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
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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
Arm title	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

Arm title	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 (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	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: Enzalutamide 160 mg once daily	
Reporting group title	Control
Reporting group description: 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:

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

End point type	Primary

End point timeframe:

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:

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[1]
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 (± 4.4)	1 (± 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:

No formal analysis was performed due to too few events.

End point type	Secondary

End point timeframe:

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:

The local clinical lab were used for all laboratory evaluation. Hb, LPK, B-lymphocytes, CRP, IL-6, ASAT, ALAT, ALP, Krea, D-dimer
Different units and concentration were used for different parameters.

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	0[2]	0[3]		
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[4]	5[5]		
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

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

Gout	Additional description: Gout period		
subjects affected / exposed	1 / 30 (3.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain	Additional description: Pain in wrist		
subjects affected / exposed	1 / 30 (3.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Mucosal infection	Additional description: Mucosal infection groins		
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	Another member in the DSMB was included. -Two more sites -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) -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. -Added a inclusion criteria that the patients should not have had more than 3 days in hospital at inclusion -Exclusion criterias were modified: -Instead of previous enzalutamide and tamoxifen treatment only we broadened it to include all hormonal treatment for prostate or breast cancer. -NOAK (Non-vitamin-K antagonist anticoagulants) was allowed and Clopidogrel was included as exclusion criteria -"Unstable cardiovascular disease" was changed to "current symptoms of unstable cardiovascular disease" -Immunosuppressive medication was specified to allow any corticosteroids used for COVID-19 and up to 10mg/day equivalent dose of prednisolone prior to inclusion. -Transitory Ischemic Attack was allowed -"Previous seizure" was specified to "Epileptic seizure " -Excluded registration of concomitant medication in the form of topical administrated treatments -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" -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. The incorrect phrasing "symptoms and deaths due to COVID-19 should not be reported as SAE or SUSAR" was deleted. 2 ICF forms signed by doctor and patient separately allowed
02 February 2021	Adding one in the steering group -Adding "Pharmacokinetic interaction of enzalutamide with other drugs" as a secondary objective -Adverse events relatedness was updated to also include the definition "unlikely related" to study drug. -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.

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