2 SYNOPSIS

<table>
<tr><td colspan="2">TITLE OF THE STUDY:
A single centre, exploratory, phase II, cross-over, randomised trial, evaluating the effect of spontaneously breathing Helium/Oxygen 65%/35%, to either spontaneously breathing Nitrogen/Oxygen 65%/35% or Non-Invasive Ventilated Nitrogen/Oxygen 65%/35% on the Six-Minute Walking Distance in severe COPD patients</td></tr>
<tr><td colspan="2">INVESTIGATOR(S):
Dr. med. Jens Geiseler, Germany</td></tr>
<tr><td colspan="2">STUDY CENTRE(S):
Asklepios Fachkliniken, München-Gauting, Germany</td></tr>
<tr><td colspan="2">PUBLICATION (REFERENCE):
Not applicable.</td></tr>
<tr><td>STUDY PERIOD (YEARS):
Date of first enrolment: 10 October 2010
Date of last completed: 15 March 2011
(study closure due to low recruitment)</td><td>PHASE OF DEVELOPMENT:
Phase II</td></tr>
<tr><td colspan="2">OBJECTIVES:
Primary objective:
To evaluate the distance walked by patients with severe Chronic Obstructive Pulmonary Disease (COPD) during a Six-Minute Walk Test (6MWT) while breathing Helium/Oxygen 65%/35% compared to either breathing Nitrogen/Oxygen 65%/35% or receiving Medicinal Oxygen 100% (Non-Invasive Ventilation (NIV) with a F_IO_2 of 0.35).</td></tr>
<tr><td colspan="2">METHODOLOGY:
Single centre, exploratory, randomised, open, cross-over study.</td></tr>
<tr><td colspan="2">NUMBER OF SUBJECTS (PLANNED AND ANALYZED):
Planned:
24 evaluable patients.
Analyzed:
2 patients completed the study,
1 patient discontinued after Visit 2.</td></tr>
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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Inclusion criteria: - Male or female aged ≥ 45 and ≤ 75 years old, - Patient with documented clinical diagnosis of stage III/IV COPD *(according to GOLD 2008 guidelines)*, - Patient with stable COPD defined by no significant increase in COPD medication, no treatment for COPD in an emergency, no acute intensive care setting and no intake of antibiotics in the four weeks prior to selection *(Visit 0)*, - Current or ex-smoker with a smoking history of 10 pack-years or more, - Patient treated on a regular basis with NIV for hypercapnia, - Patient having dated and signed his/her written informed consent after full explanation of the study by the investigator, prior to participation
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NO. Helium/Oxygen 65%/35% (Batch No. 80017999) Nitrogen/Oxygen 65%/35% (Batch No. 80018999) Medicinal Oxygen 100% (Non-Invasive Ventilation [NIV] with a F_IO_2 of 0.35) (Batch No. 80020999)
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NO. Not applicable.
DURATION OF TREATMENT: Total planned study duration for one individual was up to one month maximum after Visit 0.

CRITERIA FOR EVALUATION:

Pharmacokinetic parameters (if applicable):

Not applicable.

Efficacy:

Primary efficacy:

Six-Minute Walking Distance measured while breathing Helium/Oxygen 65%/35% compared to its measurement on either breathing Nitrogen/Oxygen 65%/35% or receiving NIV with a F_IO_2 of 0.35

Secondary efficacy:

- Dyspnoea and leg fatigue evaluated with the modified Borg scale,
- Premature definitive discontinuation of the 6MWT,
- Pulmonary function parameters,
- Arterialised capillary blood gases,

Safety:

Safety variables included AEs, pulse rate, oxygen saturation, blood pressure, respiration rate, electrocardiogram (ECG), and physical examination.

STATISTICAL METHODS:

Considering the small number of patients it was agreed with the sponsor that the analysis of the primary and secondary efficacy parameters as stated in the protocol will not be performed.

It was agreed by the sponsor to display only listings for primary and secondary parameters, as well as for safety parameters.

SUMMARY - CONCLUSIONS

Pharmacokinetic results

Not applicable.

Efficacy results:

From the limited data available from this study, it is not possible to make conclusions regarding the efficacy objectives.

Safety results:

No adverse events and no serious adverse events were reported during the study. There were no withdrawals due to AEs.

No clinically relevant findings or clinically relevant changes from Baseline in vital signs and physical examinations were observed during the study. There were no clinically relevant changes in ECG identified.

Date of the report: 30 April 2012