SYNOPSIS

Name of Sponsor: **Oxygen Biotech s.r.o.** **Italská 2581/67** **120 00 Prague 2 – Vinohrady** **Czech Republic**	**Individual Study Table Referring to Part of the Dossier** **Volume:**	*(For National Authority Use only)*
Name of Finished Product: Conbriza®		
Name of Active Ingredient: Bazedoxifene	**Page:**	

Title of study:
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.
Protocol No.: OB001
EudraCT No.: 2021-000320-35

Investigators:
Prof. MUDr. Martina Vašáková, Ph.D. (Principal Investigator)
MUDr. Lucie Hoznauerová (Sub-investigator)
MUDr. Jiří Škopek, Ph.D. (Coordinator)

Study centre(s):
Czech Republic (1 centre):
Pneumology Clinic of the 1st Faculty of Medicine, Charles University and Thomayer University Hospital
Vídeňská 800, 140 59 Prague 4 – Krč

Publication (reference)

Studied period:	**Phase of development:**
Study initiation date (FVFP): 07 April 2021 Study completion date (LVLP): 28 May 2021	Phase II

Objectives:
The purpose of this study was to confirm safety and tolerability of bazedoxifene administration in patients with viral infection of SARS-CoV-2, to verify the potential of the registered drug Conbriza® (bazedoxifene) in the treatment or modulation of a highly contagious pandemic disease COVID-19, which mainly affects people with reduced defence abilities (elderly, immunosuppressed, with associated diseases), and to detect the possible anti-viral effect of bazedoxifene.

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

Secondary objectives:
- Changes in clinical status of subject (using 7-point ordinal scale): on Day 0, Day 5 and 21 – 28;
- Influence of subjects' clinical condition (symptom score) between baseline and day 14 (or day of discharge);
- Monitoring the frequency of subjects whose condition worsens into a critical state necessitating a ventilator;
- Time to normalization of chosen blood parameters;
- Length of hospital stay;
- Rate of virus elimination from upper respiratory tract secretions.

Methodology:
This study was a phase II, open label, monocentric pilot study to evaluate the safety and potential effect of bazedoxifene on the clinical development of the disease COVID-19. In addition to standard of care, the investigational medicinal product Conbriza® (bazedoxifene) was orally administered to adult subjects who were admitted to hospital with moderate to severe COVID-19 pneumonia.
The screening visit was done within 5 days prior to Day 1 (baseline, start of IMP administration) and it could have happened in the same day as baseline (Day 1). The study treatment duration was 5 to 14 days as per investigator opinion and all enrolled subjects were administered with active treatment of Conbriza®. After treatment period, subjects were followed up to EoS Visit scheduled on Day 28, although allowed visit window for EoS was Day 21 to Day 28.
The end of the study as a whole was defined as the date of the last visit of the last subject in the study.
The study was conducted in accordance with Good Clinical Practice (ICH-GCP E6 (R2), the Declaration of Helsinki as well as relevant national and international legislation relating to the conduct of clinical trials. The trial was submitted to the respective Ethics Committees and National Regulatory Authorities for approval.

Name of Sponsor: **Oxygen Biotech s.r.o.** **Italská 2581/67** **120 00 Prague 2 – Vinohrady** **Czech Republic**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Conbriza®		
Name of Active Ingredient: Bazedoxifene		

Number of patients (planned and analysed):
Planned: 8-10 subjects.
Included and completed: 3 subjects.

Diagnosis and main criteria for inclusion:
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. The SARS-CoV-2 infection needed to be laboratory-confirmed within 14 days prior to randomization. If the subject was woman of childbearing potential, she must have had a negative pregnancy test at screening and must have agreed to use highly effective contraceptive method. All subjects needed to have an ability to cooperate and express her/his consent with the study participation.

Investigational Medicinal Product (IMP), dose and mode of administration, batch number:

Active treatment: bazedoxifene film-coated tablet 20 mg, oral administration:

- on Day 1: once daily (*quaque die, QD*) 2 tablets of 20 mg (i.e., 40 mg of bazedoxifene QD), regardless of food intake;
- from Day 2 to EoT: once daily (*quaque die, QD*) 1 tablet of 20 mg, regardless of food intake, preferably with morning medication.

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.
Batch number: DW1510.

Duration of treatment:
Screening: Within 5 days prior to Day 1 (baseline, start of IMP administration). It could have happened in the same day as baseline (Day 1).
Treatment period: From Day 1 till Day 5 at minimum and till day 14 at maximum as per investigator opinion.
Follow-up period: From End of Treatment (EoT) till Day 21 or up to 28. Allowed visit window for End of Study (EoS) was Day 21 to Day 28.

Criteria for evaluation:

Safety measurements:

All aspects of subject safety throughout this study were regularly monitored, including but not limited to all SAEs, AEs, clinical laboratory data, and other relevant safety data.

Each AE was assessed by the Investigator with regard to the following categories:

- *Intensity*: Investigators should have assessed the severity of AEs according to National Cancer Institute CTCAE Version 4.0.
- Causality*:* The Investigator assessed the causality/relationship between the study drug and the AE.

In addition to the severity rating, each AE was classified by the Investigator as “serious” or “not serious”.

Other measurements:

- 7-point ordinal scale to assess the changes in clinical status: on Day 0, Day 5 and 21 – 28;
- Symptom score to evaluate the influence of subjects' clinical condition: between baseline and day 14 (or day of discharge);
- Frequency of subjects whose condition worsens into a critical state necessitating a ventilator;
- Time to normalization of chosen blood parameters; venous blood sampling was performed to determine: basic parameters (blood count with differential leukocyte count, coagulation, D/dimers, CRP, Na, K, Ca, ALT, AST, LDH, bilirubin, urea, creatinine, ferritin, IL-6, peripheral blood flow cytometry with determination of basic T cell subpopulations) and other immunological parameters (IgM, IgA and IgG on SARS-CoV-2, CD3 +, CD4 +, CD8 + and lymphocyte subpopulations, T-reg. lymphocytes, TH17);

- Length of hospital stay;
- Rate of virus elimination from upper respiratory tract secretions; virological examinations (PCR) from nasopharyngeal smear once a week till EoS (e.g., day 1, 8, 15 and day 21-28) were performed (if possible). Antigen assessments could have replaced the PCR only for fast inclusion of patients into the study (not allowed to replace PCR from day 1 to day 21-28).

Statistical methods:

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. The primary objective of the study was the safety of administration in patients treated with SoC to which bazedoxifene had been added.

With regard to the low volume of data, the secondary objectives were again statistically difficult to fully comprehend, and they were the first data with subsequent use to demonstrate the trend for other types of studies. The secondary objectives were the assessments of changes in clinical status of patients using 7-point ordinal scale, changes according to the symptom score, frequency of deterioration of patients to severe disease with supportive lung ventilation, time to normalization of chosen blood parameters, length of hospital stay, rate of virus elimination from upper respiratory tract secretions.

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.

No interim analysis was planned, but the sponsor regularly monitored all aspects of subject safety throughout this study.

The statistical analysis was conducted in compliance with the ICH Topic E9, Statistical Principles for Clinical Trials and the Statistical Analysis Plan finalised and approved by the sponsor and the study statistician before database lock. Analyses were conducted using Statistical Analysis System (SAS®) software, version 9.4 (SAS Institute, Cary, NC, USA).

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS

A total of 3 adult subjects were screened, enrolled, treated with Conbriza® (bazedoxifene), and completed this open label, monocentric pilot study.

The screenings were performed on the same day as first IMP administration, i.e. on Day 1 (Baseline) in all enrolled subjects at the Pneumology Clinic of the First Faculty of Medicine, Charles University and Thomayer University Hospital in Prague.

All 3 subjects were administered with IMP during the hospital stay by study personnel, and 2 of them also at home after discharging from the hospital. They received Conbriza® 40 mg (2x20 mg) QD on Day 1 following with Conbriza® 20 mg QD during the treatment period. The IMPs were administered orally once daily at noon. The treatment duration was 5, 7 and 14 days, and the treatment compliance was 100% in all enrolled subjects.

The follow-up period started on EoT and finished with EoS Visit performed on Day 28 for each subject, and none was hospitalized on that visit.

Table 1. Disposition of patients and reasons for premature discontinuation

	Bazedoxifene n (%)
Number of subjects in study	3
Number of subjects who received at least one dose of study treatment	3 (100%)
Number of subjects who completed study treatment	3 (100%)
Number of subjects who discontinued study treatment	0
Number of subjects who completed study	3 (100%)
Number of subjects who discontinued study	0

Name of Sponsor: Oxygen Biotech s.r.o. Italská 2581/67 120 00 Prague 2 – Vinohrady Czech Republic	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Conbriza®		
Name of Active Ingredient: Bazedoxifene		

BASELINE CHARACTERISTICS

Among all enrolled subjects, there were two females (33.3%) and one male (66.7%) of white race with mean age (± SD) of 56.3 ± 9.61 years. One subject was overweight and two were obese with mean BMI of 32.80 kg/m^2 (range 29.4-38.9): mean weight was 89.67 ± 7.506 kg and mean height was 166.00 ± 8.54 cm. All 3 subjects (100%) received at least one concomitant medication. Only one (33.3%) had at least one previous medication (it was a fluid resuscitation administered intravenous five times within 3 days).

Table 2. Demographic and baseline characteristics

Parameter	Statistic	Bazedoxifene (N = 3)
Male	n (%)	1 (33.3 %)
Female	n (%)	2 (66.7 %)
Race - White	n (%)	3 (100 %)
Ethnicity - Not Hispanic or Latino	n (%)	3 (100 %)
Age [years]	Mean (SD)	56.3 (9.61)
Weight [kg]	Mean (SD)	89.67 (7.506)
Height [cm]	Mean (SD)	166.0 (8.54)
BMI [kg/m^2]	Mean (SD)	32.80 (5.294)
Previous medication		
Number of subjects with at least one PM	n (%)	1 (33.3%)
FR (No.: 5)	n (%)	1 (33.3%)
Concomitant medication		
Number of subjects with at least one CM	n (%)	3 (100%)
Solu-medrol	n (%)	3 (100%)
Controloc	n (%)	3 (100%)
Medrol	n (%)	2 (66.7%)
Clexane	n (%)	2 (66.7%)
Ortanol	n (%)	2 (66.7%)
Plasmalyte	n (%)	2 (66.7%)
Veklury	n (%)	2 (66.7%)
Metformin	n (%)	1 (33.3%)
Fraxiparine	n (%)	1 (33.3%)
Letrox	n (%)	1 (33.3%)
Remdesivir	n (%)	1 (33.3%)
Sefotak	n (%)	1 (33.3%)
Trajenta	n (%)	1 (33.3%)
Xarelto	n (%)	1 (33.3%)
Zinnat	n (%)	1 (33.3%)

n = Number of subjects, SD = Standard deviation, PM = Previous medication, FR = Fluid resuscitation (intravenous), CM = Concomitant medication.

Name of Sponsor: Oxygen Biotech s.r.o. Italská 2581/67 120 00 Prague 2 – Vinohrady Czech Republic	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Conbriza®		
Name of Active Ingredient: Bazedoxifene		

SAFETY RESULTS

After the analysis of the data of 3 enrolled and treated adult subjects, there were no safety issues observed. In the study, no serious adverse events occurred, no adverse events leading to death occurred.

No adverse events occurred after the treatment started. Only one AE of mild intensity (Grade 1) in one subject was reported before the first IMP administration (D-dimers elevation). In the course of the study, during the IMP administration, the level of D-dimers in subject has significantly decreased. This AE was not considered as related to study treatment.

All three subjects were requiring supplemental oxygen at treatment start, there was no patient whose clinical condition worsened into a state necessitating a ventilator.

No other clinically significant findings were reported in hematology, biochemistry, immunology and urinalysis parameters.

The table below summarises all adverse events in the study.

Table 3. Summary of all adverse events

	Bazedoxifene (N = 3)		
Adverse event	**E**	**n**	**%**
Any AE			
Number of subjects with at least one AE		1	33.3
Number of different AEs	1		
Total number of AEs	1		
D-dimer elevation: 3160 µg/L	1	1	33.3

AE = Adverse event.
n = Number of subjects experiencing the event, % = Percentage of subjects, E = Number of events.
D-dimer elevation (3160 µg/L) occurred before administration of the first dose of Conbriza.

CONCLUSION

The OB001 study (EudraCT No. 2021-000320-35) was a phase II, open label, monocentric pilot study to evaluate the safety and potential effect of bazedoxifene on the clinical development of the disease COVID-19. In addition to standard of care, the investigational medicinal product Conbriza® (bazedoxifene) was orally administered to adult subjects who were admitted to hospital with moderate to severe COVID-19 pneumonia.

A total of 3 adult subjects, two females and one male, were screened, enrolled, treated with orally administered Conbriza®, and completed this study. Mean age was 56.3 years (range 46-65), mean BMI 32.80 kg/m^2 (range 29.4-38.9). All subjects were requiring supplemental oxygen at treatment start, there was no subject whose clinical condition worsened into a state necessitating a ventilator.

All 3 subjects were administered with IMP during the hospital stay by study personnel at the Pneumology Clinic of the First Faculty of Medicine, Charles University and Thomayer University Hospital in Prague, and 2 of them also at home after discharging from the hospital. They received Conbriza® 40 mg (2x20 mg) QD on Day 1 following with Conbriza® 20 mg QD during the treatment period. The treatment duration was 5, 7 and 14 days, and the treatment compliance was 100% in all enrolled subjects. The follow-up period started on EoT and finished with EoS Visit performed on Day 28 for each subject, and none was hospitalized on that visit.

The safety of bazedoxifene in patients with COVID-19 disease was the primary objective of the study. It was assessed by incidence and spectrum of reported AEs, and laboratory and clinical findings. The secondary objectives also included safety assessments. The safety analysis set comprised all 3 enrolled subjects.

Name of Sponsor: **Oxygen Biotech s.r.o.** **Italská 2581/67** **120 00 Prague 2 – Vinohrady** **Czech Republic**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Conbriza®		
Name of Active Ingredient: Bazedoxifene		

After the analysis of the data of those three subjects, there were no safety issues observed. No serious adverse events occurred, no adverse events leading to death occurred.

No adverse events occurred after the treatment started. Only one AE of mild intensity in one subject was reported before the first IMP administration, and it was not considered as related to study treatment.

No other clinically significant findings were reported in hematology, biochemistry, immunology and urinalysis parameters.

Date of the report: 27 May 2022
Version of the report: Final version