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 worlwide 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	25.6	25.9	
inter-quartile range (Q1-Q3)	23.6 to 29.4	23.8 to 29.3	-
Preoperative Left Ventricular Ejection Fraction (LVEF) Units: percent			
arithmetic mean	64.9	64.1	
standard deviation	± 7.5	± 7.8	-
Euroscore 2 Units: percent			
arithmetic mean	1.5	1.26	
standard deviation	± 1.2	± 0.9	-
Aortic-cross clamping time Units: minute			
median	61	60.5	
inter-quartile range (Q1-Q3)	48 to 72	46 to 71	-
Cardiopulmonary bypass time Units: minute			
median	77	73.5	
inter-quartile range (Q1-Q3)	60 to 101	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: centimetreH20				
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	5 / 151 (3.31%)	5 / 150 (3.33%)	
occurrences (all)	5	5	
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	4 / 151 (2.65%)	0 / 150 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	4 / 151 (2.65%)	1 / 150 (0.67%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 151 (1.99%)	1 / 150 (0.67%)	
occurrences (all)	3	1	
Diaphragmatic disorder			
subjects affected / exposed	7 / 151 (4.64%)	4 / 150 (2.67%)	
occurrences (all)	7	4	
Bronchial disorder			
subjects affected / exposed	1 / 151 (0.66%)	2 / 150 (1.33%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	2 / 151 (1.32%)	1 / 150 (0.67%)	
occurrences (all)	2	1	
Cholestasis			
subjects affected / exposed	1 / 151 (0.66%)	4 / 150 (2.67%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 151 (1.99%)	1 / 150 (0.67%)	
occurrences (all)	3	1	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	10 / 151 (6.62%)	6 / 150 (4.00%)	
occurrences (all)	10	6	
Renal failure			

subjects affected / exposed	2 / 151 (1.32%)	2 / 150 (1.33%)	
occurrences (all)	2	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: