



Clinical trial results:

Time to transit Recovery After treatment with Naloxegol in cardiac Surgery Intensive care Trial

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-000087-26 |
| Trial protocol | FR |
| Global end of trial date | 03 March 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 17 June 2023 |
| First version publication date | 17 June 2023 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 2019/09 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04433390 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | CMC Ambroise Pare |
| Sponsor organisation address | 25-27 boulevard Victor Hugo, Neuilly-sur-Seine, France, 92200 |
| Public contact | Service de recherche clinique, CMC Ambroise Pare, +33 10146415079, recherche@clinique-a-pare.fr |
| Scientific contact | Service de recherche clinique, CMC Ambroise Pare, +33 10146415079, recherche@clinique-a-pare.fr |

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 | 24 February 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 March 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Prove that the administration of Naloxegol in the perioperative period of cardiac surgery reduces the duration of the postoperative ileus.

Protection of trial subjects:

This clinical trial was approved by a Committee for Protection of Human Subjects (CPP OUEST III - CPP 20.03.22/SI CNRIPH 20.02.25.46201) and the french national agency for medicines and health products safety (ANSM MEDAECNAT-2020-02-00024). The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice. Prior to inclusion, written informed consent was obtained from all subjects after a thorough oral and written participant information had been given.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 14 October 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 305 |
| Worldwide total number of subjects | 305 |
| EEA total number of subjects | 305 |

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) | 181 |
| From 65 to 84 years | 123 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Patients were included from October 2020 to January 2022.

Patients scheduled for cardiac surgery with cardiopulmonary bypass were informed of the study protocol during the cardiology visit. They were included before the surgery after signing informed consent. We enrolled patient over 18 years-old with social security.

Pre-assignment

Screening details:

Exclusion criteria : Allergy to Naloxegol or opioid antagonist; Severe hepatic failure; GFR<60ml/min; Treatment with cytochrome P450 3A4 inhibitor, laxative or methadone; History of gastro-intestinal obstruction or digestive arteritis; Alteration of the blood-brain-barrier or gastrointestinal lining; Cancer with risk of gastroduodenal perforation.

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 305 |
| Number of subjects completed | 304 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|----------------------|
| Reason: Number of subjects | Cancelled surgery: 1 |
|----------------------------|----------------------|

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------|
| Arm title | Naloxegol |
|------------------|-----------|

Arm description:

One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Naloxegol 12,5 mg and 25mg |
| Investigational medicinal product code | |
| Other name | Moventig |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One naloxegol 12.5 mg tablet will be administrated 2hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|--------------|
| Investigational medicinal product name | Inert Tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| Number of subjects in period 1 | Naloxegol | Placebo |
|--------------------------------|-----------|---------|
| Started | 153 | 151 |
| Treated | 151 | 150 |
| Completed | 151 | 150 |
| Not completed | 2 | 1 |
| Consent withdrawn by subject | 1 | 1 |
| Cancelled surgery | 1 | - |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Treated |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Naloxegol |

Arm description:

One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Naloxegol 12,5 mg and 25mg |
| Investigational medicinal product code | |
| Other name | Moventig |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One naloxegol 12.5 mg tablet will be administrated 2hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|--------------|
| Investigational medicinal product name | Inert Tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| Number of subjects in period 2 | Naloxegol | Placebo |
|--------------------------------|-----------|---------|
| Started | 151 | 150 |
| Transit recovery | 151 | 148 |
| Completed | 151 | 148 |
| Not completed | 0 | 2 |
| Adverse event, serious fatal | - | 2 |

Period 3

| | |
|------------------------------|---|
| Period 3 title | Transit recovery |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Naloxegol |

Arm description:

One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Naloxegol 12,5 mg and 25mg |
| Investigational medicinal product code | |
| Other name | Moventig |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One naloxegol 12.5 mg tablet will be administrated 2hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|--------------|
| Investigational medicinal product name | Inert Tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: As defined in the clinical trial protocol, we analyze the baseline characteristics and the end points for the patients treated and recovering transit.

The number of subjects treated and recovering transit are the number of subjects reported to be in the baseline period.

So the baseline period is the period 3 « Transit Recovery » and not the period 1 « Overall Period ».

| Number of subjects in period 3^[2] | Naloxegol | Placebo |
|---|-----------|---------|
| Started | 151 | 148 |
| Completed | 151 | 148 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: As defined in the clinical trial protocol, we analyze the baseline characteristics and the end points for the patients treated and recovering transit.

The number of subjects treated and recovering transit are the number of subjects reported to be in the baseline period.

So the number of subjects reported to be in the baseline period are not the same as the worldwide enrolled in the trial.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Naloxegol |
|-----------------------|-----------|

Reporting group description:

One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| Reporting group values | Naloxegol | Placebo | Total |
|--|-----------|---------|-------|
| Number of subjects | 151 | 148 | 299 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 81 | 96 | 177 |
| From 65-84 years | 69 | 52 | 121 |
| 85 years and over | 1 | 0 | 1 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.0 | 61.7 | |
| standard deviation | ± 10.6 | ± 10.0 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 27 | 28 | 55 |
| Male | 124 | 120 | 244 |
| Hypertension | | | |
| Units: Subjects | | | |
| Yes | 76 | 85 | 161 |
| No | 75 | 63 | 138 |
| Dyslipidemia | | | |
| Units: Subjects | | | |
| Yes | 78 | 95 | 173 |
| No | 73 | 53 | 126 |
| Diabetes | | | |
| Units: Subjects | | | |
| Yes | 33 | 29 | 62 |
| No | 118 | 119 | 237 |
| Peripheral arterial disease | | | |
| Units: Subjects | | | |
| Yes | 14 | 16 | 30 |
| No | 137 | 132 | 269 |
| Smoker status | | | |
| Units: Subjects | | | |
| Current and former <3years | 51 | 59 | 110 |
| Never or former > 3years | 100 | 89 | 189 |
| Chronic obstructive pulmonary disease - COPD | | | |

| | | | |
|--|-----|-----|-----|
| Units: Subjects | | | |
| Yes | 9 | 17 | 26 |
| No | 142 | 131 | 273 |
| Sleep apnea syndrome | | | |
| Units: Subjects | | | |
| Yes | 14 | 13 | 27 |
| No | 137 | 135 | 272 |
| Prior or under treatment cancer | | | |
| Units: Subjects | | | |
| Yes | 15 | 17 | 32 |
| No | 136 | 131 | 267 |
| Prior ischemic cardiopathy | | | |
| Units: Subjects | | | |
| Yes | 33 | 40 | 73 |
| No | 118 | 108 | 226 |
| Prior abdominal surgery | | | |
| Units: Subjects | | | |
| Yes | 26 | 29 | 55 |
| No | 125 | 119 | 244 |
| Prior urologic surgery | | | |
| Units: Subjects | | | |
| Yes | 7 | 9 | 16 |
| No | 144 | 139 | 283 |
| Prior cardiac surgery | | | |
| Units: Subjects | | | |
| Yes | 4 | 4 | 8 |
| No | 147 | 144 | 291 |
| Aortic regurgitation | | | |
| Units: Subjects | | | |
| Yes | 10 | 9 | 19 |
| No | 141 | 139 | 280 |
| Aortic stenosis | | | |
| Units: Subjects | | | |
| Yes | 52 | 40 | 92 |
| No | 99 | 108 | 207 |
| Mitral regurgitation | | | |
| Units: Subjects | | | |
| Yes | 36 | 28 | 64 |
| No | 115 | 120 | 235 |
| Mitral stenosis | | | |
| Units: Subjects | | | |
| Yes | 3 | 4 | 7 |
| No | 148 | 144 | 292 |
| Ischemic cardiopathy | | | |
| Units: Subjects | | | |
| Yes | 63 | 74 | 137 |
| No | 88 | 74 | 162 |
| Type of surgery - Coronary bypass grafting | | | |
| Units: Subjects | | | |
| Yes | 63 | 74 | 137 |

| | | | |
|---|----------------------|----------------------|-----|
| No | 88 | 74 | 162 |
| Type of surgery - Aortic valve replacement Units: Subjects | | | |
| Yes | 60 | 45 | 105 |
| No | 91 | 103 | 194 |
| Type of surgery - Mitral valve replacement Units: Subjects | | | |
| Yes | 6 | 8 | 14 |
| No | 145 | 140 | 285 |
| Type of surgery - Mitral valvuloplasty Units: Subjects | | | |
| Yes | 32 | 22 | 54 |
| No | 119 | 126 | 245 |
| Type of surgery - Ascendant aorta surgery Units: Subjects | | | |
| Yes | 15 | 8 | 23 |
| No | 136 | 140 | 276 |
| Type of surgery - Tricuspid valvuloplasty Units: Subjects | | | |
| Yes | 9 | 1 | 10 |
| No | 142 | 147 | 289 |
| Body mass index (BMI) Units: kilogram(s)/square metre median inter-quartile range (Q1-Q3) | 25.6 23.6 to 29.4 | 25.9 23.8 to 29.3 | - |
| Preoperative Left Ventricular Ejection Fraction (LVEF) Units: percent arithmetic mean standard deviation | 64.9 ± 7.5 | 64.1 ± 7.8 | - |
| Euroscore 2 Units: percent arithmetic mean standard deviation | 1.5 ± 1.2 | 1.26 ± 0.9 | - |
| Aortic-cross clamping time Units: minute median inter-quartile range (Q1-Q3) | 61 48 to 72 | 60.5 46 to 71 | - |
| Cardiopulmonary bypass time Units: minute median inter-quartile range (Q1-Q3) | 77 60 to 101 | 73.5 58 to 87 | - |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Naloxegol |
| Reporting group description: One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days. | |
| Reporting group title | Placebo |
| Reporting group description: One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days. | |
| Reporting group title | Naloxegol |
| Reporting group description: One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days. | |
| Reporting group title | Placebo |
| Reporting group description: One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days. | |
| Reporting group title | Naloxegol |
| Reporting group description: One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days. | |
| Reporting group title | Placebo |
| Reporting group description: One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days. | |

Primary: Transit recovery

| | |
|--|------------------|
| End point title | Transit recovery |
| End point description: The primary endpoint was the time of postoperative gastrointestinal transit recovery after the cardiac surgery defined as the time interval in hours between the anesthetic induction and the emission of the first significant stool. | |
| End point type | Primary |
| End point timeframe: 30 days | |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 76 (69.3 to 93.5) | 78.3 (70.0 to 95.8) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Primary outcome - Mann - Whitney U test |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Evaluation of pain with post operative opioid consumption

| | |
|------------------------|--|
| End point title | Evaluation of pain with post operative opioid consumption |
| End point description: | Evaluation of pain with post operative opioid consumption in equivalent morphine in milligram. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| | | | | |
|---------------------------------------|------------------|------------------|--|--|
| End point values | Naloxegol | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: milligram(s) | | | | |
| median (inter-quartile range (Q1-Q3)) | 778 (596 to 941) | 758 (618 to 945) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Opioid consumption - Mann - Whitney U test |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.69 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Evaluation of pain with EVA at day 1

| | |
|------------------------|--|
| End point title | Evaluation of pain with EVA at day 1 |
| End point description: | Evaluation of pain with visual analogue scale (VAS) at day 1. Pain VAS visual analogue scale ranging from 0 to 10 (0=no pain, 10=worst possible pain). |
| End point type | Secondary |

End point timeframe:

1 days post-surgery

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: No unit | | | | |
| median (inter-quartile range (Q1-Q3)) | 2 (1 to 3) | 2 (1 to 3) | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Pain score D1 - Mann Whitney test |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.83 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Evaluation of pain with EVA at day 2

| | |
|------------------------|--|
| End point title | Evaluation of pain with EVA at day 2 |
| End point description: | Evaluation of pain with visual analogue scale (VAS) at day 2. Pain VAS visual analogue scale ranging from 0 to 10 (0=no pain, 10=worst possible pain). |
| End point type | Secondary |
| End point timeframe: | 2 days post surgery |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: No unit | | | | |
| median (inter-quartile range (Q1-Q3)) | 1 (0 to 1) | 1 (0 to 2) | | |

