



## Clinical trial results:

**Oxygen therapy for cluster headache. A mask comparison trial. A single-blinded, placebo-controlled, crossover study.**

### Summary

EudraCT number	2011-006182-18
Trial protocol	DK
Global end of trial date	06 February 2016

### Results information

Result version number	v1 (current)
This version publication date	12 August 2016
First version publication date	12 August 2016

### Trial information

#### Trial identification

Sponsor protocol code	15.12.12
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01589588
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Danish Headache Center
Sponsor organisation address	nordre ringvej 57, glostrup, Denmark, 2600
Public contact	Mads Barloese, Danish Headache Center, 45 38632062, GLO-hovedpine@regionh.dk
Scientific contact	Mads Barloese, Danish Headache Center, 45 38632062, GLO-hovedpine@regionh.dk

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	06 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2016
Global end of trial reached?	Yes
Global end of trial date	06 February 2016
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

This study will investigate the possible difference in treatment effect between three different oxygen delivery systems in the acute treatment of cluster headaches

Protection of trial subjects:

All adverse events throughout the study will be recorded. All adverse events will be categorized as serious or non-serious, expected or not expected and the relationship with masks and treatment and placebo given. In assessing whether an adverse reaction expected or not expected we will use the product resume of Airapy and Oxygen AGA.

The experiment is reported to the GCP-unit Region capital as follows with announced and unannounced visits. The trial is blind. A key so that it can always be seen what treatment the patient has received when. If the patient experiences unpleasant side-effects of one of the masks he can use his usual attack treatment after 15 minutes. The trial takes place in a hospital where there is immediate access to medical expertise. It is possible to immediately unblinding of the study using randomiseringsnøglen located at trial site.

Conducted a clinical report form (CRF) for each patient throughout the study. This is designed according GCP unit guidelines

Background therapy:

preventive medication was stable one week prior to inclusion and during the trial. Patients were allowed rescue medication after 15 minutes of trial therapy,

Evidence for comparator:

High flow oxygen is known to relief patients within 15 minutes (cohen 2009) and a small open label study showed that DVO might be more efficient than high flow oxygen, rozen 2011

Actual start date of recruitment	01 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

Notes:

### Subjects enrolled per age group

In utero	0
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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)	57
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

We included 57 CH patients from the Danish Headache Center, a tertiary headache center, between June 2012 and December 2014. Hereof, 31 CH patients also participated in an inpatient sleep study (Project ID: H-2-2012-016). Twenty-six CH-patients participated only in the mask comparison trial.

### Pre-assignment

Screening details:

The inclusion criteria were age between 18 and 65 years; CH diagnosis according to International Classification of Headache Disorders, second edition (ICHD-II) criteria ; regular attack and cluster frequency for at least two years; average attack frequency of two to eight attacks per day prior to inclusion; cluster duration of more than two weeks;

### Pre-assignment period milestones

Number of subjects started	57
Number of subjects completed	10 <sup>[1]</sup>

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	not enough attacks: 45
Reason: Number of subjects	latex allergy: 1
Reason: Number of subjects	Protocol deviation: 1

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.

Justification: 57 patients were enrolled. 42 patients had attacks. The trial is 4 way cross over.

### Period 1

Period 1 title	baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Patients were blinded for gas type and not mask type. Author MB generated the random sequence with the Microsoft Excel SLUMP function. The list was kept in the trial master file during the trial. Blinding of the mask type currently used was deemed impossible but patients were blinded to the contents of the gas cylinders. The gas cylinders were exactly the same size and covered with black plastic wrapping during the trial. A sticker with the numbers 1–4 distinguished the cylinders

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	DVO Demand valve oxygen

Arm description:

Demand Valve oxygen

Arm type	Active comparator
Investigational medicinal product name	Conoxia,
Investigational medicinal product code	
Other name	Oxygen, 100%
Pharmaceutical forms	Gas and solvent for dispersion for injection/infusion
Routes of administration	Inhalation use

Dosage and administration details:

according to RR and TV

<b>Arm title</b>	Optimask
Arm description: Optimask	
Arm type	Active comparator
Investigational medicinal product name	Conoxia,
Investigational medicinal product code	
Other name	Oxygen, 100%
Pharmaceutical forms	Gas and solvent for dispersion for injection/infusion
Routes of administration	Inhalation use
Dosage and administration details: 15 L/min	
<b>Arm title</b>	Simple Mask
Arm description: Simple mask	
Arm type	Active comparator
Investigational medicinal product name	Conoxia,
Investigational medicinal product code	
Other name	Oxygen, 100%
Pharmaceutical forms	Gas and solvent for dispersion for injection/infusion
Routes of administration	Inhalation use
Dosage and administration details: 15 L/min	
<b>Arm title</b>	Placebo
Arm description: Place with DVO	
Arm type	Placebo
Investigational medicinal product name	AIRAPY
Investigational medicinal product code	
Other name	eq air
Pharmaceutical forms	Gas and solvent for dispersion for injection/infusion
Routes of administration	Inhalation use
Dosage and administration details: Accodring to RR and TV	

<b>Number of subjects in period 1</b>	DVO Demand valve oxygen	Optimask	Simple Mask
Started	31	32	28
Completed	31	32	28

<b>Number of subjects in period 1</b>	Placebo
Started	11
Completed	11



## Baseline characteristics

### Reporting groups

Reporting group title	baseline
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Reporting group description:

57 patients included in trial

Reporting group values	baseline	Total	
Number of subjects	57	57	
Age categorical			
mean 45 years, range 21-65			
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)	57	57	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age (years)			
Units: years			
arithmetic mean	45		
full range (min-max)	21 to 65	-	
Gender categorical			
gender			
Units: Subjects			
Female	15	15	
Male	42	42	
Chronic or episodic type			
Chronic=CCH Episodic=ECH			
Units: Subjects			
CCH	26	26	
ECH	31	31	

## End points

### End points reporting groups

Reporting group title	DVO Demand valve oxygen
Reporting group description: Demand Valve oxygen	
Reporting group title	Optimask
Reporting group description: Optimask	
Reporting group title	Simple Mask
Reporting group description: Simple mask	
Reporting group title	Placebo
Reporting group description: Place with DVO	

### Primary: Two-point reduction on a five-point rating scale

End point title	Two-point reduction on a five-point rating scale
End point description: The primary endpoint was a two-point reduction on a five-point rating scale within 15 minutes (min).	
End point type	Primary
End point timeframe: 15 minutes	

End point values	DVO Demand valve oxygen	Optimask	Simple Mask	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	28	11
Units: effekt/no effect				
Effect	16	14	11	5
No effect	15	18	17	6

Attachments (see zip file)	FIGUR 4.xlsx
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### Statistical analyses

Statistical analysis title	logistic reg
Comparison groups	Optimask v Simple Mask v DVO Demand valve oxygen v Placebo



Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.411 <sup>[2]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Notes:

[1] - After 15min of therapy, the percentage of patients that were either pain free or had a two-point decrease on the five-point rating scale was 40%, 44% and 52% on the SM, OM and DVO, respectively (Figure 4). We completed a logistic analysis of all attacks for the primary outcome regarding pain relief within 15min of oxygen therapy, but could not show any significant differences (p=0.411).

[2] - non sig

## Secondary: Mask preference

End point title	Mask preference <sup>[3]</sup>
End point description: Only patients who tried all three mask types.	
End point type	Secondary
End point timeframe: no time frame	

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: We only included patient in this analysis who had tried all three mask types

End point values	DVO Demand valve oxygen	Optimask	Simple Mask	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	21	21	
Units: percentage				
first preference.	62	33	5	

## Statistical analyses

Statistical analysis title	patient preference
Comparison groups	Simple Mask v Optimask v DVO Demand valve oxygen
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	< 0.001 <sup>[5]</sup>
Method	Chi-squared

Notes:

[4] - The majority of the CH patients preferred DVO (62%) and only 5% preferred the SM (p< 0.001). The remaining 33% favored the OM (p=0.061, compared to DVO) (Table 3). Only patients who tried all three mask types were included in this analysis (n=21).

[5] - significant

## Post-hoc: First attack Analysis

End point title	First attack Analysis <sup>[6]</sup>
End point description: We tested for informative drop-out by means of a logistic regression model for the risk of more than one attack with respect to the mask used during the first attack. In addition, we tested the association	

between the mask used during the first attack and completion of the crossover study by logistic regression.

To eliminate the possible carry-over effect, we conducted a post hoc comparative cross-sectional analysis, where only the first treated attack was included. Since this was the first attack, the randomization was intact and the risk of bias was minimized.

End point type	Post-hoc
End point timeframe:	
15 min	

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: we only included the first attack, not the second, third or fourth. This was due to risk of unequal distribution and to short a wash out period.

End point values	DVO Demand valve oxygen	Optimask	Simple Mask	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	14	13	
Units: effect, no-effect				
effect	9	3	3	
no effect	6	11	10	

## Statistical analyses

Statistical analysis title	first attack
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Statistical analysis description:

The analysis of the first attack contains 42 CH attacks (Figure 3). The DVO was significantly better than the OM at treating the CH attacks on the five-point rating scale at 15min with an OR of 5.5 ( $p=0.042$ ). The DVO was borderline better than the SM with an OR of 5.0 ( $p=0.056$ ). There was no difference between SM and OM ( $p=0.918$ ). Pooling the data and comparing the DVO to both SM and OM, the DVO is significantly better ( $p=0.018$ ).

Comparison groups	DVO Demand valve oxygen v Optimask v Simple Mask
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.018
Method	Regression, Logistic

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14 days

Adverse event reporting additional description:

Four adverse events happened after the trial, including one serious, but all were assessed to be unrelated to oxygen therapy.

Assessment type	Systematic
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### Dictionary used

Dictionary name	gcp manual
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Dictionary version	1.0
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### Reporting groups

Reporting group title	total population
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Reporting group description:

only 42 patients received trial therapy.

Serious adverse events	total population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
thopping chest pain	Additional description: One patient developed throbbing chest pain one week after oxygen inhalation but the cardiac follow-up was negative (ECG, troponins and heart CT).		
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	total population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 42 (7.14%)		
General disorders and administration site conditions			
Influenza			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
nose bleed	Additional description: nosebleed one week after inhalation		

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
increase in headache frequency	Additional description: increased frequency. Interpreted as normal fluctuation of disease		
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2013	Inclusion of more patients and extension of trial period.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

patients did not suffer from four attacks and therefor the cross over is not complete and a peer protocol analysis is not possible.
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Notes: