



## 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 inducers

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:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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 <sup>[1]</sup> |
|----------------------------|--------------------|

|                              |     |
|------------------------------|-----|
| 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 |
|-----------|---------|

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**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:**

Placebo matching 12 mg of Polyoxidonium IV on the Days 1, 2, 3

Placebo matching 12 mg of Polyoxidonium IM on the Days 5, 7, 9, 11, 13, 15, 17

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| Consent withdrawn by subject          | 3              | 1       |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

| 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)<br>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

|                                                                                                                                                                                                                                                                                               |                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                             | 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

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | 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:<br>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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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:<br>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:<br>The values of the changes in the clinical status score compared to baseline |                                                                              |
| End point type                                                                                        | Secondary                                                                    |
| End point timeframe:<br>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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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:<br>The values of the changes in the clinical status score compared to baseline |                                                                               |
| End point type                                                                                        | Secondary                                                                     |
| End point timeframe:<br>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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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

|                        |                                                                               |
|------------------------|-------------------------------------------------------------------------------|
| 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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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:<br>The values of the changes in the clinical status score compared to baseline |                                                                                  |
| End point type                                                                                        | Secondary                                                                        |
| End point timeframe:<br>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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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:<br>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:<br>The values of the changes in the clinical status score compared to baseline |                                                                                   |
| End point type                                                                                        | Secondary                                                                         |
| End point timeframe:<br>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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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

|                                                                                                                                                                                                                     |                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                   | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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                  |                                       |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | 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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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                 |                                        |

| <b>End point values</b>              | 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

|                                                                                                                                   |                           |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                                 | SAR v. 1.1 of 03 Jun 2021 |
| Statistical analysis description:<br>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:<br>Day 29 |                                        |

| <b>End point values</b>              | 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

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | 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            |                                                        |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | 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**

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | 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            |                                                           |

| <b>End point values</b>               | 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

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | 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            |                            |

| <b>End point values</b>              | 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

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | 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

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | 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

|                                         |                           |
|-----------------------------------------|---------------------------|
| <b>Statistical analysis title</b>       | 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            |                  |

| <b>End point values</b>     | 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

|                                                                                              |                           |
|----------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                            | 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 %

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

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



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18 May 2020       | <ol style="list-style-type: none"><li>1. Posology and Mode of Administration is updated</li><li>2. The telephone contact visits are added to the Visit Schedule.</li><li>2. Additional contact visits are added.</li><li>3. C-reactive protein (CRP) is added to the Biochemistry panel.</li><li>4. Data Safety Monitoring Board and Interim Analysis are described in details.</li><li>5. DSMB functions are described in detail.</li><li>6. Storage and Unblinding section is updated</li><li>7. Exclusion Criteria # 17 changed to: "17. Participation in any clinical study within 30 days before enrolment in this study."</li><li>8. SUSARs section is updated</li><li>9. Info about Data Safety Monitoring Board and Interim Analysis is added</li><li>10. The PPS population is added to Populations for Analyses section</li></ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 30 June 2020      | <ol style="list-style-type: none"><li>1. List of countries-participants is updated</li><li>2. Timepoints for test SARS-COV-2 are clarified</li><li>3. Timepoints for safety tests and HIV, syphilis, Hepatitis B tests are clarified</li><li>4. Telephone contact visits procedures are clarified</li><li>5. IP preparation procedures are described in detail</li><li>6. Section Randomization is updated</li></ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 10 September 2020 | <ol style="list-style-type: none"><li>1. Study title is changed.</li><li>2. Dosage and Dosage Schedule are clearly reflected in the Protocol</li><li>3. The following inclusion criterion has been added: "Hospitalized at the time of recruitment".</li><li>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.</li><li>5. Updated the list of adequate methods of contraception for inclusion in the study.</li><li>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.</li><li>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.</li><li>8. The following excl. criteria have been added:<ul style="list-style-type: none"><li>- Administration of convalescent plasma or IVIg for coronavirus disease COVID-19 therapy ever.</li><li>- Administration of any live vaccine within 4 weeks before screening or intending to receive a live vaccine during the study.</li><li>- 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®).</li></ul></li><li>9. Withdrawal criteria were removed:<ul style="list-style-type: none"><li>- 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.</li><li>- Allergic reaction to the study products that leads to the discontinuation of treatment.</li><li>- Termination of the study.</li><li>- Death of the patient.</li></ul></li></ol> |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26 October 2020 | <p>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.</p> <p>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.</p> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

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## 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: