



## Clinical trial results:

### Palliation of dyspnea with morphine in patients with interstitial lung disease

#### Summary

EudraCT number	2015-002533-22
Trial protocol	DK
Global end of trial date	06 February 2019

#### Results information

Result version number	v1 (current)
This version publication date	20 February 2020
First version publication date	20 February 2020

#### Trial information

##### Trial identification

Sponsor protocol code	EB-1
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02622022
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus C, Denmark,
Public contact	Dept of respiratory diseases, Aarhus University Hospital, karbends@rm.dk
Scientific contact	Dept of respiratory diseases, Aarhus University Hospital, karbends@rm.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	01 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2019
Global end of trial reached?	Yes
Global end of trial date	06 February 2019
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To investigate if morphine hydrochloride administered for 7 days is safe and attenuates dyspnea in patients with interstitial lung disease and dyspnea

Protection of trial subjects:

All patients were provided with a prescription of macrogol to counteract constipation

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Denmark: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

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**Subjects enrolled per age group**

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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)	5
From 65 to 84 years	30
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Fibrotic interstitial lung disease

### Period 1

Period 1 title	Intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Morphine

Arm description:

Morphine oral drops 5 mg 4 times daily + 5 mg max. 4 times daily

Arm type	Experimental
Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

5 drops four times daily

<b>Arm title</b>	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

5 drops four times daily

<b>Number of subjects in period 1</b>	Morphine	Placebo
Started	18	18
Completed	17	18
Not completed	1	0
Adverse event, non-fatal	1	-



## Baseline characteristics

### Reporting groups

Reporting group title	Morphine
Reporting group description:	
Morphine oral drops 5 mg 4 times daily + 5 mg max. 4 times daily	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Morphine	Placebo	Total
Number of subjects	18	18	36
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)	2	3	5
From 65-84 years	16	14	30
85 years and over	0	1	1
Age continuous			
Units: years			
median	72.5	75	
inter-quartile range (Q1-Q3)	70 to 80	73 to 78	-
Gender categorical			
Units: Subjects			
Female	3	3	6
Male	15	15	30

## End points

### End points reporting groups

Reporting group title	Morphine
Reporting group description: Morphine oral drops 5 mg 4 times daily + 5 mg max. 4 times daily	
Reporting group title	Placebo
Reporting group description: -	

### Primary: change in VAS dyspnea score during last week

End point title	change in VAS dyspnea score during last week
End point description:	
End point type	Primary
End point timeframe: One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: cm				
arithmetic mean (standard error)	-1.1 ( $\pm$ 0.33)	-0.35 ( $\pm$ 0.46)		

### Statistical analyses

Statistical analysis title	t-test
Comparison groups	Placebo v Morphine
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	t-test, 2-sided

### Secondary: Change in VAS cough during last week

End point title	Change in VAS cough during last week
End point description:	
End point type	Secondary
End point timeframe: One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: cm				
arithmetic mean (standard error)	-0.15 ( $\pm$ 0.24)	-0.07 ( $\pm$ 0.34)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in 6 minute walk test

End point title	Change in 6 minute walk test
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: m				
arithmetic mean (standard error)	10 ( $\pm$ 9)	5 ( $\pm$ 6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Respiratory rate

End point title	Change in Respiratory rate
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: / minute				
arithmetic mean (standard error)	-0.8 ( $\pm$ 1.1)	2.6 ( $\pm$ 1.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: PaO2

End point title	PaO2
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: kPA				
median (inter-quartile range (Q1-Q3))	-0.6 (-1.3 to 0.9)	-0.2 (-0.8 to 1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in PaCO2

End point title	Change in PaCO2
End point description:	
End point type	Secondary
End point timeframe:	
One week	



End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Kpa				
arithmetic mean (standard error)	0.2 ( $\pm$ 0.1)	0.02 ( $\pm$ 0.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in systolic blood pressure

End point title	Change in systolic blood pressure
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: mmHg				
arithmetic mean (standard error)	1.2 ( $\pm$ 4.9)	0.1 ( $\pm$ 2.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in respiratory rate

End point title	Change in respiratory rate
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: pr minute				
arithmetic mean (standard error)	-0.8 ( $\pm$ 1.1)	2.6 ( $\pm$ 1.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Heart rate

End point title	Change in Heart rate
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: pr minute				
arithmetic mean (standard error)	-2.1 ( $\pm$ 2.5)	-5.2 ( $\pm$ 2.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in KBILD score

End point title	Change in KBILD score
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: points				
arithmetic mean (standard error)	2.9 ( $\pm$ 1.6)	1.6 ( $\pm$ 1.5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Leicester cough score

End point title	Change in Leicester cough score
End point description:	
End point type	Secondary
End point timeframe:	
One week	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: points				
arithmetic mean (standard error)	1.2 ( $\pm$ 0.4)	0.2 ( $\pm$ 0.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in GAD score

End point title	Change in GAD score
End point description:	
End point type	Secondary
End point timeframe:	
One week	

<b>End point values</b>	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: Points				
arithmetic mean (standard error)	-0.4 (± 0.7)	-0.6 (± 0.8)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

One week

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	Morphine
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Morphine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Morphine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)	11 / 18 (61.11%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 18 (27.78%)	5 / 18 (27.78%)	
occurrences (all)	5	5	
Dizziness			
subjects affected / exposed	12 / 18 (66.67%)	8 / 18 (44.44%)	
occurrences (all)	12	8	
Confusional arousal			
subjects affected / exposed	7 / 18 (38.89%)	2 / 18 (11.11%)	
occurrences (all)	7	2	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	7 / 18 (38.89%)	2 / 18 (11.11%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	8 / 18 (44.44%)	4 / 18 (22.22%)	
occurrences (all)	8	4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported