Clinical trial results:
An open-label, multicenter study to evaluate the dose, efficacy, safety and tolerability of PDNO (Nitrosooxypropanol) infusion in patients with pulmonary hypertension after cardiopulmonary bypass (CPB) surgery for coronary artery bypass grafting (CABG) or mitral or aortic valve repair or replacement with or without CABG

Summary

EudraCT number	2021-005032-30
Trial protocol	SE
Global end of trial date	29 April 2024
Results information	
Result version number	v1 (current)
This version publication date	25 February 2026
First version publication date	25 February 2026

Trial information

Trial identification	
Sponsor protocol code	2021-PDNO-003
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Attgeno AB
Sponsor organisation address	Fogdevreten 2, Solna, Sweden, 17165
Public contact	Christofer Adding, Attgeno AB, +46 70 788 67 66, christofer.adding@attgeno.com
Scientific contact	Christofer Adding, Attgeno AB, +46 70 788 67 66, christofer.adding@attgeno.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	29 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2024
Global end of trial reached?	Yes
Global end of trial date	29 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
To evaluate the dose-range efficacy of PDNO on pulmonary vascular resistance (PVR) in patients undergoing CPB surgery with post-operative aPH.

The primary objective of "Part I" of the study is reported, as the sponsor decided to run "Part II" as a seperate Phase 2b study.

Protection of trial subjects:

Safety data from the pre-clinical studies and the completed Phase I study did not reveal any safety issues that would outweigh the expected benefits of the study. The clinical benefit of this hemodynamic study was to identify the dose range of PDNO that is safe and have potential beneficial efficacy in patients with aPH that undergo cardiac surgery. The direct benefit for participating patients was limited to possible advantages from extended investigations and potential benefit from reduced pulmonary blood pressure during the short infusion time. This dose finding study would provide vital hemodynamic data which would aid in the design of the continued clinical development program, including the phase III study. Thus, the clinical benefit of the use of PAC would outweigh the potential complications of the PAC insertion and expected drug related adverse events. The Principal Investigator at each clinic ascertained that adequate facilities, procedures and skilled personnel were available to handle emergency situations should they have occurred during the study. An internal iSRC monitored emerging safety data over the course of the study. Study assessments were considered sufficient to meet the scientific and medical goals for the study. Overall, it was concluded that the potential benefits from the study outweighed the potential risks for the treated patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2022
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: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	6
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

When the patients were admitted to the hospital (for elective cardiac surgery) they were screened with echocardiography and if signs of pulmonary hypertension SPAP >40 mmHg and the eligibility criteria were fulfilled, the patient was included in the study. 27 subjects were screened and 21 were included (assigned a subject number) in the study.

Period 1

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

Arms

Arm title	Experimental

Arm description:

The IMP in the experimental arm was PDNO (Nitrosooxypropanol), which consists of propylene glycol (1,2-propanediol, PD) chemically combined with nitrite, converted to NO in the blood (to be donated). PDNO is formulated at 10.5 mg/mL (100 mM) and 63.1 mg/mL (600 mM) in PD. PDNO was administered as step-wise incremental intravenous infusions in a continuous carrier infusion of sodium bicarbonate (NaHCO3-, 14 mg/mL) into a central venous catheter. The duration of treatment was approximately 2 hours (with an option to prolong the treatment if additional dosing steps were needed (10-20 minutes per dose)).

Arm type	Experimental
Investigational medicinal product name	PDNO (Nitrosooxypropanol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Prior to IMP infusion, a 15-minute placebo (NaCl) and a sodium bicarbonate buffer was given. Thereafter, the patients were planned to be dosed with up to five consecutively incrementing doses of IMP. Initial start dose of IMP was infused for 10-20 minutes. If no effect (decrease of MPAP or PVR) was seen or any stopping criteria developed, the dose was titrated up to the next dose level for 10-20 minutes and again evaluated for effect and safety. This was repeated for up to five dose levels. After the highest IMP infusion had been stopped, a 20-minute placebo (NaCl) and carrier buffer infusion were infused.

The initial dose levels were (cohort 1): 3; 10; 30; 45; and 60 nmol/kg/min of PDNO. Based on analyses of emerging data the iSRC decided on adjusted dose levels: Cohort 2 doses: 5; 10; 15; 20; 25 nmol/kg/min (PDNO), and Cohort 3 doses: 2.5; 5; 10; 15; 20 nmol/kg/min (PDNO).

Number of subjects in period 1	Experimental
Started	21
Completed	15
Not completed	6
Could not proceed due to failure to insert PAC	1

Failure To Meet Continuation Criteria	5

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	21	21	
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)	6	6	
From 65-84 years	15	15	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	12	12	

Subject analysis sets

Subject analysis set title	Full-analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who were included and received at least one dose of IMP and have observed PVR data (primary endpoint data) after IMP dosing. Here, observed PVR data is defined as at least one PVR observation during PDNO infusion

Subject analysis set title	Modified full analysis set (MFAS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All FAS patients who were judged as “evaluable” by the iSRC, i.e., to have generated conclusive data for efficacy response.

