Clinical Study Summary	
EudraCT no.	2020-002982-33
Investigational medicinal product	PDNO
2020-PDNO-002	2020-PDNO-002
Summary version and date	FINAL v1.0; 23MAY2023

AN OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF PDNO (NITROSOOXYPROPANOL) INFUSION IN COVID-19 PATIENTS WITH ACUTE PULMONARY HYPERTENSION

Study duration	First patient screened: 02MAY2021 Date of early study termination: 30APR2023
Development phase	I/II
Indication	Acute pulmonary hypertension
Sponsor signatory	Christofer Adding, MD, PhD Attgeno AB Fogdevreten 2 SE-171 65 Solna, Sweden
Coordinating Investigator	Johanna Savilampi, MD, PhD Örebro University Hospital Anaesthesiology and Intensive care SE-701 85 Örebro, Sweden
Clinical study management:	CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden

This clinical study was conducted, and essential study documentation archived, in compliance with company standard operating procedures and standards, which incorporate the requirements of the EU Clinical Studies Directive 2001/20/EC and ICH E6 (R2) guideline for good clinical practice.

1 SIGNATURES

I, the undersigned, have read this summary and confirm that to the best of my knowledge it accurately describes the study.

1.1 Sponsor signatory

DocuSigned by:

Signer Name: Christofer Adding
Signing Reason: Jag godkänner dokumentet
Signing Time: 23-maj-2023 | 12:26 CEST

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Christofer Adding, MD, PhD
Attgeno AB

2 STUDY SUMMARY

Study title

An open-label, multicenter study to evaluate the efficacy, safety and tolerability of PDNO (nitrosooxypropanol) infusion in COVID-19 patients with acute pulmonary hypertension

Study code	**EudraCT no.**
2020-PDNO-002	2020-002982-33
Study period Date of first patient screened: 02MAY2021 Date of early study termination: 30APR2023	**Phase of development** I/II

Coordinating Investigator

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Study centre(s)

Site 1: Örebro University Hospital Anaesthesiology and Intensive care SE-701 85 Örebro, Sweden	Principal Investigator: Johanna Savilampi, MD, PhD
Site 2: Danderyd University Hospital Anaesthesiology and Intensive care SE-182 57 Danderyd, Sweden	Principal Investigator: Piotr Harbut, MD, PhD
Site 3: (Site not initiated) Sahlgrenska University Hospital Intensive Care Unit 96/CIVA Department of Anaesthesia and Intensive Care SE-413 45 Gothenburg, Sweden	Principal Investigator: Kristina Svennerholm, MD, PhD

Publication (reference)

Not applicable.

Study design

This was an open-label, multicentre study evaluating the effect, safety and tolerability of intravenous PDNO infusion given to COVID-19 patients with acute pulmonary hypertension (aPH).

Objectives

Primary objective

- To evaluate the efficacy of PDNO on pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (MPAP), as measured with a pulmonary artery catheter (PAC), in patients with Covid-19 and pulmonary hypertension (PH).

Secondary objectives

- To evaluate the safety and tolerability of PDNO in patients with COVID-19.
- To evaluate general clinical outcome.
- To decide the time to non-SARS-CoV-2 infection.
- To evaluate the change in troponin I/T and BNP/NT-proBNP after PDNO dosing in patients with Covid-19 and PH.
- To evaluate the efficacy of PDNO on the pulmonary resistance.

Exploratory objectives

- To explore potential biomarkers.
- To assess presence of SARS-CoV-2 virus.

Number of subjects

Planned: Up to 16 patients treated with PDNo (with a maximum of 10 responders)

Actual: 3 patients were screened, 0 patients were included and treated in the study.

Diagnosis and main eligibility criteria

Male or female patients, age ≥ 18 years at the time of pre-screening, diagnosed with COVID-19 and with echocardiographic signs of pulmonary artery systolic pressure (PASP) >40 mmHg were considered for inclusion in the study.

Patients with a history of chronic PH, known New York Heart Association (NYHA) Functional Class III or IV symptoms; left heart failure with ejection fraction (EF) < 35%; acute coronary syndrome within 3 months prior to the study; a body mass index (BMI) >45 kg/m^2; estimated glomerular filtration rate (eGFR) of <30 mL/min; clinically significant cardiac dysfunction; need of norepinephrine infusion of >0.25 µg/kg/min or the use of two vasopressors; methaemoglobin (MetHb) >3%; PCO2>7; haemoglobin <80 g/dL; indication of liver disease; thrombocytopenia; prothrombin time/international ratio >1.4, pregnancy; or any other clinically significant disease or disorder were excluded from participation in the study.

Methodology

Pre-screening and consenting

Conscious patients admitted to the hospital with the suspected or confirmed diagnosis of Covid-19 were pre-screened and informed about the study pre-intensive care unit (ICU) admission or at ICU-admission, both orally and written. Patients who consented to participation had to leave a written informed consent.

Visit 1 - Screening

Covid-19 diagnosed patients, who previously consented to study participation, who were treated at an ICU were to be screened for participation. The patient was to be screened with echocardiography and if the patient has signs of PH (PASP > 40 mmHg) and fulfilled all other eligibility criteria the patient was to be included for participation in the study and the treatment with study drug could be initiated.

Visit 2 – Treatment to 7 days post-infusion

On the day of start of IMP infusion, the patient was to be prepared for pre-dose assessments. A PAC, a CVC and a radial arterial catheter were to be inserted. Placement of PAC and CVC catheters was to be confirmed by x-ray. An observation period over 2 hours prior to the start of IMP infusion, where placebo (NaCl) and a sodium bicarbonate buffer were to be given, was to be started and baseline assessments of mean MPAP, pulmonary capillary wedge pressure (PCWP), CO and calculated PVR,

vital signs, ECG, safety laboratory parameters and biomarkers were to be performed. As a routine, administration of norepinephrine, or other vasopressor support infusion, at a dose chosen by the investigator, was to be prepared, connected to the CVC and ready to be started at any time concomitantly with the PDNO infusion, as judged by the investigator. In addition, atropine (0.5 mg) and ephedrine (5-10 mg) were to be prepared and ready to be injected intravenously as decided by the investigator.

The patients were to be carefully monitored during and after infusion. Vital signs (including pulse oximetry) and ECG were to be checked at regular intervals. Blood pressure was to be continuously controlled via intra-arterial blood pressure monitoring. It was important that all research subjects were kept in supine position and that any need to change body position (*e.g.,* to prone position) was preceded by appropriate preparations and careful precautions to avoid that this triggers severe systemic hypotension.

The patients were to start IMP infusion at the dose of 3 nmol/kg/min, which was to be iv infused for a minimum of 5 minutes. If no effect (decrease of MPAP or PVR) was seen or any stopping criteria developed, the dose was to be titrated up to the next dose for a minimum of 5 minutes. The dose was to be increased every 5-15 minutes until the maximum dose (120 nmol/kg/min), or a target effect on MPAP/PVR was reached, or if any stop criteria were present. The target effect was defined as either MPAP decrease more than 30% or PVR decrease more than 50% (compared to values at last measurement pre-PDNO/end of placebo) and no further dose increase should be done.

Patients who showed no or minor effect on MPAP/PVR (defined as neither decrease of MPAP over 15% nor decrease of PVR over 30%) after the PDNO infusion (non-responders) were to be discontinued from PDNO dosing after dose titration (up to 120 nmol/kg/min). Non-responders were to be followed with the same follow-up schedule as responders.

Note: In responding patients, dose titration was to be stopped and the present dose continued, even if target dose according to above was not reached, if either oxygen desaturation < 88% requiring a FiO2 to max 0.6 or a maximal increase < 10% if FiO2 is ≥ 0.6 or systemic hypotension: MAP < 60 mmHg with need of concomitant use of norepinephrine (maximal dose of 0.3 µg/kg/min).

A patient who had a beneficial effect of PDNO (responder) was to continue at the optimal titrated dose up to 4 hours (including time for dose titration). After 4 hours PDNO, the PDNO infusion was to be weaned, stepwise with the same dose levels as for dose titration (*e.g.,* 90 nmol/kg/min reduced to 80 nmol/kg/min and next to 70 nmol/kg/min etc.). Every 2 hours a new attempt of weaning was to be done. After 8 hours, adding other pulmonary vasodilating treatment according to standard care was to be considered. In the case that repeated attempts to wean the PDNO infusion failed, the Principal Investigator could request to continue the PDNO infusion. If supported by the Sponsor's Medical Representative after consulting external experts as needed, the PDNO infusion could be continued up to 14 days.

The PAC was to be removed 3 hours after successful weaning of the PDNO infusion. The arterial catheter was to be removed 6 hours after the end of IMP infusion, unless the Principal Investigator decided otherwise based on the continued standard treatment of the patient.

For all patients, efficacy, safety, and tolerability were to be assessed before, during and 1, 2, 3 and 7 days after the end of the PDNO iv infusion.

The first 4 patients were to start at the lowest dose (3 nmol/kg/min). The first 4 patients were to be dosed one by one. Data from the IMP infusion period and an additional 6-hours data after the end of infusion were to be evaluated by the iSRC for each patient before the next patient could start treatment. After 4 patients had been treated, the iSRC was to evaluate all 4 and decide on the subsequent dosing schedule and a potentially increased starting dose for upcoming patients.

Visit 3 - 14 days after end of infusion, follow-up visit

A follow-up visit to assess general outcome and AEs was to be performed at 14 days after the end of IMP infusion. The visit could be conducted as a telephone visit.

Visit 4 - 21 days after end of infusion, follow-up visit

A follow-up visit to assess general outcome and AEs was to be performed at 21 days after the end of IMP infusion. The visit could be conducted as a telephone visit.

Visit 5 – 30 days after end of infusion, End-of-study-visit

A final end-of-study visit was to take place on Day 30±2 days after the end of PDNO infusion to assess general outcome and AEs. The visit could be conducted as a telephone visit.

Investigational medicinal products (IMP)

PDNO consists of propylene glycol (1,2-propanediol, PD) chemically combined with NO (to be donated). The drug substance was formulated as an inherent mixture of 4 structure analogues. The mixture consists of an equilibrium of the 2 regioisomers 1-(nitrosooxy) propan-2-ol and 2-(nitrosooxy) propan-1-ol. In addition, each regioisomer is a racemic mixture. The drug substance PDNO stands in equilibrium with its own vehicle PD.

PDNO is a clear yellowish liquid. It is formulated at 10.5 mg/mL (100 mM) and 63.1 mg/mL (600 mM) in PD and is intended for simultaneous iv administration with sodium bicarbonate buffer solution 14 mg/mL in accordance with the pharmacy manual. PDNO will be supplied in 20 mL bottles.

PDNO was to be administered as an iv infusion of 5-15 minutes respectively for the increased planned dose titration steps: 3, 10, and thereafter steps of max 10 nmol/kg/min until the target effect on MPAP/PVR or a maximal dose of 120 nmol/kg/min was reached.

Placebo (NaCl, commercially available dilution solution for parenteral use, 9 mg/mL) was to be administered during the 120 minutes observation period prior to start of IMP infusion.

Duration of treatment

Treatment with PDNO 4 hours, plus time needed for safe weaning (with an option to prolong the treatment up to 14 days if considered appropriate by the Principal Investigator)

Duration of patient's involvement in the study

Each patient was estimated to participate in the study for a treatment period of approximately a 1-day treatment and a 30-day follow-up period.

Efficacy assessments

MPAP, PCWP, CO, central venous pressure (CVP),
PVR and SVR via PAC
General outcome
Time to SARS-CoV free

Safety assessments

AEs
Vital signs
ECG
Safety laboratory
Troponin I/T, BNP/NT-proBNP sampling

Exploratory assessments

Biomarker sampling
SARS-CoV-2 quantification in sputum/tracheal secretion and plasma

Statistical methods

To assess the stability of the MPAP and PVR levels during the placebo observation period, a one-sided paired Wilcoxon signed rank test was to be performed on the 5% significance level comparing the first and last assessment timepoint during the observation period for each response variable respectively. The null hypothesis was that the levels of the response variables would remain the same for both assessment time points. If the test proved a significant lowering of the response variable levels however, this hypothesis was to be rejected and no further statistical testing was to be performed, since this would be judged to be too unreliable.

Providing a non-significant test above, another one-sided paired Wilcoxon signed rank test was to be performed comparing the responding subjects baseline levels in MPAP and PVR to the corresponding levels 10 minutes after reaching each subject's up-titrated target dose, for each response variable respectively. The null hypothesis was that the levels in the response variable were the same. However, if significance was proved using the 5% significance level, the null hypothesis was rejected in favour of the alternative hypothesis that treatment with the IMP significantly reduced the levels of the response variables.

Continuous data were to be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value. Categorical data were to be presented as counts and percentages. When applicable, summary data were to be presented by treatment, and by assessment time. Individual patient data were to be listed by patient number, treatment, and, where applicable, by assessment time. All descriptive summaries and statistical analyses were to be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC). Baseline was defined as the visit with last data collection point prior to the first administration of IMP. No imputation of missing data was to be performed.

Reason for early study termination

The study was planned early during the COVID-19 pandemic when it was shown that increased pulmonary arterial pressure greatly increased the mortality risk in SARS-CoV-2-infected patients admitted to the ICU. Since the availability of vaccines, and with only two participating sites in the trial a drastic drop in the number of available patients was seen. According to the participating investigators the clinical presentation and pathophysiology of COVID-19 patients requiring an ICU has changed during the pandemic, and today none of the patients require treatment to prevent right ventricular failure (RVF), possibly due to aggressive treatment regimens with anticoagulants and cortisol. Since WHO have also re-categorized the COVID-19 pandemic from public health emergency of international concern (PHEIC) to an "established and ongoing health issue" the Sponsor has now concluded to close the study.

The study has no included patients and will therefore not contribute to the risk-benefit assessment of the IMP (PDNO).

Summary of screened patients

Screening number	Screening date	Eligible (yes/no)	Reason for non-inclusion
SF-1-S001	02MAY2021	No	Exclusion criterion #4: Acute coronary syndrome (non ST elevation myocardial infarction [non-STEMI], ST elevation myocardial infarction [STEMI], unstable angina pectoris [AP]), myocardial infarction, stroke, transient ischemic attack (TIA), AV block III within 3 months prior to informed consent or QTcF >450 ms at the time of screening. Exclusion criterion #8: PCO2 > 7 at screening.
SF-1-S002	10MAY2021	No	Inclusion criterion #4: Diagnosed with echocardiographic signs of pulmonary artery systolic pressure (PASP) >40 mmHg, as estimated by doppler defined echocardiography using a modified Bernoulli equation: PASP ≈ 4 (tricuspid regurgitant jet velocity)2 + CVP. After insertion of the PAC, a MPAP ≥20 mmHg will allow continued participation and start of PDNO infusion. If MPAP is <20 mm Hg, the patient is considered a screen failure and may be replaced.
SF-1-S003	28MAY2021	No	Inclusion criterion #4: Diagnosed with echocardiographic signs of pulmonary artery systolic pressure (PASP) >40 mmHg, as estimated by doppler defined echocardiography using a modified Bernoulli equation: PASP ≈ 4 (tricuspid regurgitant jet velocity)2 + CVP. After insertion of the PAC, a MPAP ≥20 mmHg will allow continued participation and start of PDNO infusion. If MPAP is <20 mm Hg, the patient is considered a screen failure and may be replaced.

Summary of results

No results available.

Conclusions

No conclusions available.