



## Clinical trial results:

### A prospective, multicenter, randomized PHASE II clinical trial of enzalutamide treatment to decrease the morbidity in patients with Corona virus disease 2019 (COVID-19)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2020-002027-10 |
| Trial protocol           | SE             |
| Global end of trial date | 26 May 2021    |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 18 April 2022 |
| First version publication date | 18 April 2022 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | COVIDENZA |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04475601 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Norrlands universitetssjukhus  |
| Sponsor organisation address | Department of surgery and perioperative science, M31 By 6M, third floor Umeå university, Umeå, Sweden, 90185 |
| Public contact               | Andreas Josefsson, Norrlands universitetssjukhus, +46 0703805395, andreas.josefsson@umu.se                   |
| Scientific contact           | Andreas Josefsson, Norrlands universitetssjukhus, +46 0703805395, andreas.josefsson@umu.se                   |

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                       | 01 November 2021 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 26 May 2021      |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 26 May 2021      |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

Clinical status as assessed by the 7-point ordinal scale up to 30 days after inclusion

Protection of trial subjects:

AE were assessed, for all patients, from the time of signed informed consent until 45 days.

All reported SAEs that had not been resolved by the end of the study was followed up until the event had subsided (or disappeared), the condition was stabilized, the event was otherwise explained or the study subject was lost to follow-up.

Data Safety Monitoring Board (DSMB) met regularly until patients had been followed for at least 3 weeks. The DSMB was able to stop randomization for safety reasons.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 29 July 2020 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Sweden: 42 |
| Worldwide total number of subjects   | 42         |
| EEA total number of subjects         | 42         |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 25 |
| From 65 to 84 years                       | 17 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subject eligibility (that subjects fulfill all inclusion criteria and do not meet any exclusion criteria) was established before inclusion, treatment, or randomization. An eligibility form was used prior to randomization in the eCRF.

### Period 1

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

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Intervention |

Arm description:

Enzalutamide 160 mg once daily

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Enzalutamide |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

160mg once daily (4x40mg tablets) for 5 days

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Control |
|------------------|---------|

Arm description:

Standard of care

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| Number of subjects in period 1 | Intervention | Control |
|--------------------------------|--------------|---------|
| Started                        | 30           | 12      |
| Completed                      | 29           | 9       |
| Not completed                  | 1            | 3       |
| Adverse event, serious fatal   | -            | 1       |
| Consent withdrawn by subject   | 1            | 2       |

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values                                | Overall trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 42            | 42    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 0             | 0     |  |
| Adolescents (12-17 years)                             | 0             | 0     |  |
| Adults (18-64 years)                                  | 30            | 30    |  |
| From 65-84 years                                      | 12            | 12    |  |
| 85 years and over                                     | 0             | 0     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 11            | 11    |  |
| Male  | 31            | 31    |  |

## End points

### End points reporting groups

|  |              |
|--|--------------|
| Reporting group title  | Intervention |
| Reporting group description:<br>Enzalutamide 160 mg once daily |              |
| Reporting group title  | Control      |
| Reporting group description:<br>Standard of care               |              |

### Primary: Clinical status as assessed by the 7-point ordinal scale

|   |  |
|---|--|
| End point title   | Clinical status as assessed by the 7-point ordinal scale |
| End point description:<br>Clinical status as assessed by the 7-point ordinal scale up to 30 days after inclusion:<br>1) Not hospitalized, no limitations on activities.<br>2) Not hospitalized, limitation on activities;<br>3) Hospitalized, not requiring supplemental oxygen;<br>4) Hospitalized, requiring supplemental oxygen;<br>5) Hospitalized, on non-invasive ventilation or high flow oxygen devices;<br>6) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);<br>7) Death; |  |
| End point type  | Primary  |
| End point timeframe:<br>Clinical status as assessed by the 7-point ordinal scale up to 30 days after inclusion.   |  |

| End point values             | Intervention    | Control         |  |  |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type           | Reporting group | Reporting group |  |  |
| Number of subjects analysed  | 30              | 12              |  |  |
| Units: 7 point ordinal scale |                 |                 |  |  |
| number (not applicable)      | 30              | 12              |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Intention to treat statistical analysis |
| Statistical analysis description:<br>All randomized subjects were included in the ITT analysis set. |   |
| Comparison groups   | Intervention v Control                  |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 42                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | < 0.05                     |
| Method                                  | Regression, Cox            |

Notes:

[1] - Clinical parameters and laboratory assessments were summarized in total and stratified for gender, center and study arm.

Continuous variables were summarized using standard statistical measures, i.e. the number of observations, number of missing observations, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum. Categorical variables were summarized in frequency tables.

## Secondary: Safety evaluation

|                 |                   |
|-----------------|-------------------|
| End point title | Safety evaluation |
|-----------------|-------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

45 days

| End point values            | Intervention    | Control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 12              |  |  |
| Units: Events               | 30              | 12              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of supplemental oxygen

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Duration of supplemental oxygen |
|-----------------|---------------------------------|

End point description:

Total days of extra oxygen described as any additional oxygen given to the patient at any time during the day between 00-24.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 45 days

| End point values            | Intervention    | Control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 29              | 10              |  |  |
| Units: Days                 |                 |                 |  |  |
| median (standard deviation) | 6 ( $\pm$ 4.4)  | 1 ( $\pm$ 0.7)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Need of mechanical ventilation

|   |                                |
|---|--------------------------------|
| End point title   | Need of mechanical ventilation |
| End point description:<br>No formal analysis was performed due to too few events. |                                |
| End point type  | Secondary                      |
| End point timeframe:<br>Evaluated for 30 days and after 6 months.                 |                                |

| End point values            | Intervention    | Control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 12              |  |  |
| Units: Number               | 2               | 1               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory assessment

|  |                       |
|--|-----------------------|
| End point title  | Laboratory assessment |
| End point description:<br>The local clinical lab were used for all laboratory evaluation. Hb, LPK, B-lymphocytes, CRP, IL-6, ASAT, ALAT, ALP, Krea, D-dimer<br>Different units and concentration were used for different parameters. |                       |
| End point type   | Secondary             |
| End point timeframe:<br>Day 0, 2, 4 and 6  |                       |



| End point values                     | Intervention     | Control          |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 0 <sup>[2]</sup> | 0 <sup>[3]</sup> |  |  |
| Units: Units per ml                  |                  |                  |  |  |
| arithmetic mean (standard deviation) | ()               | ()               |  |  |

Notes:

[2] - This analysis compose of many different parameters. No individual mean deviation can be reported.

[3] - This analysis compose of many different parameters. No individual mean deviation can be reported.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Virus load assessment

|                        |   |
|------------------------|---|
| End point title        | Virus load assessment   |
| End point description: | PCR based SARS-CoV-2 measurement from upper respiratory tract |
| End point type         | Secondary   |
| End point timeframe:   | Day 0, 2, 4 and 6   |

| End point values              | Intervention      | Control          |  |  |
|-------------------------------|-------------------|------------------|--|--|
| Subject group type            | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed   | 16 <sup>[4]</sup> | 5 <sup>[5]</sup> |  |  |
| Units: Delta CT               |                   |                  |  |  |
| median (full range (min-max)) | -6 (-20 to 6)     | -1 (-8 to 4.5)   |  |  |

Notes:

[4] - Day 6

[5] - Day 6

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hospital stay (days)

|                        |  |
|------------------------|--|
| End point title        | Hospital stay (days)                     |
| End point description: |  |
| End point type         | Secondary                                |
| End point timeframe:   | Evaluated for 45 days and after 6 months |

| End point values            | Intervention    | Control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 29              | 10              |  |  |
| Units: Days                 |                 |                 |  |  |
| median (standard deviation) | 9 (± 3)         | 6 (± 4.4)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Re-admission to hospital due to rebound COVID-19

|  |  |
|--|--|
| End point title  | Re-admission to hospital due to rebound COVID-19 |
| End point description:   |  |
| Any hospitalization any time during any day between 00-24 will be considered as admitted to the hospital that day. Only if the patient has been home from one day to the next it will be described as re-admission (and at least 12 hours). Any worsening symptoms considered to be a consequence from COVID-19 requiring re-hospitalization is regarded as a rebound event. Rehabilitation at hospital with stable symptoms is not regarded as a rebound event. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Evaluated for 45 days and after 6 months   |  |

| End point values            | Intervention    | Control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 12              |  |  |
| Units: Number               | 1               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mortality at 6 months

|                        |                       |
|------------------------|-----------------------|
| End point title        | Mortality at 6 months |
| End point description: |                       |
|                        |                       |
| End point type         | Secondary             |
| End point timeframe:   |                       |
| 6 months               |                       |

| <b>End point values</b>     | Intervention    | Control         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 12              |  |  |
| Units: Number               | 0               | 1               |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

45 days

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 5.0 |
|--------------------|-----|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Intervention |
|-----------------------|--------------|

Reporting group description:

Treated with Enzalutamid

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                            | Intervention    | Control         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 4 / 30 (13.33%) | 2 / 12 (16.67%) |  |
| number of deaths (all causes)                     | 0               | 1               |  |
| number of deaths resulting from adverse events    | 0               | 1               |  |
| Nervous system disorders                          |                 |                 |  |
| Transient ischaemic attack                        |                 |                 |  |
| subjects affected / exposed                       | 1 / 30 (3.33%)  | 0 / 12 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                        |                 |                 |  |
| Gastritis   |                 |                 |  |
| subjects affected / exposed                       | 0 / 30 (0.00%)  | 1 / 12 (8.33%)  |  |
| 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   |                 |                 |  |
| Pneumomediastinum                                 |                 |                 |  |
| subjects affected / exposed                       | 1 / 30 (3.33%)  | 0 / 12 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Respiratory failure                               |                 |                 |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1          |  |
| Respiratory disorder                            | Additional description: Worsening of respiratory symptoms |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 12 (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                     |   |                |  |
| Pyelonephritis                                  |   |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 12 (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: 0 %

| Non-serious adverse events                            | Intervention  | Control        |  |
|---|---|----------------|--|
| Total subjects affected by non-serious adverse events |   |                |  |
| subjects affected / exposed                           | 12 / 30 (40.00%)  | 1 / 12 (8.33%) |  |
| Investigations  |   |                |  |
| Alanine aminotransferase increased                    | Additional description: Reported as increased ASAT and ALAT |                |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)  | 0 / 12 (0.00%) |  |
| occurrences (all)                                     | 1   | 0              |  |
| Aspartate aminotransferase increased                  | Additional description: Reported as ASAT and ALAT increased |                |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)  | 0 / 12 (0.00%) |  |
| occurrences (all)                                     | 1   | 0              |  |
| Vascular disorders                                    |   |                |  |
| Hypertension  |   |                |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)  | 0 / 12 (0.00%) |  |
| occurrences (all)                                     | 1   | 0              |  |
| Cardiac disorders                                     |   |                |  |
| Sinus tachycardia                                     |   |                |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)  | 0 / 12 (0.00%) |  |
| occurrences (all)                                     | 1   | 0              |  |
| Nervous system disorders                              |   |                |  |

|   |  |                     |  |
|---|--|---------------------|--|
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Seizure   | Additional description: Partial epilepsy                   |                     |  |
| subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal disorders   |  |                     |  |
| Dyspnea   | Additional description: Breathing difficulties             |                     |  |
| subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Cough   | Additional description: Increased coughing in the evenings |                     |  |
| subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders  |  |                     |  |
| Rash maculo-papular   | Additional description: Red, itching dots on leg           |                     |  |
| subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Renal and urinary disorders<br>Urinary incontinence<br>subjects affected / exposed<br>occurrences (all) | 0 / 30 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1 |  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 30 (3.33%)<br>1  | 0 / 12 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders   |  |                     |  |

|                             |  |                |  |
|-----------------------------|--|----------------|--|
| Gout                        | Additional description: Gout period              |                |  |
|                             | 1 / 30 (3.33%)                                   | 0 / 12 (0.00%) |  |
| subjects affected / exposed |  |                |  |
| occurrences (all)           | 1  | 0              |  |
| Musculoskeletal pain        | Additional description: Pain in wrist            |                |  |
|                             | 1 / 30 (3.33%)                                   | 0 / 12 (0.00%) |  |
| subjects affected / exposed |  |                |  |
| occurrences (all)           | 1  | 0              |  |
| Infections and infestations |  |                |  |
|                             | Additional description: Mucosal infection groins |                |  |
| Mucosal infection           |  |                |  |
| subjects affected / exposed | 1 / 30 (3.33%)                                   | 0 / 12 (0.00%) |  |
| occurrences (all)           | 1  | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 20 August 2020    | 2 more sites included  |
| 08 September 2020 | <p>Another member in the DSMB was included.</p> <ul style="list-style-type: none"><li>-Two more sites</li><li>-Clarifying the primary end-point is assessed by time to changes in clinical status including both worsening (need of mechanical ventilation) and improving (discharge from hospital)</li><li>-Definition of the secondary end-point was clarified from Admission to ICU to need of mechanical ventilation. -Including the possibility to analyze virus load in naso-pharynx swabs also in the following phases of the study.</li><li>-Added a inclusion criteria that the patients should not have had more than 3 days in hospital at inclusion</li><li>-Exclusion criterias were modified:</li><li>-Instead of previous enzalutamide and tamoxifen treatment only we broadened it to include all hormonal treatment for prostate or breast cancer.</li><li>-NOAK (Non-vitamin-K antagonist anticoagulants) was allowed and Clopidogrel was included as exclusion criteria</li><li>-"Unstable cardiovascular disease" was changed to "current symptoms of unstable cardiovascular disease"</li><li>-Immunosuppressive medication was specified to allow any corticosteroids used for COVID-19 and up to 10mg/day equivalent dose of prednisolone prior to inclusion.</li><li>-Transitory Ischemic Attack was allowed</li><li>-"Previous seizure" was specified to "Epileptic seizure "</li><li>-Excluded registration of concomitant medication in the form of topical administrated treatments</li><li>-Defined re-hospitalization event to include "Any worsening symptoms considered to be a consequence from COVID-19 requiring re-hospitalization is regarded as a rebound event. Rehabilitation at hospital with stable symptoms is not regarded as a rebound event"</li><li>-In the section of AE there is a list of symptoms that was not mandatory to report as adverse events because they were symptoms of COVID-19 disease (e.g fever). Hospitalization due to COVID-19 - phrase deleted.</li><li>The incorrect phrasing "symptoms and deaths due to COVID-19 should not be reported as SAE or SUSAR" was deleted.</li><li>2 ICF forms signed by doctor and patient separately allowed</li></ul> |
| 02 February 2021  | <p>Adding one in the steering group</p> <ul style="list-style-type: none"><li>-Adding "Pharmacokinetic interaction of enzalutamide with other drugs" as a secondary objective</li><li>-Adverse events relatedness was updated to also include the definition "unlikely related" to study drug.</li><li>-All blood samples at 6 months were excluded from the protocol. The scientific value of assessing laboratory parameters at 6 months in the study is no longer judged to be higher compared to the risk of reinfection with SARS-CoV-2 at the 6 months follow- up, both due the outcome of the study and the ongoing vaccination programme. All these analysis were excluded from the statistical analysis section.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes



| Date             | Interruption   | Restart date |
|------------------|--|--------------|
| 29 November 2020 | Recruitment stop after recommendation from Data Safety Monitoring Board. | -            |

Notes:

## Limitations and caveats

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

The study was stopped early due to inferiority after safety analysis.

Notes:

## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34980495>