Clinical trial results:
A multi-centre, adaptive, randomized, double-blind, placebo-controlled comparative clinical study of the safety and efficacy of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) in patients with coronavirus disease (COVID-19).

Summary

EudraCT number	2020-001782-37
Trial protocol	SK
Global end of trial date	05 March 2021

Results information

Result version number	v1 (current)
This version publication date	04 September 2021
First version publication date	04 September 2021
Summary attachment (see zip file)	CSR Synopsis (ICH_Synopsis_CSR_PO-COV-III-20_06.07.21.pdf)

Trial information

Trial identification

Sponsor protocol code	PO-COV-III-20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04381377
WHO universal trial number (UTN)	-
Other trial identifiers	ID RCB: 2020-001782-37/1

Notes:

Sponsors

Sponsor organisation name	NPO Petrovax Pharm, LLC
Sponsor organisation address	1 Sosnovaya St., Pokrov village, Podolsk, Moscow region, Russian Federation, 142143
Public contact	PVX Clinical Trials Information, NPO Petrovax Pharm, LLC, +7 495730-75-45*125, dodonovns@petrovax.ru
Scientific contact	PVX Clinical Trials Information, NPO Petrovax Pharm, LLC, +7 495730-75-45*125, dodonovns@petrovax.ru

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2021
Global end of trial reached?	Yes
Global end of trial date	05 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess safety and efficacy of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) in comparison with placebo in hospitalized patients with coronavirus disease (COVID-19).

Protection of trial subjects:

Insurance against damage to health as a result of the clinical trial has been concluded

Background therapy:

Background therapy is based on the available international and national guidelines that are in force during the study period.
The following medications (in any dosage form except for the drug products that are used to treat COVID-19 according to the local and/or international guidelines that are in force during the study) are prohibited:
• Antiviral medications
• Immunomodulators (except for the IP)
• Immunostimulants
• Immunosuppressants
• Interferon and interferon inductors

Evidence for comparator:

The use of placebo in the comparison group is primarily associated with masking and blinding, which increases the reliability of the data.
Considering that the standard treatment of coronavirus disease (COVID-19, SARS-CoV-2) has not been developed at the time of the study conduction, the group of comparison in the study PO-COV-III-20 uses placebo.
All the enrolled patients have received full treatment in accordance with the available international and national guidelines that are in force during the study period.

Actual start date of recruitment	28 April 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	Slovakia: 9
Country: Number of subjects enrolled	Russian Federation: 385
Worldwide total number of subjects	394
EEA total number of subjects	9

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)	299
From 65 to 84 years	95
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 28 Apr 2020 (the first patient screened) in Russia.
End of recruitment date: 05 Feb 2021 - the last patient in the study was screened in Slovakia.
The last patient's last visit was done 05 Mar 2021.

Pre-assignment

Screening details:

The patient screening had to be done one day before or at the same date as the randomization.
From the 399 patients screened: 5 patients failed the screening, 394 were randomized.

Pre-assignment period milestones

Number of subjects started	399[1]
Number of subjects completed	394

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious fatal: 2
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Physician decision: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 5 subjects were not randomized due to the following reasons:
Adverse event, serious fatal - 2 subjects
Consent is withdrawn by subject -1 subject
Physician decision - 2 subjects,

Period 1

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

Blinding implementation details:

Masked IP use. Access to randomization codes was provided to unblinded Sponsor/CRO team members only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Polyoxidonium®

Arm description:

Dose 12 mg IV on Days 1, 2, 3, then IM on Days 5, 7, 9, 11, 13, 15, 17

Arm type	Experimental
Investigational medicinal product name	Polyoxidonium®
Investigational medicinal product code	
Other name	Azoximer bromide
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

12 mg IV on the Days 1, 2, 3
12 mg IM on the Days 5, 7, 9, 11, 13, 15, 17

Arm title	Placebo

Arm description:

Placebo matching 12 mg of Polyoxidonium IV on Days 1, 2, 3, then IM on Days 5, 7, 9, 11, 13, 15, 17

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Placebor mathcing 12 mg of Polyoxidonium IV on the Days 1, 2, 3
Placebor mathcing 12 mg of Polyoxidonium IM on the Days 5, 7, 9, 11, 13, 15, 17

Number of subjects in period 1	Polyoxidonium®	Placebo
Started	195	199
Completed	185	186
Not completed	10	13
Adverse event, serious fatal	5	10
Physician decision	1	1
Consent withdrawn by subject	3	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Polyoxidonium®
Reporting group description:	
Dose 12 mg IV on Days 1, 2, 3, then IM on Days 5, 7, 9, 11, 13, 15, 17	
Reporting group title	Placebo
Reporting group description:	
Placebo matching 12 mg of Polyoxidonium IV on Days 1, 2, 3, then IM on Days 5, 7, 9, 11, 13, 15, 17	

Reporting group values	Polyoxidonium®	Placebo	Total
Number of subjects	195	199	394
Age categorical			
Male and female hospitalized patients of 18-95 y.o. with COVID-19.			
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)	155	144	299
From 65-84 years	40	55	95
85 years and over	0	0	0
Adults 65-85 years	0	0	0
Age continuous			
Units: years			
arithmetic mean	54.3	56.0	
standard deviation	± 13.3	± 12.6	-
Gender categorical			
Both male and female patients are allowed for enrolment			
Units: Subjects			
Female	99	97	196
Male	96	102	198
Severity of disease			
Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% or tachypnoea (respiratory rate ≥ 24 breaths/min) Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.			
Units: Subjects			
Severe disease	105	102	207
Mild-moderate disease	90	97	187

Subject analysis sets	
Subject analysis set title	All enrolled patients
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients that were enrolled in the study and randomized, according to the treatment assignments.

Reporting group values	All enrolled patients		
Number of subjects	394		
Age categorical			
Male and female hospitalized patients of 18-95 y.o. with COVID-19.			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	299		
From 65-84 years	95		
85 years and over			
Adults 65-85 years			
Age continuous			
Units: years			
arithmetic mean	55.1		
standard deviation	± 13.0		
Gender categorical			
Both male and female patients are allowed for enrolment			
Units: Subjects			
Female	196		
Male	198		
Severity of disease			
Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% or tachypnoea (respiratory rate ≥ 24 breaths/min) Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.			
Units: Subjects			
Severe disease	207		
Mild-moderate disease	187		

End points

End points reporting groups

Reporting group title	Polyoxidonium®
Reporting group description:	
Dose 12 mg IV on Days 1, 2, 3, then IM on Days 5, 7, 9, 11, 13, 15, 17	
Reporting group title	Placebo
Reporting group description:	
Placebo matching 12 mg of Polyoxidonium IV on Days 1, 2, 3, then IM on Days 5, 7, 9, 11, 13, 15, 17	
Subject analysis set title	All enrolled patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients that were enrolled in the study and randomized, according to the treatment assignments.	

Primary: Clinical status at Day 15

End point title	Clinical status at Day 15
End point description:	
The ordinal scale is used to estimate a proportional odds model, which is fitted with clinical status at day 15 as the outcome, treatment group as the main explanatory variable, and with randomization stratification variables as the other explanatory variables. The primary hypothesis test is based on a test of whether the common odds ratio for treatment is equal to one. It was evaluated the model fit using a goodness-of-fit likelihood ratio test. A stratified hypothesis test to account for baseline severity of disease is used. The distribution of clinical status at day 15 is summarized by treatment arm as percentages.	
End point type	Primary
End point timeframe:	
Day 15	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	196		
Units: 7 point ordinal scale				
1. Not hospitalized, no limitations on activities	44	47		
2. Not hospitalized, limitation on activities	23	15		
3. Hospitalized, not requiring supplemental oxygen	109	119		
4. Hospitalized, requiring supplemental oxygen	8	4		
5. Hospitalized, on non-invasive ventilation or hi	1	1		
6. Hospitalized, on invasive mechanical ventilatio	1	0		
7. Death	4	10		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

Statistical analysis of the data collected during the study is performed with the use of programming language R for statistical computing (version 3.6.0 or higher), statistical software SAS (version 9.4 or higher) or other special software that ensures adequate quality of the results.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	superiority
Method	Proportional odds module
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.7

Secondary: The 7-point ordinal scale: time to improvement by one category from admission on the ordinal scale.

End point title	The 7-point ordinal scale: time to improvement by one category from admission on the ordinal scale.

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	186		
Units: day				
arithmetic mean (standard deviation)	15.6 (± 9.6)	16.3 (± 10.3)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo

Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9935
Method	Regression, Cox

Secondary: Clinical status of the patient (according to 7-point ordinal scale) on day 3

End point title	Clinical status of the patient (according to 7-point ordinal scale) on day 3

End point description:

End point type	Secondary

End point timeframe:

Day 3

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	198		
Units: score				
arithmetic mean (standard deviation)	3.85 (± 0.95)	3.88 (± 0.98)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

No statistically significant difference between Placebo and Polyoxidonium® groups was found.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Clinical status of the patient (according to 7-point ordinal scale) on day 5

End point title	Clinical status of the patient (according to 7-point ordinal scale) on day 5

End point description:

End point type	Secondary

End point timeframe:
Day 5

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	198		
Units: score				
arithmetic mean (standard deviation)	3.70 (± 0.96)	3.76 (± 0.94)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description:	
No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Clinical status of the patient (according to 7-point ordinal scale) on day 8

End point title	Clinical status of the patient (according to 7-point ordinal scale) on day 8
End point description:	
The values of the changes in the clinical status score compared to baseline	
End point type	Secondary
End point timeframe:	
Day 8	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	197		
Units: score				
arithmetic mean (standard deviation)	3.42 (± 0.97)	3.46 (± 1.16)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description: No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Clinical status of the patient (according to 7-point ordinal scale) on day 11

End point title	Clinical status of the patient (according to 7-point ordinal scale) on day 11
End point description: The values of the changes in the clinical status score compared to baseline	
End point type	Secondary
End point timeframe: Day 11	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	197		
Units: score				
arithmetic mean (standard deviation)	3.05 (± 1.03)	3.09 (± 1.28)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description: No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Clinical status of the patient (according to 7-point ordinal scale) on day

29	
End point title	Clinical status of the patient (according to 7-point ordinal scale) on day 29
End point description:	
End point type	Secondary
End point timeframe:	
Day 29	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	195		
Units: score				
arithmetic mean (standard deviation)	1.34 (± 1.08)	1.43 (± 1.37)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description:	
No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: The 7-point ordinal scale: change of the clinical status of the patient on day 3	
End point title	The 7-point ordinal scale: change of the clinical status of the patient on day 3
End point description:	
The values of the changes in the clinical status score compared to baseline	
End point type	Secondary
End point timeframe:	
Day 3	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	198		
Units: score change				
arithmetic mean (standard deviation)	-0.03 (± 0.42)	-0.01 (± 0.50)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description:	
No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: The 7-point ordinal scale: change of the clinical status of the patient on day 5

End point title	The 7-point ordinal scale: change of the clinical status of the patient on day 5
End point description:	
The values of the changes in the clinical status score compared to baseline	
End point type	Secondary
End point timeframe:	
Day 5	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	198		
Units: score change				
arithmetic mean (standard deviation)	-0.18 (± 0.59)	-0.13 (± 0.61)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description:	
No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo

Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: The 7-point ordinal scale: change of the clinical status of the patient on day 8

End point title	The 7-point ordinal scale: change of the clinical status of the patient on day 8

End point description:

The values of the changes in the clinical status score compared to baseline

End point type	Secondary

End point timeframe:

Day 8

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	197		
Units: score change				
arithmetic mean (standard deviation)	-0.48 (± 0.85)	-0.44 (± 0.96)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

No statistically significant difference between Placebo and Polyoxidonium® groups was found.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: The 7-point ordinal scale: change of the clinical status of the patient on day 11

End point title	The 7-point ordinal scale: change of the clinical status of the patient on day 11

End point description:

The values of the changes in the clinical status score compared to baseline

End point type	Secondary

End point timeframe:
Day 11

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	197		
Units: score change				
arithmetic mean (standard deviation)	-0.85 (± 1.01)	-0.81 (± 1.13)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description:	
No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Placebo v Polyoxidonium®
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: The 7-point ordinal scale: change of the clinical status of the patient on day 29

End point title	The 7-point ordinal scale: change of the clinical status of the patient on day 29
End point description:	
The values of the changes in the clinical status score compared to baseline	
End point type	Secondary
End point timeframe:	
Day 29	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	195		
Units: score change				
arithmetic mean (standard deviation)	-2.55 (± 1.14)	-2.46 (± 1.32)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

No statistically significant difference between Placebo and Polyoxidonium® groups was found.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first

End point title	The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	189		
Units: day				
arithmetic mean (standard deviation)	8.9 (± 7.8)	8.6 (± 5.8)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

The values of NEWS scores change in the Placebo and Polyoxidonium treatment arms were compared. Mann-Whitney U-test with Benjamini-Yekutieli correction was used for analysis.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4603
Method	Regression, Cox

Secondary: Change in NEWS from baseline to day 3

End point title	Change in NEWS from baseline to day 3

End point description:

End point type	Secondary

End point timeframe:

Day 3

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	196		
Units: value				
arithmetic mean (standard deviation)	-0.90 (± 1.83)	-0.67 (± 2.05)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

No statistically significant difference between Placebo and Polyoxidonium® groups was found.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in NEWS from baseline to day 5

End point title	Change in NEWS from baseline to day 5

End point description:

End point type	Secondary

End point timeframe:

Day 5

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	195		
Units: value				
arithmetic mean (standard deviation)	-1.59 (± 2.09)	-1.36 (± 2.48)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description: No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in NEWS from baseline to day 8

End point title	Change in NEWS from baseline to day 8
End point description:	
End point type	Secondary
End point timeframe: Day 8	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: value				
arithmetic mean (standard deviation)	-2.43 (± 2.74)	-2.21 (± 3.02)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description: No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo

Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in NEWS from baseline to day 11

End point title	Change in NEWS from baseline to day 11

End point description:

End point type	Secondary

End point timeframe:

Day 11

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	181		
Units: value				
arithmetic mean (standard deviation)	-3.08 (± 3.07)	-2.86 (± 3.01)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

No statistically significant difference between Placebo and Polyoxidonium® groups was found.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in NEWS from baseline to day 15

End point title	Change in NEWS from baseline to day 15

End point description:

End point type	Secondary

End point timeframe:

Day 15

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	177		
Units: value				
arithmetic mean (standard deviation)	-3.63 (± 3.24)	-3.66 (± 3.23)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Statistical analysis description: No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in NEWS from baseline to day 29

End point title	Change in NEWS from baseline to day 29
End point description:	
End point type	Secondary
End point timeframe: Day 29	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	143		
Units: value				
arithmetic mean (standard deviation)	-4.05 (± 3.41)	-3.99 (± 3.40)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:	
No statistically significant difference between Placebo and Polyoxidonium® groups was found.	
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Oxygenation free days in the first 28 days (to day 29)

End point title	Oxygenation free days in the first 28 days (to day 29)
End point description:	
End point type	Secondary
End point timeframe:	
Whole study	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	199		
Units: day				
arithmetic mean (standard deviation)	24.17 (± 6.01)	24.24 (± 5.19)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7614
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence and duration of new oxygen use during the study

End point title	Incidence and duration of new oxygen use during the study
End point description:	
End point type	Secondary
End point timeframe:	
Whole study	

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	199		
Units: patients				
Patients with new oxygen incidence	16	19		
Patients without new oxygen incidence	179	180		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7242
Method	Fisher exact

Secondary: Duration of new oxygen use

End point title	Duration of new oxygen use

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	23		
Units: day				
arithmetic mean (standard deviation)	2.47 (± 2.37)	3.22 (± 2.24)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2473
Method	Wilcoxon (Mann-Whitney)

Secondary: Mechanical ventilator-free days in the first 28 days (to day 29)

End point title	Mechanical ventilator-free days in the first 28 days (to day 29)

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	199		
Units: day				
arithmetic mean (standard deviation)	28.93 (± 0.57)	28.79 (± 1.16)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1664
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence of new mechanical ventilation use

End point title	Incidence of new mechanical ventilation use

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	199		
Units: patients				
Patients with new mechanical ventilation use	1	5		
Patients without new mechanical ventilation use	194	194		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2153
Method	Fisher exact

Secondary: Duration of new mechanical ventilation use

End point title	Duration of new mechanical ventilation use

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	5		
Units: day				
arithmetic mean (standard deviation)	5.00 (± 0)	3.60 (± 2.70)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo

Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5582
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of hospitalization

End point title	Duration of hospitalization

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	199		
Units: day				
arithmetic mean (standard deviation)	17.98 (± 6.49)	17.57 (± 5.78)		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021
Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9653
Method	Wilcoxon (Mann-Whitney)

Secondary: 28-day mortality

End point title	28-day mortality

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Polyoxidonium ®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	199		
Units: patients				
Alive	189	189		
Dead	6	10		

Statistical analyses

Statistical analysis title	SAR v. 1.1 of 03 Jun 2021

Statistical analysis description:

No statistically significant difference between Placebo and Polyoxidonium® groups was found.

Comparison groups	Polyoxidonium® v Placebo
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	% (95% CI)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the ICF signing till the follow-up/Early Termination visit (in the period of Screening only the SAEs and AEs related to the study procedures are registered)

Adverse event reporting additional description:

The safety is evaluated (from signing the ICF to the follow-up/Early Termination visit) based on the following:
– Cumulative rate of SAEs during the study.
– Cumulative rate of ARs registered during the study and related to the IP administration.
– Discontinuation of treatment (for any reason).
– Results of haematolo

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Polyoxidonium
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Polyoxidonium	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 194 (4.12%)	12 / 198 (6.06%)	
number of deaths (all causes)	6	10	
number of deaths resulting from adverse events	6	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon neoplasm			
subjects affected / exposed	0 / 194 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	3 / 194 (1.55%)	3 / 198 (1.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Angina unstable			

subjects affected / exposed	1 / 194 (0.52%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident	Additional description: On 17-Aug-2020 the subject developed SAE – cerebrovascular accident. The SAE was classified as severe (grade 3) and medically important SAE. Drug treatment was assigned. Overall outcome of SAE was classified as "recovered/resolved".		
subjects affected / exposed	1 / 194 (0.52%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 194 (1.03%)	4 / 198 (2.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 4	
Immune system disorders			
Cytokine storm			
subjects affected / exposed	0 / 194 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 194 (0.52%)	3 / 198 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pulmonary embolism			
subjects affected / exposed	1 / 194 (0.52%)	0 / 198 (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	0 / 194 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial sepsis			

subjects affected / exposed	1 / 194 (0.52%)	0 / 198 (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: 1 %

Non-serious adverse events	Polyoxidonium	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 194 (34.02%)	71 / 198 (35.86%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	18 / 194 (9.28%)	20 / 198 (10.10%)	
occurrences (all)	18	20	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 194 (2.58%)	9 / 198 (4.55%)	
occurrences (all)	5	9	
Oxygen saturation decreased			
subjects affected / exposed	5 / 194 (2.58%)	3 / 198 (1.52%)	
occurrences (all)	8	3	
Blood creatine increased			
subjects affected / exposed	0 / 194 (0.00%)	4 / 198 (2.02%)	
occurrences (all)	0	4	
C-reactive protein increased			
subjects affected / exposed	3 / 194 (1.55%)	2 / 198 (1.01%)	
occurrences (all)	3	2	
Blood glucose increased			
subjects affected / exposed	2 / 194 (1.03%)	2 / 198 (1.01%)	
occurrences (all)	2	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 194 (1.03%)	1 / 198 (0.51%)	
occurrences (all)	2	1	
Hypotension			
subjects affected / exposed	1 / 194 (0.52%)	2 / 198 (1.01%)	
occurrences (all)	1	2	
Cardiac disorders			

Cardiopulmonary failure			
subjects affected / exposed	3 / 194 (1.55%)	3 / 198 (1.52%)	
occurrences (all)	3	3	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 194 (2.58%)	2 / 198 (1.01%)	
occurrences (all)	5	2	
Dizziness			
subjects affected / exposed	0 / 194 (0.00%)	2 / 198 (1.01%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	6 / 194 (3.09%)	3 / 198 (1.52%)	
occurrences (all)	6	3	
Anaemia			
subjects affected / exposed	1 / 194 (0.52%)	3 / 198 (1.52%)	
occurrences (all)	1	3	
Thrombocytopenia			
subjects affected / exposed	2 / 194 (1.03%)	2 / 198 (1.01%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 194 (2.06%)	3 / 198 (1.52%)	
occurrences (all)	4	4	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 194 (1.03%)	4 / 198 (2.02%)	
occurrences (all)	2	4	
Asthenia			
subjects affected / exposed	0 / 194 (0.00%)	2 / 198 (1.01%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 194 (3.61%)	4 / 198 (2.02%)	
occurrences (all)	10	4	
Respiratory, thoracic and mediastinal disorders			

Respiratory failure			
subjects affected / exposed	2 / 194 (1.03%)	5 / 198 (2.53%)	
occurrences (all)	2	6	
Cough			
subjects affected / exposed	0 / 194 (0.00%)	2 / 198 (1.01%)	
occurrences (all)	0	2	
Hypoxia			
subjects affected / exposed	0 / 194 (0.00%)	2 / 198 (1.01%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	3 / 194 (1.55%)	0 / 198 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 194 (1.03%)	1 / 198 (0.51%)	
occurrences (all)	2	1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 194 (1.55%)	0 / 198 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 194 (0.52%)	6 / 198 (3.03%)	
occurrences (all)	1	6	
Hypoalbuminaemia			
subjects affected / exposed	2 / 194 (1.03%)	1 / 198 (0.51%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2020	1. Posology and Mode of Administration is updated 2. The telephone contact visits are added to the Visit Schedule. 2. Additional contact visits are added. 3. C-reactive protein (CRP) is added to the Biochemistry panel. 4. Data Safety Monitoring Board and Interim Analysis are described in details. 5. DSMB functions are described in detail. 6. Storage and Unblinding section is updated 7. Exclusion Criteria # 17 changed to:"17. Participation in any clinical study within 30 days before enrolment in this study." 8. SUSARs section is updated 9. Info about Data Safety Monitoring Board and Interim Analysis is added 10. The PPS population is added to Populations for Analyses section
30 June 2020	1.List of coutries-participants is updated 2. Timepoints for test SARS-COV-2 are clarified 3. Timepoints for safety tests and HIV, syphilis, Hepatitis B tests are clarified 4. Telephone contact visits procedures are clarified 5. IP preparation procedures are described in detail 6. Section Randomization is updated
10 September 2020	1. Study title is changed. 2. Dosage and Dosage Schedule are clearly reflected in the Protocol 3. The following inclusion criterion has been added: “Hospitalized at the time of recruitment”. 4. The following inclusion criterion: “The patient (or his/her legal representative, if the patient is not able to sign the form) can understand all protocol requirements, perform the study procedures, and agree to all limitations specified in the protocol” was added. 5. Updated the list of adequate methods of contraception for inclusion in the study. 6. The criterion: Need for the prohibited medications Has been updated to: Need for prohibited medications that are not part of the locally/internationally approved treatment of COVID-19. 7. The excl. criterion about concomitant medication has been updated to: Concomitant use of medications cytostatic drugs (including but not limited to alkylating agents, platinum analogues, dna intercalating agents, anticancer antibiotics, mitosisinhibitors, taxanes, topoisomerase inhibitors, antimetabolites) to treat a concomitant disease. 8. The following excl. criteria have been added: - Administration of convalescent plasma or IVIg for coronavirus disease COVID-19 therapy ever. - Administration of any live vaccine within 4 weeks before screening or intending to receive a live vaccine during the study. - Administration or intending to receive an EBP device to remove pro-inflammatory cytokines from the blood, such as a cytokine filtering or absorption device (for example, CytoSorb®). 9. Withdrawal criteria were removed: - SAEs or AEs that do not classify as serious, but that could jeopardize health or well-being of the patient with further development, as judged by the investigator. - Allergic reaction to the study products that leads to the discontinuation of treatment. - Termination of the study. - Death of the patient.

26 October 2020	It was added to the protocol that patients in an unconscious state can be enrolled in the study, including those in the drug-induced hibernation. In order to be included in the study prior to any study procedures, the patient should, if possible, sign a Patient Information Sheet with an Informed Consent Form. In the absence of the possibility of making a decision by the patient due to his/her critical condition, the decision to include the patient in this study is made by a Concilium consisting of 3 doctors. As soon as the patient is able to read and understand the information in the Patient Information Sheet with the Informed Consent Form for health reasons, he/she will be asked, if he/she voluntarily wishes to continue participating in the study, to sign and date the Patient Information Sheet and the Informed Consent Form. The procedure for holding the Concilium of doctors is described in detail in Section 11.3.

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.

No limitations

Notes: