Part A - BAY1097761 Active Dose 2
Reporting group description:	
Subject received BAY1097761 dose 2 by inhalation for up to 14 days.	
Reporting group title	Part A - Placebo
Reporting group description:	
Subject received matching placebo for up to 14 days.	

Reporting group values	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo
Number of subjects	29	30	31
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 56.90 ± 16.82	 60.10 ± 17.80	 61.97 ± 11.26
Gender Categorical Units: Subjects			
Female	8	7	11
Male	21	23	20

Reporting group values	Total		
Number of subjects	90		
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 -	 	
Gender Categorical Units: Subjects			
Female	26		
Male	64		

End points

End points reporting groups

Reporting group title	Part A - BAY1097761 Active Dose 1
Reporting group description:	
Subject received BAY1097761 dose 1 by inhalation for up to 14 days.	
Reporting group title	Part A - BAY1097761 Active Dose 2
Reporting group description:	
Subject received BAY1097761 dose 2 by inhalation for up to 14 days.	
Reporting group title	Part A - Placebo
Reporting group description:	
Subject received matching placebo for up to 14 days.	
Subject analysis set title	Full analysis set (FAS-A)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects randomized to Part A who received at least one inhalation and could provide baseline as well as post-randomization data for at least one CUI component. Subjects were analyzed as randomized.	
Subject analysis set title	Safety analysis set (SAF-A)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomized to Part A who received at least one inhalation. Subjects were analyzed according to the intervention they actually received.	

Primary: Ventilator-free survival (VFS) in Part B subjects

End point title	Ventilator-free survival (VFS) in Part B subjects[1]
End point description:	
Ventilator-free survival (VFS, number of subjects alive and not on invasive mechanical ventilation)	
End point type	Primary
End point timeframe:	
in Part B at Study Day 28 (planned), while study terminated before Part B	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Study terminated before Part B, hence no results for this endpoint.

End point values	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: subjects				

Notes:

[2] - Study terminated before Part B initiation, Part A CUI results reported below.

[3] - Study terminated before Part B initiation, Part A CUI results reported below.

[4] - Study terminated before Part B initiation, Part A CUI results reported below.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Utility Index (CUI) in Part A subjects

End point title	Clinical Utility Index (CUI) in Part A subjects

End point description:

Clinical Utility Index (CUI) is a summary measure used to compare different treatments, the index score will range between 0 and 1. CUI is derived from: Extravascular lung water index (EVLWi), Oxygenation index (OI), Non-pulmonary Sequential Organ Failure Assessment (npSOFA) score.

End point type	Secondary

End point timeframe:

up to 28 days

End point values	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[5]	30[6]	31[7]	
Units: scores				
median (confidence interval 95%)	0.410 (0.293 to 0.525)	0.642 (0.509 to 0.755)	0.621 (0.488 to 0.731)	

Notes:

[5] - FAS-A

[6] - FAS-A

[7] - FAS-A

Statistical analyses

Statistical analysis title	Bayesian model for CUI dose 2 vs. placebo

Statistical analysis description:

Bayesian mixed model for CUI with the overall estimates and active treatment vs. placebo results

Comparison groups	Part A - BAY1097761 Active Dose 2 v Part A - Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Median difference (final values)
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.155
upper limit	0.196

Notes:

[8] - Posterior Probability of Difference Active Treatment - Placebo > 0 was 60.3%

Statistical analysis title	Bayesian model for CUI dose 1 vs. placebo

Statistical analysis description:

Bayesian mixed model for CUI with the overall estimates and active treatment vs. placebo results

Comparison groups	Part A - BAY1097761 Active Dose 1 v Part A - Placebo

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Median difference (final values)
Point estimate	-0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.374
upper limit	-0.033

Notes:

[9] - Posterior Probability of Difference Active Treatment - Placebo > 0 was 1.2%

Secondary: VFS in Part A subjects

End point title	VFS in Part A subjects

End point description:

Ventilator-free survival (VFS, number of subjects alive and not on invasive mechanical ventilation)

End point type	Secondary

End point timeframe:

At Day 28 and Day 60

End point values	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[10]	30[11]	31[12]	
Units: subjects				
Day 28	15	20	20	
Day 60	15	23	23	

Notes:

[10] - SAF-A

[11] - SAF-A

[12] - SAF-A

Statistical analyses

Statistical analysis title	Bayesian for VFS at Day 28 dose 2 vs. placebo

Statistical analysis description:

The estimates and active treatment vs. placebo for the Bayesian analysis for VFS at Study Day 28

Comparison groups	Part A - BAY1097761 Active Dose 2 v Part A - Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Median difference (final values)
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.212
upper limit	0.249

Notes:

[13] - Posterior Probability of Difference Active Treatment - Placebo > 0 was 56.9%.

Statistical analysis title	Bayesian for VFS at Day 28 dose 1 vs. placebo

Statistical analysis description:

The estimates and active treatment vs. placebo for the Bayesian analysis for VFS at Study Day 28

Comparison groups	Part A - BAY1097761 Active Dose 1 v Part A - Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Median difference (final values)
Point estimate	-0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.358
upper limit	0.112

Notes:

[14] - Posterior Probability of Difference Active Treatment - Placebo > 0 was 16.0%.

Secondary: All-cause mortality in Part A and Part B subjects

End point title	All-cause mortality in Part A and Part B subjects

End point description:

All-cause mortality is defined as proportion of deceased study subjects at a corresponding study day.

End point type	Secondary

End point timeframe:

At Day 28, Day 60 and Day 90 (Part A only, study terminated before Part B)

End point values	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[15]	30[16]	31[17]	
Units: subjects				
Day 28	7	6	6	
Day 60	9	7	7	
Day 90	11	7	7	

Notes:

[15] - SAF-A

[16] - SAF-A

[17] - SAF-A

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants who still require invasive mechanical ventilation support in Part A and Part B subjects

End point title	Proportion of participants who still require invasive mechanical ventilation support in Part A and Part B subjects

End point description:

Proportion of participants who still require invasive mechanical ventilation support at Study Day 28 / 60

End point type	Secondary

End point timeframe:

At Day 28 and Day 60 (Part A only, study terminated before Part B)

End point values	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[18]	30[19]	31[20]	
Units: subjects				
Day 28	7	4	5	
Day 60	5	0	1	

Notes:

[18] - FAS-A

[19] - FAS-A

[20] - FAS-A

Statistical analyses

No statistical analyses for this end point

Secondary: Ventilator-free days (VFDs) in Part A and Part B subjects

End point title	Ventilator-free days (VFDs) in Part A and Part B subjects

End point description:

End point type	Secondary

End point timeframe:

Within Day 28 and Day 60 (Part A only, study terminated before Part B)

End point values	Part A - BAY1097761 Active Dose 1	Part A - BAY1097761 Active Dose 2	Part A - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[21]	30[22]	31[23]	
Units: days				
arithmetic mean (standard deviation)				
Day 28	9.17 (± 10.35)	10.73 (± 9.37)	9.84 (± 9.13)	
Day 60	25.72 (± 25.80)	35.03 (± 21.10)	32.35 (± 22.05)	

Notes:
[21] - SAF-A
[22] - SAF-A
[23] - SAF-A

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A treatment-emergent AE was defined as an AE observed or reported after the first administration of study drug or if it started before the first administration of study drug and worsens on treatment, and not later than 2 days after end of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Part A - BAY1097761 Active Dose 1

Reporting group description:

Subject received BAY1097761960 dose 1 by inhalation for up to 14 days.

Reporting group title	Part A - Placebo

Reporting group description:

Subject received matching placebo for up to 14 days.

Reporting group title	Part A - BAY1097761 Active Dose 2

Reporting group description:

Subject received BAY1097761960 dose 2 by inhalation for up to 14 days.

Serious adverse events	Part A - BAY1097761 Active Dose 1	Part A - Placebo	Part A - BAY1097761 Active Dose 2
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 29 (34.48%)	13 / 31 (41.94%)	14 / 30 (46.67%)
number of deaths (all causes)	11	7	7
number of deaths resulting from adverse events	3	6	5
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Endotracheal intubation complication			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weaning failure			

subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Shock			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Pericarditis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuromyopathy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Quadriparesis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 29 (3.45%)	2 / 31 (6.45%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Intra-abdominal haematoma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 29 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			

subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diaphragmatic rupture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 29 (13.79%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia serratia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 29 (3.45%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

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

Non-serious adverse events	Part A - BAY1097761 Active Dose 1	Part A - Placebo	Part A - BAY1097761 Active Dose 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 29 (51.72%)	17 / 31 (54.84%)	18 / 30 (60.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 29 (10.34%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Hypotension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
Jugular vein thrombosis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Atrial fibrillation			
subjects affected / exposed	3 / 29 (10.34%)	1 / 31 (3.23%)	3 / 30 (10.00%)
occurrences (all)	4	2	3
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 29 (3.45%)	5 / 31 (16.13%)	3 / 30 (10.00%)
occurrences (all)	1	5	3
Thrombocytopenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 29 (3.45%)	3 / 31 (9.68%)	0 / 30 (0.00%)
occurrences (all)	1	3	0
Nausea			
subjects affected / exposed	0 / 29 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Rectal haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 29 (6.90%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	2	2	1
Pulmonary embolism			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
Insomnia			

subjects affected / exposed	1 / 29 (3.45%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 29 (10.34%)	0 / 31 (0.00%)	5 / 30 (16.67%)
occurrences (all)	3	0	5
Infections and infestations			
Herpes simplex reactivation			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Septic shock			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 31 (0.00%)	3 / 30 (10.00%)
occurrences (all)	3	0	3
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Hypoalbuminaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 31 (6.45%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 31 (0.00%)	4 / 30 (13.33%)
occurrences (all)	3	0	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2021	Amendment 1 (v2.0) dated 31 MAR 2021: Version to implement recommendations of the independent Data Monitoring Committee.
18 May 2022	Amendment 2 (v3.0) dated 18 MAY 2022: Version to implement changes resulting from pandemic impact on ICUs and strain on the hospital workforce.

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.

Study terminated after Part A, before Part B initiation.

Notes: