



## Clinical trial results:

### Use of Methylnaltrexone for the Treatment of Opioid Induced Constipation & Gastro-Intestinal Stasis in Intensive Care Patients (MOTION)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-004687-37   |
| Trial protocol           | GB               |
| Global end of trial date | 28 February 2018 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 24 October 2018 |
| First version publication date | 24 October 2018 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 14SM2335 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN75305839 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Joint Research Compliance Office, Imperial College London  |
| Sponsor organisation address | Room 221, Medical School Building, St Mary's Campus, Norfolk Place, London, United Kingdom, W2 1PG |
| Public contact               | Parind Patel, Imperial College Healthcare NHS Trust, +44 2083831878, parind.patel@nhs.net          |
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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                       | 20 February 2018 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 24 November 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 February 2018 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of Methylnaltrexone in producing laxation in patients sedated with opioid infusions.

Protection of trial subjects:

All patients were treated in an intensive care unit with constant 1:1 nursing care to ensure safety and comfort, and minimise any distress.

Background therapy:

In order to ensure that patients were treated as early as possible we compared Methylnaltrexone to Placebo in the management of OIC, after 48 hours of not opening bowels but having been given regular laxatives. If bowels were not opened after 72 hours of randomisation into the trial, rescue laxatives as per local ICU policy, were administered.

Evidence for comparator:

Evidence to date suggests that Methylnaltrexone is beneficial in treating Opioid-Induced-Constipation (OIC) in patients when response to laxatives has not been sufficient. Constipation and gut dysfunction are a major concern in intensive care patients. There may also be additional benefits in reducing infection and immunosuppression, and hence an overall improvement in patient outcome.

The efficacy and safety of Methylnaltrexone in the treatment of OIC have been evaluated in two multicentre, randomised, double-blind, placebo-controlled phase III trials involving adults with advanced illness (life expectancy of 1 - 6 months) who were receiving palliative care. Patients maintained their usual laxative regimen and the primary endpoint was rescue-free laxation. Secondary endpoints included time to laxation, pain scores, opioid withdrawal symptoms and adverse events. The landmark published trial compared Methylnaltrexone with placebo. Methylnaltrexone improved the laxation rate within four hours of the first dose compared with placebo [48% vs. 15% ( $p < 0.001$ )]. Of the patients who did respond within four hours of the first dose, half responded within 30 minutes.

Case reports have also reported an immediate effect of Methylnaltrexone administration on bowel motility, with restored bowel function within 15 minutes of subcutaneous/intravenous injection. Finally, a retrospective chart review of 88 non-surgical critical care patients receiving Fentanyl infusions was conducted at the Hammersmith Hospital, Imperial College NHS Trust over a 10 week period in 2009. 15 patients met the criteria of constipation despite treatment with Senna and Sodium Docusate. Six of seven Methylnaltrexone patients responded to one or two doses with laxation within 24 hours versus 0/8 for conventional rescue therapy ( $p=0.001$ ). There were no adverse effects from either rescue laxative therapies.

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 14 September 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 | United Kingdom: 84 |
|--------------------------------------|--------------------|

|                                    |    |
|------------------------------------|----|
| Worldwide total number of subjects | 84 |
| EEA total number of subjects       | 84 |

Notes:

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### 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                       | 35 |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted in 4 ICUs within the UK with a target of recruiting 84 patients (allowing a drop out rate of 5%). The first patient was recruited on 14/09/2015 and the last patient was recruited on 15/07/2017, with a maximum follow up of 28 days in ICU.

### Pre-assignment

Screening details:

All patients who were clinically judged to potentially be constipated due to opioids, were screened against the inclusion and exclusion criteria to be eligible for the study. A total of 609 patients were screened in the study between 22/09/2015 and 15/07/2017.

### 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, Carer, Assessor, Subject |

Blinding implementation details:

Unblinded research nurses were responsible for randomising patients and administering the study drug. Blinded nurses were responsible for data entry and bedside nurses who cared for patients were also blinded.

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Methylnaltrexone |

Arm description:

Methylnaltrexone

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | Methylnaltrexone                      |
| Investigational medicinal product code |                                       |
| Other name                             | Methylnaltrexone Bromide              |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Patients weighing 38-61kg received 8mg (0.4mls) Methylnaltrexone diluted in 50mls Normal Saline and patients weighing 62-114kg received 12mg (0.6mls) diluted in 50mls Normal Saline.

In patients with severe renal impairment (creatinine clearance < 30ml/min), the dose of Methylnaltrexone administered was reduced to: 4mg (38-61kg) and 8mg (62-114kg).

Study drug was administered over 15 minutes via an indwelling intravenous catheter.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Normal Saline (Placebo) |
|------------------|-------------------------|

Arm description:

Normal Saline (Placebo)

|  |                         |
|--|-------------------------|
| Arm type                               | Placebo                 |
| Investigational medicinal product name | Normal Saline (Placebo) |
| Investigational medicinal product code |                         |
| Other name                             |                         |
| Pharmaceutical forms                   | Solution for infusion   |
| Routes of administration               | Intravenous use         |

Dosage and administration details:

Placebo (Normal Saline) was prepared in an exactly identical syringe to study drug, containing Normal Saline. Placebo was administered over 15 minutes via an indwelling intravenous catheter.

| <b>Number of subjects in period 1</b> | Methylnaltrexone | Normal Saline<br>(Placebo) |
|---------------------------------------|------------------|----------------------------|
| Started                               | 41               | 43                         |
| Completed                             | 39               | 43                         |
| Not completed                         | 2                | 0                          |
| Consent withdrawn by subject          | 2                | -                          |

## Baseline characteristics

### Reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title                                   | Methylnaltrexone        |
| Reporting group description:<br>Methylnaltrexone        |                         |
| Reporting group title                                   | Normal Saline (Placebo) |
| Reporting group description:<br>Normal Saline (Placebo) |                         |

| Reporting group values   | Methylnaltrexone | Normal Saline (Placebo) | Total |
|--|------------------|-------------------------|-------|
| Number of subjects   | 41               | 43                      | 84    |
| Age categorical<br>Units: Subjects   |                  |                         |       |
| Adults (18-64 years)   | 25               | 23                      | 48    |
| From 65-84 years   | 16               | 19                      | 35    |
| 85 years +   | 0                | 1                       | 1     |
| Age continuous<br>Units: years   |                  |                         |       |
| arithmetic mean  | 55.6             | 58.6                    |       |
| standard deviation   | ± 14.8           | ± 17.3                  | -     |
| Gender categorical<br>Units: Subjects  |                  |                         |       |
| Female   | 14               | 12                      | 26    |
| Male   | 27               | 31                      | 58    |
| Reason for ICU admission   |                  |                         |       |
| Medical (non operative) includes: respiratory, post cardiac arrest, head injury, multiple trauma, infection, neurologic, cardiovascular, drug overdose, haemorrhage, post respiratory arrest, seizure disorder, aspiration/poisoning/toxicities, COPD, cardiogenic shock, gastrointestinal, neoplasm and rhythm disturbance.<br>Surgical - emergency (operative) includes: cardiovascular, craniotomy, multiple trauma, head trauma, heart valve surgery, neurologic and respiratory.<br>Surgical - elective (operative) includes: heart valve surgery, respiratory and respiratory insufficiency. |                  |                         |       |
| Units: Subjects  |                  |                         |       |
| Medical (non operative)  | 31               | 34                      | 65    |
| Surgical - emergency (operative)   | 10               | 6                       | 16    |
| Surgical - elective (operative)  | 0                | 3                       | 3     |
| Type of opioid<br>Units: Subjects  |                  |                         |       |
| Fentanyl   | 29               | 35                      | 64    |
| Remifentanyl   | 9                | 7                       | 16    |
| Morphine   | 2                | 0                       | 2     |
| Remifentanyl until 1 hour before randomisation   | 0                | 1                       | 1     |
| Off opioids  | 1                | 0                       | 1     |
| Other sedatives  |                  |                         |       |
| Other sedatives include: propofol, midazolam, midazolam + propofol, midazolam + clonidine, propofol + clonidine, propofol + dexmedetomidine, ketamine  |                  |                         |       |
| Units: Subjects  |                  |                         |       |
| Other sedatives  | 34               | 36                      | 70    |
| None   | 7                | 7                       | 14    |

|   |              |              |    |
|---|--------------|--------------|----|
| Vasoactive drugs  |              |              |    |
| Vasoactive drugs include: noradrenaline, noradrenaline + vasopressin, noradrenaline + other, adrenaline, dobutamine, GTN, metaraminol, labetalol + hydralazine, noradrenaline + vasopressin + other, and other. |              |              |    |
| Units: Subjects   |              |              |    |
| Vasoactive drugs  | 25           | 27           | 52 |
| None  | 16           | 16           | 32 |
| Selective Digestive Decontamination (SDD)   |              |              |    |
| Units: Subjects   |              |              |    |
| None  | 37           | 33           | 70 |
| Selective Digestive Decontamination (SDD)   | 4            | 10           | 14 |
| Traumatic Brain Injury (TBI)  |              |              |    |
| Units: Subjects   |              |              |    |
| Traumatic Brain Injury (TBI)  | 8            | 7            | 15 |
| None  | 33           | 36           | 69 |
| Richmond Agitation Sedation Score (RASS)  |              |              |    |
| Units: number   |              |              |    |
| median  | -5.0         | -4.0         |    |
| inter-quartile range (Q1-Q3)  | -5.0 to -4.0 | -5.0 to -4.0 | -  |
| Total APACHE II Score   |              |              |    |
| Units: number   |              |              |    |
| arithmetic mean   | 18.0         | 18.2         |    |
| standard deviation  | ± 6.3        | ± 6.1        | -  |
| Baseline opioid dose - Fentanyl   |              |              |    |
| Units: mcg/h  |              |              |    |
| median  | 100          | 150          |    |
| inter-quartile range (Q1-Q3)  | 100 to 200   | 100 to 200   | -  |
| Baseline opioid dose - Remifentanyl   |              |              |    |
| Units: mcg/h  |              |              |    |
| median  | 480          | 158          |    |
| inter-quartile range (Q1-Q3)  | 292 to 684   | 96 to 301    | -  |

## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title                                   | Methylnaltrexone        |
| Reporting group description:<br>Methylnaltrexone        |                         |
| Reporting group title                                   | Normal Saline (Placebo) |
| Reporting group description:<br>Normal Saline (Placebo) |                         |

### Primary: Rescue-free laxation

|   |                      |
|---|----------------------|
| End point title   | Rescue-free laxation |
| End point description:<br>The primary outcome event is significant laxation (at least 100mls volume) without rescue laxatives being given. The time to rescue free laxation is measured from randomisation. For patients with no event, the observation is censored at the date rescue laxatives were given. If non were given, this was censored at 96 hours after randomisation. If the first laxation volume is not reported, it is assumed not be a significant laxation since non-significant laxations were not being reported. |                      |
| End point type  | Primary              |
| End point timeframe:<br>Rescue-free laxation within 96 hours of randomisation   |                      |

| End point values                     | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|--------------------------------------|------------------|-------------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed          | 39               | 43                      |  |  |
| Units: subjects                      |                  |                         |  |  |
| Rescue-free laxation within 96 hours | 12               | 15                      |  |  |
| Laxation after rescue laxatives      | 10               | 13                      |  |  |
| No laxation                          | 2                | 2                       |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Time to event                              |
| Statistical analysis description:<br>The null hypothesis is that there is no difference in time to rescue free laxation in the Methylnaltrexone and Placebo groups.<br>Allowing for a drop-out rate of 5% (patients who withdraw consent after regaining consciousness), with 42 subjects in each arm, this study had 85% power to detect a difference of 33% (48% vs, 15%) in the proportion of patients with rescue-free laxation within 12 hours at the 5% level (using a two-tailed log-rank test).<br>Stratified by ICU. |  |
| Comparison groups   | Methylnaltrexone v Normal Saline (Placebo) |



|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 82                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.22            |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.42              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.816             |
| upper limit                             | 2.461             |

## Secondary: Gastric Residual Volume (GRV)

|                        |                               |
|------------------------|-------------------------------|
| End point title        | Gastric Residual Volume (GRV) |
| End point description: |                               |
| End point type         | Secondary                     |
| End point timeframe:   |                               |
| Days 1-28 in ICU.      |                               |

| End point values                      | Methylnaltrexone  | Normal Saline (Placebo) |  |  |
|---------------------------------------|-------------------|-------------------------|--|--|
| Subject group type                    | Reporting group   | Reporting group         |  |  |
| Number of subjects analysed           | 39                | 43                      |  |  |
| Units: mls                            |                   |                         |  |  |
| median (inter-quartile range (Q1-Q3)) |                   |                         |  |  |
| GRV while on study drug               | 0.0 (0.0 to 40.0) | 0.0 (0.0 to 25.0)       |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Difference in GRV between treatments       |
| Comparison groups                       | Methylnaltrexone v Normal Saline (Placebo) |
| Number of subjects included in analysis | 82   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.05                                     |
| Method                                  | Wilcoxon (Mann-Whitney)                    |

## Secondary: Toleration of enteral feed

|                 |                            |
|-----------------|----------------------------|
| End point title | Toleration of enteral feed |
|-----------------|----------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1-28 in ICU.

| End point values                                | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|---|------------------|-------------------------|--|--|
| Subject group type                              | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed                     | 39               | 43                      |  |  |
| Units: days                                     |                  |                         |  |  |
| No. days enteral feed data available/applicable | 531              | 707                     |  |  |
| No. days full enteral feed achieved             | 174              | 225                     |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Difference in target enteral feed          |
| Comparison groups                       | Methylnaltrexone v Normal Saline (Placebo) |
| Number of subjects included in analysis | 82   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | < 0.0001                                   |
| Method                                  | Wilcoxon (Mann-Whitney)                    |

### Secondary: Requirement of prokinetics

|                 |                            |
|-----------------|----------------------------|
| End point title | Requirement of prokinetics |
|-----------------|----------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1-28 in ICU.

| End point values            | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|-----------------------------|------------------|-------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed | 40               | 43                      |  |  |
| Units: Subjects             |                  |                         |  |  |
| Metoclopramide              | 15               | 13                      |  |  |
| Erythromycin                | 10               | 7                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Average No. of bowel movements per day

|                 |  |
|-----------------|--|
| End point title | Average No. of bowel movements per day |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1-28 in ICU.

| End point values                      | Methylnaltrexone    | Normal Saline (Placebo) |  |  |
|---------------------------------------|---------------------|-------------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group         |  |  |
| Number of subjects analysed           | 39                  | 43                      |  |  |
| Units: Number                         |                     |                         |  |  |
| median (inter-quartile range (Q1-Q3)) |                     |                         |  |  |
| Days 1-3 - no rescue                  | 0.33 (0.00 to 1.00) | 0.67 (0.00 to 1.67)     |  |  |
| Days 1-3 - after rescue(s)            | 1.50 (0.50 to 2.50) | 1.33 (0.00 to 1.50)     |  |  |
| Days 4-28 - no rescue                 | 1.08 (0.33 to 1.80) | 2.00 (1.44 to 2.50)     |  |  |
| Days 4-28 - after rescue(s)           | 1.18 (0.00 to 2.00) | 1.63 (1.00 to 2.42)     |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Mean number of bowel movements per day     |
| Comparison groups                       | Methylnaltrexone v Normal Saline (Placebo) |
| Number of subjects included in analysis | 82   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.58 <sup>[1]</sup>                      |
| Method                                  | Wilcoxon (Mann-Whitney)                    |

Notes:

[1] - Days 1-3.

P value Days 4-28 = 0.0055

## Secondary: Incidence of diarrhoea

|                        |                        |
|------------------------|------------------------|
| End point title        | Incidence of diarrhoea |
| End point description: |                        |
| End point type         | Secondary              |
| End point timeframe:   |                        |
| Days 1-28 in ICU.      |                        |

| End point values            | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|-----------------------------|------------------|-------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed | 39               | 43                      |  |  |
| Units: subjects             |                  |                         |  |  |
| Diarrhoea at least once     | 23               | 36                      |  |  |
| Type 7 stool at least once  | 23               | 36                      |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Incidence of diarrhoea                     |
| Comparison groups                       | Methylnaltrexone v Normal Saline (Placebo) |
| Number of subjects included in analysis | 82   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.0152                                   |
| Method                                  | Chi-squared                                |

### Secondary: Change of opioid dose from baseline to 4 hours after first study drug dose

|                        |  |
|------------------------|--|
| End point title        | Change of opioid dose from baseline to 4 hours after first study drug dose |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Days 1-28 in ICU.      |  |

| End point values              | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|-------------------------------|------------------|-------------------------|--|--|
| Subject group type            | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed   | 39               | 43                      |  |  |
| Units: subjects               |                  |                         |  |  |
| Total on fentanyl at baseline | 28               | 35                      |  |  |
| Fentanyl dose reduced         | 1                | 0                       |  |  |

|                                   |    |    |  |  |
|-----------------------------------|----|----|--|--|
| Fentanyl dose remained same       | 22 | 30 |  |  |
| Fentanyl dose increased           | 3  | 3  |  |  |
| Total on remifentanyl at baseline | 9  | 7  |  |  |
| Remifentanyl dose reduced         | 3  | 0  |  |  |
| Remifentanyl dose remained same   | 3  | 3  |  |  |
| Remifentanyl dose increased       | 2  | 1  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of Clostridium difficile infection: PCR or Toxin positive

|                 |   |
|-----------------|---|
| End point title | Incidence of Clostridium difficile infection: PCR or Toxin positive |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1-28 in ICU

| End point values                            | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|---|------------------|-------------------------|--|--|
| Subject group type                          | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed                 | 39               | 43                      |  |  |
| Units: % of patients                        |                  |                         |  |  |
| Percentage of patients - infection reported | 8                | 16                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mortality: 28 days

|                 |                    |
|-----------------|--------------------|
| End point title | Mortality: 28 days |
|-----------------|--------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Survival status at 28 days post-randomisation

| End point values            | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|-----------------------------|------------------|-------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed | 39               | 43                      |  |  |
| Units: subjects             |                  |                         |  |  |
| Died <28 days               | 10               | 2                       |  |  |
| Alive at 28 days            | 29               | 41                      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Expected numbers of deaths in each treatment group (based on baseline assessments)

|                 |  |
|-----------------|--|
| End point title | Expected numbers of deaths in each treatment group (based on baseline assessments) |
|-----------------|--|

End point description:

It was assessed whether risk of death at entry to the study might explain the observed difference in mortality between the two arms. This was done using the following measures: Knaus, APACHE UK 2013, APACHE UK 2015, ICNARC model 2013, ICNARC model 2015 and SAPSII score.

The expected numbers based on APACHE UK 2015 are reported here.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Expected number of deaths from baseline risk

| End point values            | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|-----------------------------|------------------|-------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed | 38               | 42                      |  |  |
| Units: Number               |                  |                         |  |  |
| Expected number of deaths   | 11               | 12                      |  |  |
| Observed number of deaths   | 10               | 2                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of Ventilator Associated Penumonia (VAP)

|                 |  |
|-----------------|--|
| End point title | Incidence of Ventilator Associated Penumonia (VAP) |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1-7 in ICU.

| <b>End point values</b>               | Methylnaltrexone | Normal Saline (Placebo) |  |  |
|---------------------------------------|------------------|-------------------------|--|--|
| Subject group type                    | Reporting group  | Reporting group         |  |  |
| Number of subjects analysed           | 41               | 43                      |  |  |
| Units: subjects                       |                  |                         |  |  |
| median (inter-quartile range (Q1-Q3)) |                  |                         |  |  |
| Randomisation                         | 6.0 (5.0 to 7.0) | 6.0 (4.0 to 6.0)        |  |  |
| Day 1                                 | 6.0 (4.0 to 7.0) | 6.0 (5.0 to 6.0)        |  |  |
| Day 4                                 | 6.0 (5.0 to 7.0) | 6.0 (4.0 to 7.0)        |  |  |
| Day 7                                 | 7.0 (5.0 to 8.0) | 6.0 (5.0 to 7.0)        |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Days 1-28 in ICU. Fatal or life threatening SAEs were reported on the day that local sites became aware of the event (within 24 hours).

Adverse event reporting additional description:

Clinical outcomes from ICU admission were exempt from adverse event reporting, unless the investigator deemed the event to be related to the administration of study drug.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Methylnaltrexone |
|-----------------------|------------------|

Reporting group description:

Methylnaltrexone

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Normal Saline (Placebo) |
|-----------------------|-------------------------|

Reporting group description:

Normal Saline (Placebo)

| Serious adverse events                                | Methylnaltrexone | Normal Saline (Placebo) |  |
|---|------------------|-------------------------|--|
| Total subjects affected by serious adverse events     |                  |                         |  |
| subjects affected / exposed                           | 2 / 40 (5.00%)   | 2 / 43 (4.65%)          |  |
| number of deaths (all causes)                         | 0                | 0                       |  |
| number of deaths resulting from adverse events        | 0                | 0                       |  |
| Cardiac disorders                                     |                  |                         |  |
| Cardiac arrest  |                  |                         |  |
| subjects affected / exposed                           | 1 / 40 (2.50%)   | 1 / 43 (2.33%)          |  |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 1                   |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0                   |  |
| Gastrointestinal disorders                            |                  |                         |  |
| Perforated abdominal viscous (perforated colon on CT) |                  |                         |  |
| subjects affected / exposed                           | 0 / 40 (0.00%)   | 1 / 43 (2.33%)          |  |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 1                   |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0                   |  |
| Respiratory, thoracic and mediastinal disorders       |                  |                         |  |
| Respiratory distress                                  |                  |                         |  |



|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 40 (2.50%) | 0 / 43 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Methylnaltrexone                        | Normal Saline (Placebo) |  |
|---|---|-------------------------|--|
| Total subjects affected by non-serious adverse events |   |                         |  |
| subjects affected / exposed                           | 9 / 40 (22.50%)                         | 12 / 43 (27.91%)        |  |
| Gastrointestinal disorders                            |   |                         |  |
| Diarrhoea   |   |                         |  |
| subjects affected / exposed                           | 8 / 40 (20.00%)                         | 11 / 43 (25.58%)        |  |
| occurrences (all)                                     | 8                                       | 11                      |  |
| Rectal cancer metastatic                              |   |                         |  |
| subjects affected / exposed                           | 0 / 40 (0.00%)                          | 1 / 43 (2.33%)          |  |
| occurrences (all)                                     | 0                                       | 1                       |  |
| Skin and subcutaneous tissue disorders                |   |                         |  |
| Rash  | Additional description: Rash over torso |                         |  |
| subjects affected / exposed                           | 1 / 40 (2.50%)                          | 0 / 43 (0.00%)          |  |
| occurrences (all)                                     | 1                                       | 0                       |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 04 April 2016     | Changes made to trial protocol: <ul style="list-style-type: none"><li>- Page 7 - Change of wording under population eligibility; removal of 'from admission to ICU'</li><li>- Page 14 - Change of wording under design, regarding possible addition of new sites. Change of 'GICU' to 'ICU' so that CICU patients can be included in the study</li><li>- Page 15 - Change of inclusion criteria; removal of 'following ICU admission' and change in exclusion criteria - 'abdominal surgery' to 'GI tract surgery'</li><li>- Other administrative changes</li></ul> |
| 16 June 2016      | Addition of 2 sites: <ul style="list-style-type: none"><li>- Royal Surrey County Hospital (never recruited in the end)</li><li>- Nottingham University Hospitals (never came on board)</li></ul>  |
| 07 September 2016 | Addition of one participating site: <ul style="list-style-type: none"><li>- Queen Elizabeth Hospital, King's Lynn</li></ul>   |
| 30 January 2017   | <ul style="list-style-type: none"><li>- Changes to trial protocol inclusion criteria, to additionally include ICU patients sedated with opioids for a total of 12 hours (consecutive or non-consecutive) in the past 48 hours.</li><li>- Wording changes in Patient Information Sheets and Consent Forms.</li><li>- Notification of updated SmPC for Relistor (Methylnaltrexone) that will be used for the next safety reporting period.</li></ul>  |
| 10 January 2018   | To amend trial protocol definition of "end of trial" to allow for retrospective mortality outcome data collection, to be added to our analyses.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported