Clinical trial results:
Open label, monocentric pilot study to evaluate safety and efficacy of Bazedoxifene in addition to Standard of Care in hospitalized COVID-19 patients suffering from moderate to severe Pneumonia

Summary

EudraCT number	2021-000320-35
Trial protocol	CZ
Global end of trial date	06 December 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	Synopsis_OB001 (Synopsis_OB001.pdf)

Trial information

Trial identification

Sponsor protocol code	OB001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Oxygen Biotech s.r.o.
Sponsor organisation address	Italská 2581/67, Prague 2 – Vinohrady, Czechia, 120 00
Public contact	Tomáš Pacák, Oxygen Biotech s.r.o., admin@oxygenbiotech.com
Scientific contact	Tomáš Pacák, Oxygen Biotech s.r.o., admin@oxygenbiotech.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety of bazedoxifene in patients with COVID-19 disease assessed by incidence and spectrum of reported AEs, and laboratory and clinical findings.

Protection of trial subjects:

When obtaining informed consent, the subject's state of health was considered, and the investigator extensively informed each subject of the objectives, benefits, risks and requirements imposed by the study. The subject was provided with an information and consent form in clear, simple language. He/she was allowed ample time to inquire about details of the study and to decide whether or not to participate in the study. The subjects were aware of the possible risks of their participation in the clinical trial and the possibility at any time without consequences to terminate their participation in the clinical trial. The subjects were also informed about the measures that were taken for the protection of personal data and also the fact that in case of damage to health due to the conduct of the trial were in compliance with the legislation in force liability insurance for the investigator and sponsor through which is secured and any compensation to the trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	2
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted in the Czech Republic (CR) in 1 centre of Thomayer University Hospital, Prague and 3 subjects were selected in total, all of them were included in CR, and all subjects completed the study. Study began on 07-04-2021 when the 1st patient signed ICF. The recruitment was stopped on 06-12-2021 based on strategic decision of sponsor.

Pre-assignment

Screening details:

The screening was initiated after subject's informed consent had been obtained. The screening visit was performed within 5 days prior to Day 1 (baseline, start of IMP administration). It could have happened in the same day as baseline (Day 1).

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Arm of treatment period

Arm description:

Only one arm was designed for this study. All subjects were assigned to receive active treatment of Conbriza® (bazedoxifene) in addition to SoC in COVID-19 patients.

Arm type	Experimental
Investigational medicinal product name	Bazedoxifene
Investigational medicinal product code	
Other name	Conbriza, CONBRIZA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

On Day 1: once daily 2 tablets of 20 mg (i.e., 40 mg of bazedoxifene once daily), regardless of food intake;
From Day 2 to EoT: once daily 1 tablet of 20 mg, regardless of food intake.

Note: Only in exceptional circumstances of subjects admitted to hospital in the evening, if the first dose of the IMP was administered at 6 PM and later, subject would have received only 1 tablet of Conbriza® 20 mg on Day 1 and continued with the next dose in the morning of the Day 2.

Number of subjects in period 1	Arm of treatment period
Started	3
Completed	3

Period 2	
Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Arm of follow-up period

Arm description:

Only one arm was designed for this study, and all 3 enrolled subjects continued into the Follow-up period. In this period, no study treatment was administered to the subjects.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Arm of follow-up period
Started	3
Completed	3

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	3	3	
Age categorical			
The target population was adult patients aged between 18 and 75 with presence of COVID 19 pneumonia (clinical manifestations and Xray or CT evidence) who were admitted to hospital due to moderate to severe symptoms of pneumonia as per investigator opinion.			
Units: Subjects			
Adults (18-64 years)	2	2	
From 65-84 years	1	1	
Age continuous			
Units: years			
arithmetic mean	56.3		
standard deviation	± 9.61	-	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	1	1	
Race			
Units: Subjects			
White	3	3	
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	3	3	
Weight			
Units: kilogram(s)			
arithmetic mean	89.67		
standard deviation	± 7.506	-	
Height			
Units: centimetre			
arithmetic mean	166.0		
standard deviation	± 8.54	-	
BMI			
Units: kilogram(s)/square metre			
arithmetic mean	32.80		
standard deviation	± 5.294	-	

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of

changes of the individual parameters.
Categorical data were summarized using the number and percentage of subjects in each category.
Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Reporting group values	Safety analysis set		
Number of subjects	3		
Age categorical			
The target population was adult patients aged between 18 and 75 with presence of COVID 19 pneumonia (clinical manifestations and Xray or CT evidence) who were admitted to hospital due to moderate to severe symptoms of pneumonia as per investigator opinion.			
Units: Subjects			
Adults (18-64 years)	2		
From 65-84 years	1		
Age continuous			
Units: years			
arithmetic mean	56.3		
standard deviation	± 9.61		
Gender categorical			
Units: Subjects			
Female	2		
Male	1		
Race			
Units: Subjects			
White	3		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	3		
Weight			
Units: kilogram(s)			
arithmetic mean	89.67		
standard deviation	± 7.506		
Height			
Units: centimetre			
arithmetic mean	166.0		
standard deviation	± 8.54		
BMI			
Units: kilogram(s)/square metre			
arithmetic mean	32.80		
standard deviation	± 5.294		

End points

End points reporting groups

Reporting group title	Arm of treatment period
Reporting group description:	
Only one arm was designed for this study. All subjects were assigned to receive active treatment of Conbriza® (bazedoxifene) in addition to SoC in COVID-19 patients.	
Reporting group title	Arm of follow-up period
Reporting group description:	
Only one arm was designed for this study, and all 3 enrolled subjects continued into the Follow-up period. In this period, no study treatment was administered to the subjects.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters. Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.	

Primary: Primary Objective - Incidence and spectrum of reported AEs, laboratory and clinical findings

End point title	Primary Objective - Incidence and spectrum of reported AEs, laboratory and clinical findings
End point description:	
Safety of bazedoxifene in patients with COVID-19 disease was assessed by incidence and spectrum of reported AEs, and laboratory and clinical findings.	
End point type	Primary
End point timeframe:	
Screening: Within 5 days prior to D1 (baseline). Treatment period: From D1 till D5 at minimum and till D14 at maximum as per investigator opinion. Follow up period: From EoT till D21 or up to D28. Allowed visit window for EoS was D21 to D28	

End point values	Arm of treatment period	Arm of follow-up period	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	3	
Units: number				
Number of AEs	1	1	1	
Number of SAEs	0	0	0	
Number of AEs related to study treatment	0	0	0	
No of AEs leading to study treatment discontinuati	0	0	0	
No of AEs leading to death	0	0	0	
No of clinical significant findings - hematology	1	1	1	
No of clinical significant findings - biochemistry	0	0	0	

No of clinical significant findings - immunology	0	0	0	
No of clinical significant findings - urinalysis	0	0	0	

Attachments (see zip file)	14.3.1.-13. Safety Data/Clinical Study Report_27 05 2022_14. 16.2.7.-8. Listings by patient/Clinical Study Report_27 05

Statistical analyses

Statistical analysis title	Changes of the individual parameters

Statistical analysis description:

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Comparison groups	Arm of treatment period v Safety analysis set
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Multiple parameters
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[1] - Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters.

Secondary: Secondary Objective - Changes in clinical status of subject

End point title	Secondary Objective - Changes in clinical status of subject

End point description:

Changes in clinical status of subject (using 7-point ordinal scale): on Day 0, Day 5 and Day 21 – 28.
a. Death
b. Hospitalized, on invasive mechanical ventilation or ECMO
c. Hospitalized, on non-invasive ventilation or high flow oxygen devices
d. Hospitalized, requiring supplemental oxygen
e. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
f. Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical Care
g. Not hospitalized

End point type	Secondary

End point timeframe:

On Day 0, Day 5 and Day 21 – 28.

End point values	Arm of treatment period	Arm of follow-up period	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	3	
Units: number				
Number of analysed subjects	3	3	3	

Attachments (see zip file)	14.4.1. Shift table of patients´ clinical status/Clinical Study 16.2.9.4. Listing of patient's clinical status/Clinical Study

Statistical analyses

Statistical analysis title	Changes of the individual parameters

Statistical analysis description:

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Comparison groups	Arm of treatment period v Safety analysis set
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Multiple parameters
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[2] - Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters.

Secondary: Secondary Objective - Influence of subjects' clinical condition (symptom score)

End point title	Secondary Objective - Influence of subjects' clinical condition (symptom score)

End point description:

During the study, symptoms were recorded by staff daily during hospitalization, and upon discharge from the hospital, subjects were asked to report daily temperature (morning and evening) and symptoms (once daily, in the evening) in the diary provided and they are listed below:

Days of study: 1-28
Date DD/MM/YYYY
Temperature morning
evening
Presence of cough per day, per night
heavy/attacks
Presence of fatigue
Changes in taste perception
Changes in smell perception
Gastrointestinal symptoms
Other symptoms

End point type	Secondary

End point timeframe:

Daily during hospitalization: between baseline (D1) and D14 (or day of discharge).
Upon discharge from the hospital: daily temperature (morning and evening) and symptoms (once daily, in the evening).

End point values	Arm of treatment period	Arm of follow-up period	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	3	
Units: point				
Number of analysed subjects	3	3	3	

Attachments (see zip file)	14.4.2. Summary of symptom score/Clinical Study Report_27 16.2.9.3. Listing of individual symptom score/Clinical Study

Statistical analyses

Statistical analysis title	Changes of the individual parameters

Statistical analysis description:

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Comparison groups	Arm of treatment period v Safety analysis set
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Multiple parameters
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[3] - Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters.

Secondary: Secondary Objective - Monitoring the frequency of subjects whose condition worsens into a critical state necessitating a ventilator

End point title	Secondary Objective - Monitoring the frequency of subjects whose condition worsens into a critical state necessitating a ventilator

End point description:

Clinical examinations including vital signs – blood pressure, heart and respiratory rate, temperature, O2 saturation, oxygen flow if oxygen administered and its changes were monitored daily during

hospitalization.

End point type	Secondary

End point timeframe:

Daily during hospitalisation: D1 - day of discharge.

End point values	Arm of treatment period	Arm of follow-up period	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	3	
Units: number of subjects				
Number of analysed subjects	3	3	3	

Attachments (see zip file)	14.3.14. Summary statistics and changes from BL/Clinical 14.4.4.-6. O2 saturation, Oxygen flow, Ventilator/Clinical Study 16.2.9.1.-2. Clinical assessments - Listings/Clinical Study

Statistical analyses

Statistical analysis title	Changes of the individual parameters

Statistical analysis description:

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Comparison groups	Arm of treatment period v Safety analysis set
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Multiple parameters
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[4] - Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters.

Secondary: Secondary Objective - Time to normalization of chosen blood parameters

End point title	Secondary Objective - Time to normalization of chosen blood parameters

End point description:

Hematology: hemoglobin [g/L], hematocrit [L/L], RBC count [10!12/L], WBCl count [109/L], PL count [109/L], Bas[%], Eos[%], Neu[%], Mon[%], Lym[%], MCV [fL], MCH [pg], mean corpuscular hemoglobin conc. [g/L], red cell distribution width [%], D-dimers [µg/L], PT [s], aPTT [s], INR. Biochemistry : ALT [µkat/L], AST [µkat/L], ALP [µkat/L], lactate dehydrogenase [µkat/L], Mg[mmol/L],

total bilirubin [µmol/L], direct bilirubin [µmol/L], blood area N [mmol/L], creatinine [µmol/L], P [mmol/L], Cl[mmol/L], Ca [mmol/L], K [mmol/L], Na[mmol/L], Glc[mmol/L], CRP [mg/L], ferritin [µg/L], IL-6 [ng/L].
Immunology parameters: CD3+ [% and absolute value in 109/L], CD4+ [% and absolute value in 109/L], CD8+ [% and absolute value in 109/L].
Urinalysis parameters: color, pH, specific gravity [kg/m3], RBC count [106/L], WBC count [106/L], epithelial cells [106/L], positive/negative testing for: glucose, protein, ketones, blood, casts, bacteria, crystals.

End point type	Secondary

End point timeframe:

Hematology, immunological and biochemistry examinations were performed within 60 minutes before the first administration of bazedoxifene, then on days 2, 3, 5, 7, 10, 14 and/or EoT, and if was possible after discharge from the hospital on D21 to D28 (EoS)

End point values	Arm of treatment period	Arm of follow-up period	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	3	
Units: number				
Number of analysed subjects	3	3	3	

Attachments (see zip file)	14.4.7. Summary statistics of time to 1st normal/Clinical Study 16.2.8.5.-6. Listing of abnormal and normalization/Clinical

Statistical analyses

Statistical analysis title	Changes of the individual parameters

Statistical analysis description:

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Comparison groups	Arm of treatment period v Safety analysis set
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Multiple parameters
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[5] - Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters.

Secondary: Secondary Objective - Length of hospital stay

End point title	Secondary Objective - Length of hospital stay

End point description:

The length of hospital stay was monitored during the whole study continuously.

End point type	Secondary

End point timeframe:

Continuously during the study.

End point values	Arm of treatment period	Arm of follow-up period	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	3	
Units: number				
Number of analysed subjects	3	3	3	

Attachments (see zip file)	14.4.8.-9. Lenght of hospital stay/Clinical Study Report_27 05 16.2.9.5. Length of hospital stay - per patient/Clinical Study

Statistical analyses

Statistical analysis title	Changes of the individual parameters

Statistical analysis description:

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Comparison groups	Arm of treatment period v Safety analysis set
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Multiple parameters
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[6] - Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters.

Secondary: Secondary Objective - Rate of virus elimination from upper respiratory tract secretions

End point title	Secondary Objective - Rate of virus elimination from upper respiratory tract secretions

End point description:

PCR smear done before the first IMP administration (Screening) and further samples on the day 8 (or on the day of hospital discharge, whichever came first) and further once a week till EoS, if was possible.

End point type	Secondary

End point timeframe:

Before the first IMP administration (Screening), on D8 (or the day of hospital discharche), further once a week till EoS (if possible)

End point values	Arm of treatment period	Arm of follow-up period	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	3	3	
Units: number				
Number of analysed subjects	3	3	3	

Attachments (see zip file)	16.2.8.7. Listing of NP smear (PCR) results per pt/Clinical

Statistical analyses

Statistical analysis title	Changes of the individual parameters

Statistical analysis description:

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, 95% confidence interval for mean (CI), standard deviation (SD), median, minimum and maximum values.

Comparison groups	Arm of treatment period v Safety analysis set
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Multiple parameters
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[7] - Since this was a pilot administration to a small number of subjects in order to verify primarily the safety of the product Conbriza® (bazedoxifene) in COVID-19 patients treated with standard therapy (SoC), the output of a full statistically significant result could not have been expected, but rather a trend of changes of the individual parameters.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day of signed ICF until the EoS Visit.

Adverse event reporting additional description:

Safety of bazedoxifene in patients with COVID-19 disease was assessed by incidence and spectrum of reported AEs, and laboratory and clinical findings.
All AEs were recorded on the AE eCRF at all scheduled and unscheduled visits, as well as those reported during a telephone contact throughout the study (from day of signed ICF until EoS Visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	AEs Reporting Group

Reporting group description:

AEs Reporting Group consists of all enrolled subjects.

Serious adverse events	AEs Reporting Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AEs Reporting Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
Blood and lymphatic system disorders			
D-dimer elevation	Additional description: AE of mild intensity (Grade 1) in 1 subject was reported before the 1st IMP administration: D-dimer elevation - 3160 µg/L. In the course of the study, D-dimer levels have significantly decreased. AE was not considered as related to study treatment.		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2021	Substantial Amendment n°1 to the protocol, final version dated 21 July 2021 was issued. The aim of this protocol amendment was an important update of the inclusion criterium of study participants. The change concerned the extension of the COVID-19 diagnosis interval from 7 to 14 days before enrolment. The rationale for this amendment was to increase the availability of the treatment to the patients in response to the changes in epidemiologic situation as COVID-19 was diagnosed earlier.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24077366

http://www.ncbi.nlm.nih.gov/pubmed/31978945

http://www.ncbi.nlm.nih.gov/pubmed/32007143

http://www.ncbi.nlm.nih.gov/pubmed/31986264

http://www.ncbi.nlm.nih.gov/pubmed/32031570

http://www.ncbi.nlm.nih.gov/pubmed/15271897

http://www.ncbi.nlm.nih.gov/pubmed/32171076

http://www.ncbi.nlm.nih.gov/pubmed/32167524

http://www.ncbi.nlm.nih.gov/pubmed/30995492

http://www.ncbi.nlm.nih.gov/pubmed/31958792

http://www.ncbi.nlm.nih.gov/pubmed/25898198

http://www.ncbi.nlm.nih.gov/pubmed/32273618

http://www.ncbi.nlm.nih.gov/pubmed/32303591

http://www.ncbi.nlm.nih.gov/pubmed/18665787

http://www.ncbi.nlm.nih.gov/pubmed/23871271

http://www.ncbi.nlm.nih.gov/pubmed/32871847

http://www.ncbi.nlm.nih.gov/pubmed/33527314

http://www.ncbi.nlm.nih.gov/pubmed/30648776

http://www.ncbi.nlm.nih.gov/pubmed/26424839

http://www.ncbi.nlm.nih.gov/pubmed/30885958

http://www.ncbi.nlm.nih.gov/pubmed/32678530