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
Scientific contact	Parind Patel, Imperial College Healthcare NHS Trust, +44 2083831878, parind.patel@nhs.net

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:

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
Arm title	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.

Arm title	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.

Number of subjects in period 1	Methylnaltrexone	Normal Saline (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: Methylnaltrexone	
Reporting group title	Normal Saline (Placebo)
Reporting group description: Normal Saline (Placebo)	

Reporting group values	Methylnaltrexone	Normal Saline (Placebo)	Total
Number of subjects	41	43	84
Age categorical Units: Subjects			
Adults (18-64 years)	25	23	48
From 65-84 years	16	19	35
85 years +	0	1	1
Age continuous Units: years			
arithmetic mean	55.6	58.6	
standard deviation	± 14.8	± 17.3	-
Gender categorical 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. Surgical - emergency (operative) includes: cardiovascular, craniotomy, multiple trauma, head trauma, heart valve surgery, neurologic and respiratory. Surgical - elective (operative) incudes: 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 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: Methylnaltrexone	
Reporting group title	Normal Saline (Placebo)
Reporting group description: Normal Saline (Placebo)	

Primary: Rescue-free laxation

End point title	Rescue-free laxation
End point description: 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: 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: The null hypothesis is that there is no difference in time to rescue free laxation in the Methylnaltrexone and Placebo groups. 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). 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 [1]
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

Statistical analysis title	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.

End point values	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 %

Non-serious adverse events	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: - Page 7 - Change of wording under population eligibility; removal of 'from admission to ICU' - 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 - Page 15 - Change of inclusion criteria; removal of 'following ICU admission' and change in exclusion criteria - 'abdominal surgery' to 'GI tract surgery' - Other administrative changes
16 June 2016	Addition of 2 sites: - Royal Surrey County Hospital (never recruited in the end) - Nottingham University Hospitals (never came on board)
07 September 2016	Addition of one participating site: - Queen Elizabeth Hospital, King's Lynn
30 January 2017	- 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. - Wording changes in Patient Information Sheets and Consent Forms. - Notification of updated SmPC for Relistor (Methylnaltrexone) that will be used for the next safety reporting period.
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