Clinical trial results:
Morphine for palliative treatment of refractory dyspnea in patients with advanced COPD: benefits and respiratory adverse effects

Summary

EudraCT number	2014-004899-35
Trial protocol	NL
Global end of trial date	03 June 2019

Results information

Result version number	v1 (current)
This version publication date	12 June 2021
First version publication date	12 June 2021

Trial information

Trial identification

Sponsor protocol code	MORDYC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02429050
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Maastricht University
Sponsor organisation address	Universiteitssingel 40, Maastricht, Netherlands, 6229 ER
Public contact	D. Janssen, Centre of expertise for palliative care, Maastricht UMC+, daisy.janssen@mumc.nl
Scientific contact	D. Janssen, Centre of expertise for palliative care, Maastricht UMC+, daisy.janssen@mumc.nl

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	03 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2019
Global end of trial reached?	Yes
Global end of trial date	03 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1.1) to study whether and to what extent oral administration of morphine SR improves health-related quality of life among patients with advanced COPD;
1.2) to explore whether and to what extent oral administration of morphine SR leads to adverse respiratory effects in patients with advanced COPD.

Protection of trial subjects:

Patients are monitored by a strict schedule with weekly contacts. The burden of side effects is minimized by prescribing laxatives and anti-emetics.

Background therapy:

Patients were optimally treated for COPD, including at least LAMA-LABA therapy.

Evidence for comparator: -

Actual start date of recruitment	01 May 2015
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	Netherlands: 111
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	48
From 65 to 84 years	62

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment period: November 2016 to February 2019
Number of recruited patients: 124
Country of recruitment: Netherlands
Setting of recruitment: 1 pulmonary rehabilitation center and 2 general hospitals

Pre-assignment

Screening details:

Screening criteria: diagnosis of COPD, optimal (non)pharmacological treatment, mMRC grade 2-4, no contra-indication for morphine, no history of substance misuse, no recent exacerbation of COPD.
assessed for eligibility: 1380
eligible: 464 (declined to participate due to burden project, fear of adverse effects)
randomized: 124

Period 1

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

Blinding implementation details:

Randomization was performed by a web-based random number generator using minimization and stratification for age (<55 years; 55-65 years; 65-75 years; or>75 years) and mMRC grade.

Arms

Are arms mutually exclusive?	Yes
Arm title	morphine

Arm description:

morphine treatment

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

Dosage and administration details:

dosage: 10 mg
administration frequency: 2-3 times a day with 18-2 hours in between.

Arm title	placebo

Arm description: -

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

Dosage and administration details:

placebo

Number of subjects in period 1	morphine	placebo
Started	54	57
Completed	44	51
Not completed	10	6
Consent withdrawn by subject	1	-
Adverse event, non-fatal	5	1
acute exacerbation of COPD	2	3
Lack of efficacy	1	-
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	morphine
Reporting group description: morphine treatment	
Reporting group title	placebo
Reporting group description: -	

Reporting group values	morphine	placebo	Total
Number of subjects	54	57	111
Age categorical Units: Subjects			
Adults (18-64 years)	25	23	48
From 65-84 years	29	33	62
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	65.0	65.7	
standard deviation	± 8.0	± 8.0	-
Gender categorical Units: Subjects			
Female	26	25	51
Male	28	32	60
Current smoking Units: Subjects			
yes	7	7	14
no	47	50	97
mMRC grade Units: Subjects			
grade 2	31	31	62
grade 3	20	19	39
grade 4	3	7	10
Body Mass Index Units: kg/m2			
arithmetic mean	27.6	27.2	
standard deviation	± 6.6	± 5.3	-
Pack-years Units: years			
median	40	40	
inter-quartile range (Q1-Q3)	29.8 to 51.3	30 to 50	-
exacerbations <12 months Units: number			
median	2	2	
inter-quartile range (Q1-Q3)	1 to 4	0 to 3.5	-
hospital admissions <12 months Units: number			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 1	0 to 1	-

FEV1			
Units: liters			
median	0.99	0.95	
inter-quartile range (Q1-Q3)	0.71 to 1.31	0.64 to 1.25	-

Subject analysis sets

Subject analysis set title	subgroup - morphine
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients with mMRC grade 3 or 4 at baseline in the morphine arm

Subject analysis set title	subgroup - placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients with mMRC grade 3 or 4 at baseline in the placebo arm

Reporting group values	subgroup - morphine	subgroup - placebo	
Number of subjects	23	26	
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	13	
From 65-84 years	16	12	
85 years and over	0	1	
Age continuous			
Units: years			
arithmetic mean	66.6	64.5	
standard deviation	± 8.1	± 9.0	
Gender categorical			
Units: Subjects			
Female	11	14	
Male	12	12	
Current smoking			
Units: Subjects			
yes	3	4	
no	20	22	
mMRC grade			
Units: Subjects			
grade 2	0	0	
grade 3	20	19	
grade 4	3	7	
Body Mass Index			
Units: kg/m2			
arithmetic mean	27.5	26.1	
standard deviation	± 6.1	± 6.2	
Pack-years			
Units: years			
median	40	40	
inter-quartile range (Q1-Q3)	30 to 50	27.8 to 56.3	
exacerbations <12 months			
Units: number			
median	3	4	

inter-quartile range (Q1-Q3)	2 to 4	1 to 4	
hospital admissions <12 months			
Units: number			
median	1	0	
inter-quartile range (Q1-Q3)	0 to 1	0 to 1	
FEV1			
Units: liters			
median	0.87	0.88	
inter-quartile range (Q1-Q3)	0.66 to 1.02	0.58 to 1.18	

End points

End points reporting groups	
Reporting group title	morphine
Reporting group description: morphine treatment	
Reporting group title	placebo
Reporting group description: -	
Subject analysis set title	subgroup - morphine
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup of patients with mMRC grade 3 or 4 at baseline in the morphine arm	
Subject analysis set title	subgroup - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup of patients with mMRC grade 3 or 4 at baseline in the placebo arm	

Primary: CAT score	
End point title	CAT score
End point description: mean change from baseline	
End point type	Primary
End point timeframe: assessed at 1, 2 and 4 weeks	

End point values	morphine	placebo	subgroup - morphine	subgroup - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	57	23	26
Units: score				
arithmetic mean (standard error)	-3.17 (± 0.73)	-1.00 (± 0.68)	-3.10 (± 1.12)	-1.95 (± 1.03)

Statistical analyses

Statistical analysis title	total study population
Comparison groups	morphine v placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.14
upper limit	-0.22
Variability estimate	Standard error of the mean

Statistical analysis title	subgroup analysis
Comparison groups	subgroup - morphine v subgroup - placebo
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.44
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.17
upper limit	1.84
Variability estimate	Standard error of the mean

Primary: PaCO2

End point title	PaCO2
End point description:	

End point type	Primary
End point timeframe:	
assessed at 4 weeks	

End point values	morphine	placebo	subgroup - morphine	subgroup - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	57	23	26
Units: mmHg				
arithmetic mean (standard error)	1.80 (± 1.43)	0.68 (± 1.35)	3.00 (± 2.40)	1.43 (± 2.18)

Statistical analyses

Statistical analysis title	total study population
Comparison groups	morphine v placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.55
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	5.07
Variability estimate	Standard error of the mean

Statistical analysis title	subgroup analysis
Comparison groups	subgroup - placebo v subgroup - morphine
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.59
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.95
upper limit	8.64
Variability estimate	Standard error of the mean

Secondary: PaO2	
End point title	PaO2
End point description:	

End point type	Secondary
End point timeframe:	
assessed at 4 weeks	

End point values	morphine	placebo	subgroup - morphine	subgroup - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	57	23	26
Units: mmHg				
arithmetic mean (standard error)	-2.48 (± 2.18)	0.98 (± 2.02)	-3.30 (± 3.53)	2.63 (± 3.23)

Statistical analyses

Statistical analysis title	total study population
Comparison groups	placebo v morphine
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	2.12
Variability estimate	Standard error of the mean

Statistical analysis title	subgroup analysis
Comparison groups	subgroup - morphine v subgroup - placebo
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.23
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.73
upper limit	3.9
Variability estimate	Standard error of the mean

Secondary: respiratory rate	
End point title	respiratory rate

End point description:

End point type	Secondary

End point timeframe:
assessed at 1, 2 and 4 weeks

End point values	morphine	placebo	subgroup - morphine	subgroup - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	57	23	26
Units: rate				
arithmetic mean (standard error)	-1.43 (± 0.51)	0.02 (± 0.48)	-1.47 (± 0.77)	-0.73 (± 0.71)

Statistical analyses

Statistical analysis title	total study population
Comparison groups	morphine v placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.04
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	-0.09
Variability estimate	Standard error of the mean

Statistical analysis title	subgroup analysis
Comparison groups	subgroup - morphine v subgroup - placebo
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.49
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	1.34
Variability estimate	Standard error of the mean

Secondary: Mean breathlessness 24 h

End point title	Mean breathlessness 24 h
End point description:	
End point type	Secondary
End point timeframe:	
Assessed at 2 days, 1, 2, 3 and 4 weeks	

End point values	morphine	placebo	subgroup - morphine	subgroup - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	57	23	26
Units: Numeric Rating Score				
arithmetic mean (standard error)	-0.65 (± 0.35)	-0.05 (± 0.33)	-1.13 (± 0.54)	0.17 (± 0.50)

Statistical analyses

Statistical analysis title	total study population
Comparison groups	morphine v placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.21
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.55
upper limit	0.35
Variability estimate	Standard error of the mean

Statistical analysis title	subgroup analysis

Comparison groups	subgroup - morphine v subgroup - placebo
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.08
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	0.17
Variability estimate	Standard error of the mean

Secondary: Worst breathlessness 24 h

End point title	Worst breathlessness 24 h
End point description:	
End point type	Secondary
End point timeframe:	
Assessed at 2 days, 1, 2, 3 and 4 weeks	

End point values	morphine	placebo	subgroup - morphine	subgroup - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	54	57	23	26
Units: Numeric Rating Score				
arithmetic mean (standard error)	-0.50 (± 0.31)	0.09 (± 0.30)	-0.85 (± 0.44)	0.46 (± 0.40)

Statistical analyses

Statistical analysis title	total study population
Comparison groups	morphine v placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.19
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	0.28
Variability estimate	Standard error of the mean

Statistical analysis title	subgroup analysis
Comparison groups	subgroup - morphine v subgroup - placebo
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.03
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.16
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 1 November 2016 - 3 June 2019	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0
Reporting groups	
Reporting group title	morphine
Reporting group description: morphine treatment	
Reporting group title	placebo
Reporting group description: -	

Serious adverse events	morphine	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 54 (1.85%)	2 / 57 (3.51%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 54 (1.85%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	morphine	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 54 (79.63%)	40 / 57 (70.18%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 54 (50.00%)	21 / 57 (36.84%)	
occurrences (all)	27	21	
General disorders and administration site conditions			

Insomnia			
subjects affected / exposed	16 / 54 (29.63%)	23 / 57 (40.35%)	
occurrences (all)	16	23	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 54 (29.63%)	13 / 57 (22.81%)	
occurrences (all)	16	13	
Vomiting	Additional description: vomiting and retching		
subjects affected / exposed	8 / 54 (14.81%)	10 / 57 (17.54%)	
occurrences (all)	8	10	
Constipation			
subjects affected / exposed	25 / 54 (46.30%)	17 / 57 (29.82%)	
occurrences (all)	25	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2016	expansion of inclusion criteria from mMRC grade 3 or 4 to mMRC grade 2, 3 or 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32804188

http://www.ncbi.nlm.nih.gov/pubmed/26825021