Subject analysis set title	Safety analysis set (SAS)
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of placebo or PDNO.

Reporting group values	Full-analysis set (FAS)	Modified full analysis set (MFAS)	Safety analysis set (SAS)
Number of subjects	15	12	15
Age categorical Units: Subjects			
In utero	0	0	0

Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	5	5
From 65-84 years	10	7	10
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	8	6	8
Male	7	6	7

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

The IMP in the experimental arm was PDNO (Nitrosooxypropanol), which consists of propylene glycol (1,2-propanediol, PD) chemically combined with nitrite, converted to NO in the blood (to be donated). PDNO is formulated at 10.5 mg/mL (100 mM) and 63.1 mg/mL (600 mM) in PD. PDNO was administered as step-wise incremental intravenous infusions in a continuous carrier infusion of sodium bicarbonate (NaHCO3-, 14 mg/mL) into a central venous catheter. The duration of treatment was approximately 2 hours (with an option to prolong the treatment if additional dosing steps were needed (10-20 minutes per dose)).

Subject analysis set title	Full-analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who were included and received at least one dose of IMP and have observed PVR data (primary endpoint data) after IMP dosing. Here, observed PVR data is defined as at least one PVR observation during PDNO infusion

Subject analysis set title	Modified full analysis set (MFAS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All FAS patients who were judged as "evaluable" by the iSRC, i.e., to have generated conclusive data for efficacy response.

Subject analysis set title	Safety analysis set (SAS)
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of placebo or PDNO.

Primary: Change in Pulmonary Vascular Resistance (PVR) from baseline (mean of T0 and T1, placebo) to time point T2, T3, T4, T5 and T6, respectively.

End point title	Change in Pulmonary Vascular Resistance (PVR) from baseline (mean of T0 and T1, placebo) to time point T2, T3, T4, T5 and T6, respectively.[1]

End point description:

The primary estimand for the primary endpoint was based on the individual dose-range relationship. Individually functions were estimated for the exponential decay curve y(PVR)=Ca, where =dose, y=PVR, C=constant, and where a < 1 was interpreted as a decreasing PVR curve by dose. The estimates for C and for each participant were based on actual dosing schedule and observed PVR values. The mean of all individual a:s was tested for H0: a=1 (no decrease by dose). If H0 is rejected, there is a proof for a declining dose-range relationship. The test was one-sided using the type-I error rate of 0.10.

The dose schedule for the established timepoints T2-T6 was changed during the study (decision from the iSRC). PDNO was initially given at 3, 10, 30, 45 and 60 nmol/kg/min at T2-T6. After the first three evaluable patients, doses changed to 5, 10, 15, 20, 25 nmol/kg/min at T2-T6, and further after additional three patients to 2.5, 5, 10, 15, 20 nmol/kg/min at T2-T6.

End point type	Primary

End point timeframe:

Periods of assessments: T0: start of placebo infusion (approx. after 2-5 min placebo), T1: end of placebo infusion (approx. after 8-10 min placebo), T2-T6: during PDNO infusion (each PDNO dose is approx. 15 min).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single-arm trial, and therefore two treatment arms cannot be compared in the statistical analysis section.

End point values	Modified full analysis set (MFAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: PVR (dyn*s/cm5)				
number (not applicable)	0.98			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From initiation of any study specific procedure until termination of placebo infusion (T8). From CSP v3.0, for patients collecting post-infusion blood samples (T9-T11) only AEs judged by investigator to be directly caused by the sampling were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Safety analysis set (SAS)

Reporting group description:

All patients who received at least one dose of placebo or PDNO.

Serious adverse events	Safety analysis set (SAS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (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	Safety analysis set (SAS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	9		
Surgical and medical procedures			

Pericardial operation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nervous system disorders Seizure like phenomena subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2022	Inclusion criteria no 4 pulmonary artery systolic pressure (PASP) changed from >50 mmHg to >40 mmHg. Planned study timelines has been extended to Q2 2023. Section 10.3 temperature readings allowed to be done only three times per week. Table 8.1-1 and synopsis, transesophageal/transthoracic echocardiography added at T7-T8 as specified in Table 7.1. Inclusion criteria no 3 clarification that Concomitant CryoMaze procedure and/or surgical left atrial appendix occlusion is allowed. Table 7.1-1 addition of AESI as endpoint analysis. Not listed before by mistake. Administrative update of eligibility criteria in synopsis to match section 9.4 and 9.5. Section 5 Addition of two new sites.
17 July 2023	Addition of three time points for pharmacokinetic samples (PD) after completed infusions (Sections 6.1.6.2; 6.1.7; 8.1 and tables 7.1-1 and 8.1-1). Section 6.1.7 updated with FIH data. Addition of information regarding how to store unused infusion fluids in the case of unexpected adverse events. Sections 10.4 and 10.8.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported