Final Report of the FLOAT-CS Study

1. Name of Sponsor

Dr. med. Thomas Bitter, until 31.03.2018: Klinik für Kardiologie, Herz- und Diabeteszentrum NRW, Universitätsklinik der Ruhr-Universität Bochum, Georgstr. 11, 32545 Bad Oeynhausen, since 01.04.2018: Medizinische Klinik II, Lukas-Krankenhaus, Hindenburgstr. 56, 32257 Bünde

2. Name of Finished Product

CONOXIA GO_2X (Manufacturer: Linde Gas Therapeutics GmbH, 85764 Oberschleißheim), used in a humidified and warmed mixture with ambient air

3. Name of Active Substance

Oxygen, medicinal gas, pressurized

4. Individual Study Table

not applicable

5. Title of Study

High-Flow-Therapy for the treatment of Cheyne-Stokes-Respiration in chronic heart failure (FLOAT-CS)

Study Code: HDZNRW-KA_006_TB

EudraCT No.: 2016-001357-40

List of Ethics Committee Approved Protocol Versions:

- 01.09.2016: Studienprotokoll Version 1.1 vom 18.04.2016
- 09.01.2017: Studienprotokoll Version 1.2 vom 10.10.2016
- 02.01.2018: Studienprotokoll Version 1.3 vom 11.10.2017

6. Investigators

Dr. med. Thomas Bitter (Principal Investigator), until 31.03.2018: Klinik für Kardiologie, Herz- und Diabeteszentrum NRW, Universitätsklinik der Ruhr-Universität Bochum, Georgstr. 11, 32545 Bad Oeynhausen, since 01.04.2018: Medizinische Klinik II, Lukas-Krankenhaus, Hindenburgstr. 56, 32257 Bünde

Dr. med. Henrik Fox (Deputy of Principal Investigator), Klinik für Kardiologie, Herz- und Diabeteszentrum NRW, Universitätsklinik der Ruhr-Universität Bochum, Georgstr. 11, 32545 Bad Oeynhausen

Dr. med. Olaf Oldenburg (Subinvestigator), until 31.03.2018: Klinik für Kardiologie, Herz- und Diabeteszentrum NRW, Universitätsklinik der Ruhr-Universität Bochum, Georgstr. 11, 32545 Bad Oeynhausen, since 01.04.2018: Klinik für Kardiologie, Clemenshospital, Duesbergweg 124, 48153 Münster

Dr. med. Fabian Roder (Subinvestigator), Klinik für Kardiologie, Herz- und Diabeteszentrum NRW, Universitätsklinik der Ruhr-Universität Bochum, Georgstr. 11, 32545 Bad Oeynhausen

7. Study Center

Klinik für Kardiologie, Herz- und Diabeteszentrum NRW, Universitätsklinik der Ruhr-Universität Bochum, Georgstr. 11, 32545 Bad Oeynhausen

8. Publication (reference)

not applicable

9. Studied period

The first patient was enrolled on 06.02.2017. The last patient was out on 29.11.2017.

The study was stopped on 27.03.2018 because the Sponsor and Principal Investigator Dr. Thomas Bitter left the study center on 31.03.2018. The continuation of the study by another investigator was not possible.

10. Phase of Development

IIIb

11. Objectives

To demonstrate the effectiveness and safety of nocturnal ventilation with oxygen-HFT (oxygen-high-flow-therapy) for the treatment of CSA (Cheyne-Stokes respiration) in patients with HFrEF (heart failure with reduced left ventricular ejection fraction) compared to placebo.

12. Methodology

Investigator-initiated, monocenter, prospective, randomized, blinded, placebo-controlled cross-over study.

Flow Chart (Fig. 1):

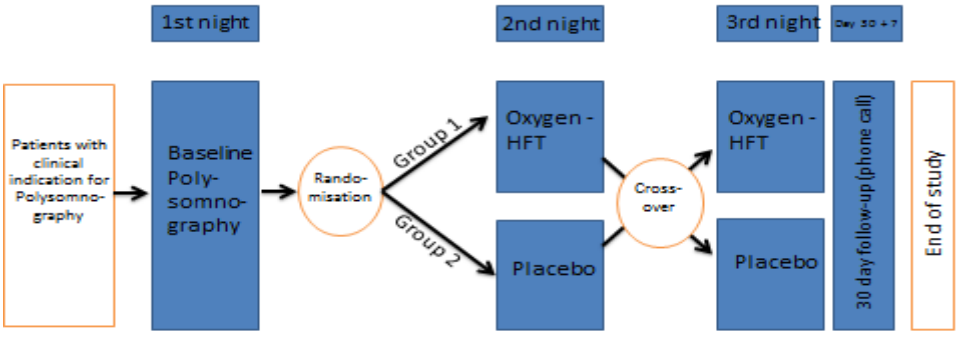

Fig. 1

The timing and the assessments of the study are outlined in the following table:

Assessment	**Enroll-ment**	**1st night* (Baseline PSG)**	**2nd night**	**3rd night**	**30 Days Follow-up*** **
Inclusion/Exclusion criteria	x				
Signed ICF	x				
Medical history, concomitant medication	x				
Demography, vital signs, NYHA class and nocturia	x				
ECG	x				
Venous blood sample (creatinine, GFR,	x				
Randomisation		x**			
Arterial line via radial artery		x	x	x	
Polysomnography		x	x	x	
Arterial blood sample (BNP, hs troponin I)		x	x	x	
Hemodynamic assessment		x	x	x	
Arterial blood gas analysis		x	x	x	
Titration of flow rate and FiO_2		x**			
Supply of study medication (oxygen) – group 1			x		
Supply of study medication (oxygen) – group 2				x	
Adverse event (AE) / Serious adverse event (SAE)		x	x	x	x

could be performed on the same day as the enrollment visit

** was be performed after the Baseline PSG if all inclusion criteria and no exclusion criteria were fulfilled

*** 30 days (+7 days) after discontinuation of study drug (SAEs to be collected, only), might have been done via phone call or clinic visit

13. Number of patients (planned and analysed)

- Planned patients: 25 randomized
- Actually enrolled patients: 14, among them:
  - Patients who were randomized, received treatment and completed the study: 7
  - Drop outs before randomization: 7 (1 patient withdrew consent, and 6 patients did not qualify for randomization due to the results of their first night cardiopulmonary polysomnographies)
- Currently active patients: 0
- Analysed patients: 0 (due to small number of randomized patients)

14. Diagnosis and criteria for inclusion and exclusion

Inclusion criteria (from Studienprotokoll Version 1.2 vom 10.10.2016 under which all patients were enrolled):

- Age 18-90 years
- NYHA II to IV
- LVEF ≤ 45% (Echo within 28 days of enrollment)
- Predominantly central sleep apnea:
  AHI ≥ 15 events per hour, with > 80% central events (apnoea or hypopnoea) and central AHI ≥ 10 events per hour
- Peak VO_2 < 90% of predicted value (CPX test within 1 month of enrollment)
- Nocturnal hypoxemic burden ≥ 25 min/night

Exclusion criteria (from Studienprotokoll Version 1.2 vom 10.10.2016 under which all patients were enrolled):

- Daytime hypercapnia (pCO_2 > 45 mmHg)
- Ongoing ventilation therapy
- Severe COPD (chronic obstructive pulmonary disease) defined as FEV1 < 50% (lung function test within 1 month of enrollment)
- Cardiothoracic surgery within the last 3 months
- Myocardial infarction within the last 6 months
- Unstable angina
- Acute myocarditis
- Stroke within the last 3 months
- Epilepsy or known cerebral damage or dementia
- Untreated restless-legs-syndrome
- Women of childbearing potential
- Participation in any clinical study

15. Test product, dose and mode of administration, batch number

During the therapy night the patients received oxygen with humidified air, fully saturated at 37° C at a flow rate of 20-50 L/min which was delivered by AIRVO 2™ (Fisher and Paykel Healthcare, New Zealand) (Fig. 2) via a nasal cannula. The settings of the maximum tolerable flow rate and the FiO_2 as determined during the titration were used at the therapy start. They might have been adjusted if needed.

Fig. 2

The heated pass-over humidifier AIRVO 2™ produced gas phase humidification and had a heated breathing tube to minimize condensation. When used at moderate airflows of approximately 25 L/min, the system delivered positive end expiratory pressure (PEEP) in the vicinity of 1-3 cm H_2O. The PEEP generated was considered to decrease the number of breaths per minute and consequently increase tidal volume and reduce dead space.

The oxygen was taken from compressed air bottles (CONOXIA GO_2X) that were also used in normal clinical routine. Therefore a batch number is not applicable.

16. Duration of Treatment

The scheduled duration of treatment per patient was 8 hours during one night from 22 o´clock to 6 o´clock.

17. Reference Therapy, dose and mode of administration, batch number

During the placebo night patients breathed ambient air. The AIRVO 2™ stayed switched off and oxygen was not used, but otherwise the setting was exactly the same as in the therapy night (patient with nasal cannula that was connected to the AIRVO 2™).

Batch number: not applicable (ambient air)

18. Criteria for evaluation: Efficacy, Safety

Primary outcome parameter:
Reduction of hypoxemic burden > 50% compared to baseline using oxygen-HFT versus placebo.

Secondary outcome parameters:
Changes in parameters listed below compared to baseline using oxygen-HFT versus placebo.

Polysomnography parameters	time in bed	min
	total sleep time	min
	sleep latency	min
	latency to S3	min
	S1 stadium/total sleep time	%
	S2 stadium/total sleep time	%
	S3 stadium/total sleep time	%
	REM sleep/total sleep time	%
	arousals/total sleep time	n
	respiratory arousals/total sleep time	n
	desaturation arousals/total sleep time	n
	average systolic blood pressure	mmHg
	average diastolic blood pressure	mmHg
	longest apnoea	s
	longest hypopnoea	s
	obstructive apnoea	h^{-1}
	mixed apnoea	h^{-1}
	central apnoea	h^{-1}
	obstructive hypopnoea	h^{-1}
	central hypopnoea	h^{-1}
	apnoea+hypopnoea total	h^{-1}
	Desaturations	h^{-1}
	time SaO_2 < 90%	%
	mean SaO_2	%
	lowest SaO_2	%
	mean desaturation	%
	cycle length	s
	ventilation length	s
	apnoea length	s
	circulatory delay	s
	time to peak ventilation	s
Blood sample parameters	BNP	pg/ml
	hs troponin I	pg/ml
Blood gas parameters	PaO_2	mmHg
	$PaCO_2$	mmHg
	SaO_2	%
	HCO_3	mmol/l
	ABE	mmol/l
	pH	
	transcutaneously measured pCO_2	mmHg
Hemodynamic assessment parameters	Cardiac output (CO)	l/min
	Cardiac index (CI)	l/min/m²
	Stroke volume (SV)	ml/beat
	Stroke volume index (SVI)	ml/beat/m²
	Stroke volume variation (SVV)	
	Systemic vascular resistance (SVR)	dynes*s/cm^5
	Systemic vascular resistance index (SVRI)	dynes*s/cm^5/m²
	Systolic and diastolic blood pressure	mmHg
	Mean arterial pressure	mmHg

Safety analysis:
see item 19. below

19. Statistical Methods

Analysis of the primary outcome parameter:
Assuming a two-sided significance level of 5 (alpha) and 90 (beta) percent of power, and an effect-size of 0.6 a sample size of at least 20 patients was calculated to be required to detect a reduction in hypoxemic burden (oxygen saturation < 90%) of 50% given a baseline hypoxemic burden of about 50% 15 and an Omega of 20.
In order to account for roughly 20% of patients who would not complete the therapy/placebo nights after randomization the study was intended to randomize a total of 25 patients to maintain 20 evaluable patients.
The primary method of analysis was an intention-to-treat analysis. As a pre-specified sub-analysis we aimed to analyse patients with an HFT usage of > 5 h during the study night as well as patients with a sleep efficiency of > 80% on the HFT study night.
It was intended to perform statistical analysis using SigmaPlot software (Version 12, Systat, Germany). Effects of oxygen-HFT versus placebo on primary and secondary endpoints were to be analysed by Anova for repeated measures after checking for normal distribution using the Shapiro-Wilk test. If no normal distribution was found, Anova on ranks test were to be performed. A p-value of < 0.05 was considered significant.

Analysis of the secondary outcome parameters:
The secondary outcome parameters were intended to be analyzed using the same statistical methods used for the primary outcome parameter.
All the secondary outcome parameter analyses were exploratory in nature and were intended to be tested at 0.05 significant level.

Safety analysis:
Safety data included adverse events, primary safety endpoints, and data for other safety evaluations.
Safety data were collected on all randomized patients.
Alert ranges:
More than three severe adverse events which were assessed as related to study drug would have led to an immediate stop of the study.
Examples:

- Hemodynamic instability (MAP < 55 mmHg or > 140 mmHg)
- Malignant arrhythmias
- Cardiac decompensation
- Other adverse hemodynamic effects
- Severe blood pressure drops
- Oxygen saturation was too low, defined as < 91% for more than 60 min in a row
- Oxygen saturation was too high, defined as > 98% for more than 60 min in a row

20. Adverse Events observed in the Study

Pat. ID	Event No.	Description	Treatment and Action	Timepoint of Occurrence	AE Type and SAE Criteria	Outcome	Relation to Study Drug
01	1	Bradycar-dia	Reduction of beta-blocker dose	between therapy night and placebo night	AE	resolved	no
01	2	Hypoten-sion	Reduction of beta-blocker dose	between therapy night and placebo night	AE	resolved	no
01	3	INR value not in therapeutic range	Adjustment of INR value under overlapping heparin treatment	after the last in-patient study night	SAE (prolonga-tion of hospitaliza-tion)	resolved	no
07	1	Non-sustained ventricular tachycardia	None	during the first (diagnostic) in-patient study night	AE	resolved	no
11	1	Worsening of heart failure	Increase of heart failure medication; orthotopic heart transplanta-tion on 27.09.2017	between discharge and 30 days follow-up	SAE (new hospitali-zation; life-threatening illness)	ongoing	no

21. Protocol Deviations

- Patient 01 did not perform a CPX test before enrollment due to an already known reduced cardiopulmonary exercise capacity. This was reported to the Ethics Committee on 21.02.2017.
- The randomization was routinely not performed before (as described in Studienprotokoll Version 1.2 vom 10.10.2016 under which all patients were enrolled), but after the first (diagnostic) study night. This procedure was accordingly amended in Studienprotokoll Version 1.3 vom 11.10.2017.
- The administration of placebo was not performed as described in Studienprotokoll Version 1.2 vom 10.10.2016 due to technical reasons. In Studienprotokoll Version 1.3 vom 11.10.2017 this procedure was accordingly amended (as outlined in item 17.).

22. Summary - Conclusions: Efficacy Results, Safety Results, Conclusion

Efficacy Results:

Since the number of patients that could be randomized before the study was stopped was too small, no efficacy results could be obtained.

Safety Results:

The clinical information summarized in this report does not require changing the benefit/risk assessment as outlined in the study protocol.

Conclusion:

Due to the early termination this study did not reach its intended objectives.

23. Date of Report

19 November 2018