



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 (\pm 0.73) | -1.00 (\pm 0.68) | -3.10 (\pm 1.12) | -1.95 (\pm 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 occurrences (all) | 16 / 54 (29.63%) 16 | 23 / 57 (40.35%) 23 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 16 / 54 (29.63%) 16 | 13 / 57 (22.81%) 13 | |
| Vomiting | Additional description: vomiting and retching | | |
| subjects affected / exposed occurrences (all) | 8 / 54 (14.81%) 8 | 10 / 57 (17.54%) 10 | |
| Constipation subjects affected / exposed occurrences (all) | 25 / 54 (46.30%) 25 | 17 / 57 (29.82%) 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>