Statistical analyses

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | Pain score D2 - Mann Whitney test |
| Comparison groups | Naloxegol v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.08 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Evaluation of pain with EVA at day 3

| | |
|------------------------|--|
| End point title | Evaluation of pain with EVA at day 3 |
| End point description: | Evaluation of pain with visual analogue scale (VAS) at day 3. Pain VAS visual analogue scale ranging from 0 to 10 (0=no pain, 10=worst possible pain). |
| End point type | Secondary |
| End point timeframe: | 3 days post surgery |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: No unit | | | | |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0) | 0 (0 to 1) | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Pain score D3 - Mann Whitney test |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.48 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Duration of hospital stay

| | |
|------------------------|----------------------------|
| End point title | Duration of hospital stay |
| End point description: | Duration of hospital stay. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: day | | | | |
| median (inter-quartile range (Q1-Q3)) | 12 (11 to 15) | 12 (10 to 14) | | |

Statistical analyses

| Statistical analysis title | Duration of hospital stay -Mann-Whitney test |
|---|--|
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Duration of ICU stay

| | |
|------------------------|-----------------------|
| End point title | Duration of ICU stay |
| End point description: | Duration of ICU stay. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: day | | | | |
| median (inter-quartile range (Q1-Q3)) | 4 (2 to 6) | 3 (2 to 5) | | |

Statistical analyses

| Statistical analysis title | Duration of ICU stay - Mann - Whitney test |
|-----------------------------------|--|
| Comparison groups | Naloxegol v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Digestive complications - PIA day 1

| | |
|------------------------|---|
| End point title | Digestive complications - PIA day 1 |
| End point description: | Digestive complications defined as intra-abdominal pressure at day 1. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: centimetreH2O | | | | |
| median (inter-quartile range (Q1-Q3)) | 5 (4 to 7) | 6 (4 to 8) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Digestive complications - PIA Day 1 - Mann Whitney |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.41 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Digestive complications - PIA day 2

| | |
|------------------------|---|
| End point title | Digestive complications - PIA day 2 |
| End point description: | Digestive complications defined as intra-abdominal pressure at day 2. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: centimetreH2O | | | | |
| median (inter-quartile range (Q1-Q3)) | 7 (5 to 9) | 7 (5 to 10) | | |

Statistical analyses

| Statistical analysis title | Digestive complication - PIA Day 2 - Mann Whitney |
|---|---|
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Digestive complications - Post operative gastric tube

| | |
|------------------------|---|
| End point title | Digestive complications - Post operative gastric tube |
| End point description: | Digestive complications defined as number of patients who require temporary nasogastric tube. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 18 | 14 | | |

Statistical analyses

| Statistical analysis title | Digestive complications - Gastric tube - Fisher |
|---|---|
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | Fisher exact |

Secondary: Digestive complications - Vomiting

| | |
|-----------------|------------------------------------|
| End point title | Digestive complications - Vomiting |
|-----------------|------------------------------------|

End point description:

Digestive complications defined as number of patients with episode of vomiting.

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

End point timeframe:

30 days

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 5 | 12 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Digestive complication - Vomiting - Fisher |
|-----------------------------------|--|

| | |
|-------------------|---------------------|
| Comparison groups | Naloxegol v Placebo |
|-------------------|---------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 299 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|--------|
| P-value | = 0.08 |
|---------|--------|

| | |
|--------|--------------|
| Method | Fisher exact |
|--------|--------------|

Secondary: Digestive complications - Ogilvie syndrome

| | |
|-----------------|--|
| End point title | Digestive complications - Ogilvie syndrome |
|-----------------|--|

End point description:

Digestive complications defined as number of patients with Ogilvie syndrome.

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

End point timeframe:

30 days

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Digestive complications - Mesenteric ischemia

| | |
|------------------------|---|
| End point title | Digestive complications - Mesenteric ischemia |
| End point description: | Digestive complications defined as number of patients with mesenteric ischemia. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Digestive complications - Need of colonoscopy

| | |
|------------------------|---|
| End point title | Digestive complications - Need of colonoscopy |
| End point description: | Digestive complications defined as number of patients with need of colonoscopy. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 0 | 2 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Digestive complication - Colonoscopy - Fisher |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.24 |
| Method | Fisher exact |

Secondary: Digestive complications - Solid food intolerance at day 2

| | |
|------------------------|---|
| End point title | Digestive complications - Solid food intolerance at day 2 |
| End point description: | Digestive complications defined as number of patients with solid food intolerance at day 2. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 21 | 24 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Digestive complication - Food intolerance - Fisher |
| Comparison groups | Placebo v Naloxegol |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.28 |
| Method | Fisher exact |

Secondary: Respiratory complications - Pneumonia

| | |
|-----------------|---------------------------------------|
| End point title | Respiratory complications - Pneumonia |
|-----------------|---------------------------------------|

End point description:

Respiratory complications defined as number of patients with pneumonia.

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

End point timeframe:

30 days

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 7 | 9 | | |

Statistical analyses

| | | | | |
|---|--|--|--|--|
| Statistical analysis title | Respiratory complications - Pneumonia - Fisher | | | |
| Comparison groups | Naloxegol v Placebo | | | |
| Number of subjects included in analysis | 299 | | | |
| Analysis specification | Pre-specified | | | |
| Analysis type | superiority | | | |
| P-value | = 0.62 | | | |
| Method | Fisher exact | | | |

Secondary: Respiratory complications - Reintubation

| | |
|-----------------|--|
| End point title | Respiratory complications - Reintubation |
|-----------------|--|

End point description:

Respiratory complications defined as number of patients with reintubation for respiratory failure.

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

End point timeframe:

30 days

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 3 | 4 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Respiratory complications - Reintubation - Fisher |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.72 |
| Method | Fisher exact |

Secondary: Respiratory complications - Invasive or not invasive ventilation at day 2

| | |
|---|---|
| End point title | Respiratory complications - Invasive or not invasive ventilation at day 2 |
| End point description: Respiratory complications defined as number of patients with invasive or not invasive ventilation at day 2. | |
| End point type | Secondary |
| End point timeframe: 30 days | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Naloxegol | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 3 | 1 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Respiratory complications-Ventilation D2-Fisher |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.62 |
| Method | Fisher exact |

Secondary: Respiratory complications -Invasive ventilation

| | |
|--|---|
| End point title | Respiratory complications -Invasive ventilation |
| End point description: Respiratory complications defined as duration of invasive ventilation. | |
| End point type | Secondary |
| End point timeframe: 30 days | |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 3 (2 to 4) | 2.5 (2 to 4) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Invasive ventilation - Mann Whitney |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.34 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Respiratory complications - Non invasive ventilation

| | |
|------------------------|--|
| End point title | Respiratory complications - Non invasive ventilation |
| End point description: | Respiratory complications defined as duration of non invasive ventilation. |
| End point type | Secondary |
| End point timeframe: | 30 days |

| End point values | Naloxegol | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0) | 0 (0 to 0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Infection complications - Sepsis

| | |
|-----------------|----------------------------------|
| End point title | Infection complications - Sepsis |
|-----------------|----------------------------------|

| | |
|--|-----------|
| End point description: | |
| Infection complications defined as number of patients with sepsis. | |
| End point type | Secondary |
| End point timeframe: | |
| 30 days | |

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Infection complications-Wound infection

| | |
|---|---|
| End point title | Infection complications-Wound infection |
| End point description: | |
| Infection complications defined as number of patients with sternal wound infection. | |
| End point type | Secondary |
| End point timeframe: | |
| 30 days | |

| End point values | Naloxegol | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 151 | 148 | | |
| Units: Number of patients | 1 | 2 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Infection complication - Sternal wound infection |
| Comparison groups | Naloxegol v Placebo |
| Number of subjects included in analysis | 299 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.62 |
| Method | Fisher exact |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of inclusion to 30 days after surgery.

Adverse event reporting additional description:

All adverse events were evaluated and followed-up by all the investigator for all patients treated (number of patients 301).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Naloxegol |
|-----------------------|-----------|

Reporting group description:

One naloxegol 12.5 mg tablet will be administrated 2 hours before surgery. One 25 mg naloxegol tablet per day will be administrated from 24h post-surgery until bowel movement; for maximum 5 days.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

One inert tablet will be administrated 2 hours before surgery. One inert tablet per day will be administrated from 24h post-surgery until bowel movement; formaximum 5 days.

| Serious adverse events | Naloxegol | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 66 / 151 (43.71%) | 56 / 150 (37.33%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | 1 | 2 | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 9 / 151 (5.96%) | 3 / 150 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 9 / 151 (5.96%) | 5 / 150 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Thrombosis | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Cardiac pacemaker insertion | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardioversion | | | |
| subjects affected / exposed | 3 / 151 (1.99%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac ablation | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial drainage | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 6 / 150 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial septal defect repair | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheostomy | | | |

| | | | |
|--|-------------------|------------------|--|
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interventional procedure | | | |
| subjects affected / exposed | 3 / 151 (1.99%) | 5 / 150 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hospitalisation | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Organ failure | | | |
| subjects affected / exposed | 21 / 151 (13.91%) | 14 / 150 (9.33%) | |
| occurrences causally related to treatment / all | 0 / 21 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| 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 | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 3 / 150 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Diaphragmatic disorder | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinal effusion | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio abnormal | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasoplegia syndrome | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 4 / 151 (2.65%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 7 / 151 (4.64%) | 3 / 150 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infarction | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac tamponade | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 3 / 150 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral perforation | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 151 (1.99%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium tremens | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Speech disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonic clonic movements | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecal vomiting | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal polyp | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cytolysis | | | |
| subjects affected / exposed | 6 / 151 (3.97%) | 8 / 150 (5.33%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 3 / 151 (1.99%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 8 / 151 (5.30%) | 13 / 150 (8.67%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asymptomatic COVID-19 | | | |
| subjects affected / exposed | 4 / 151 (2.65%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| COVID-19 pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 151 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 1 / 150 (0.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Naloxegol | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 94 / 151 (62.25%) | 75 / 150 (50.00%) | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 32 / 151 (21.19%) | 32 / 150 (21.33%) | |
| occurrences (all) | 32 | 32 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 30 / 151 (19.87%) | 10 / 150 (6.67%) | |
| occurrences (all) | 30 | 10 | |
| Bundle branch block right | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 1 / 150 (0.67%) | |
| occurrences (all) | 2 | 1 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 151 (0.66%) | 3 / 150 (2.00%) | |
| occurrences (all) | 1 | 3 | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 5 / 151 (3.31%) | 1 / 150 (0.67%) | |
| occurrences (all) | 5 | 1 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 151 (0.00%) | 3 / 150 (2.00%) | |
| occurrences (all) | 0 | 3 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|------------------------|----------------------|--|
| Thrombocytopenia subjects affected / exposed occurrences (all) | 5 / 151 (3.31%) 5 | 5 / 150 (3.33%) 5 | |
| Gastrointestinal disorders Impaired gastric emptying subjects affected / exposed occurrences (all) | 4 / 151 (2.65%) 4 | 0 / 150 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 4 / 151 (2.65%) 4 | 1 / 150 (0.67%) 1 | |
| Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all) | 3 / 151 (1.99%) 3 | 1 / 150 (0.67%) 1 | |
| Diaphragmatic disorder subjects affected / exposed occurrences (all) | 7 / 151 (4.64%) 7 | 4 / 150 (2.67%) 4 | |
| Bronchial disorder subjects affected / exposed occurrences (all) | 1 / 151 (0.66%) 1 | 2 / 150 (1.33%) 2 | |
| Hepatobiliary disorders Hepatic cytolysis subjects affected / exposed occurrences (all) | 2 / 151 (1.32%) 2 | 1 / 150 (0.67%) 1 | |
| Cholestasis subjects affected / exposed occurrences (all) | 1 / 151 (0.66%) 1 | 4 / 150 (2.67%) 4 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 3 / 151 (1.99%) 3 | 1 / 150 (0.67%) 1 | |
| Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all) | 10 / 151 (6.62%) 10 | 6 / 150 (4.00%) 6 | |
| Renal failure | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 151 (1.32%) 2 | 2 / 150 (1.33%) 2 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 151 (1.99%) | 1 / 150 (0.67%) | |
| occurrences (all) | 3 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 1 / 150 (0.67%) | |
| occurrences (all) | 2 | 1 | |
| Enterobacter infection | | | |
| subjects affected / exposed | 2 / 151 (1.32%) | 3 / 150 (2.00%) | |
| occurrences (all) | 2 | 3 | |
| Metabolism and nutrition disorders | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 151 (2.65%) | 1 / 150 (0.67%) | |
| occurrences (all) | 4 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|--|
| We performed a modified intention-to-treat analysis on the baseline characteristics and on primary/secondary endpoints for all patients treated and patients with primary endpoint. Adverse event was analyzed for all patients treated. |
|--|

Notes: