Clinical trial results:
Naloxegol and assessments of opioid induced bowel dysfunction

Summary

EudraCT number	2015-000419-42
Trial protocol	DK
Global end of trial date	18 May 2016

Results information

Result version number	v1 (current)
This version publication date	07 May 2021
First version publication date	07 May 2021
Summary attachment (see zip file)	Final study report_Naloxegol (Study report_Naloxegol.pdf)

Trial information

Trial identification

Sponsor protocol code	Nalogexol-2014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mech-Sense, Aalborg University Hospital
Sponsor organisation address	Mølleparkvej 4, Aalborg, Denmark, 9000
Public contact	Mech-Sense, Mech-Sense, Aalborg University Hospital, 45 97663523, amd@rn.dk
Scientific contact	Mech-Sense, Mech-Sense, Aalborg University Hospital, 45 97663523, amd@rn.dk

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	21 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2016
Global end of trial reached?	Yes
Global end of trial date	18 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect on naloxegol on opioid induced bowel dysfunction (OIBD) using a compressive, objective design to explore motility, secretion and sphincter function

Protection of trial subjects:

MR-scans rely on magnetism and are therefore harmless, as no radiation is involved. Subjects will fill out a form regarding metal implants/pacemaker/etc. with a medical doctor prior to the scanning.
The FLIP procedure is previously approved (N-20090008) and does not constitute an actual risk but may be associated with some discomfort.
The MTS-2 is not considered harmful, and its small size permits unhindered passage through the GI tract. However, it is not completely certain whether MR scanning of the healthy volunteers with the MTS-2 capsule remaining in the GI tract, will affect the magnetic capsule, the MR scanner or most importantly, the healthy volunteer in any way. Therefore, emphasis on precautions has been made to ensure that this does not happen.
Prolonged release opioids within therapeutic doses are considered safe to use experimentally, but administration is associated with adverse effects. In the event that the adverse effects are too cumbrous for a subject, administering an antidote intravenously such as naloxone can effectively reverse the adverse effects.
The potential risk of developing psychological dependence (substance dependence) manifested, as a morbid desire to consume opioids in order to achieve a specific psychological experience is highly improbable in therapeutic doses of prolonged release formulations. Therefore, healthy volunteers will be thoroughly screened and these factors are accounted for in exclusion criteria. All subjects are required to fill out a Subjective Opiate Withdrawal Scale (SOWS) questionnaire three days after receiving the last dose in all study periods to monitor whether any degree of dependence is developing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	25
Intermediate milestone: Number of subjects	Fulfilled in- and exclusion criteria: 25
Intermediate milestone: Number of subjects	Introduction to QST and FLIP: 25
Number of subjects completed	25

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Oxycodone+Naloxegol

Arm description:

Experimental model of opioid-induced bowel disorder (oxycodone) and active treatment (naloxegol)

Arm type	Experimental
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oxycodone was administered as an orally ingested tablet with prolonged release. Oxycodone treatment commenced of 10 mg twice on day 1 (daily dose 20 mg). The following days (day 2-4) they received 15 mg oxycodone twice (daily dose 30 mg) to maintain a steady plasma concentration and to induce effects from prolonged opioid treatment (e.g. constipation). On day 6 they were treated with oxycodone 15 mg once (daily dose 15 mg).

Investigational medicinal product name	Naloxegol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Naloxegol was administered orally as film-coated tablets. Subjects were treated with naloxegol 25 mg once a day orally (day 2-6).

Arm title	Oxycodone+Placebo

Arm description:

Experimental model of opioid-induced bowel disorder (oxycodone) and placebo matching naloxegol

Arm type	Placebo

Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oxycodone was administered as an orally ingested tablet with prolonged release. Oxycodone treatment commenced of 10 mg twice on day 1 (daily dose 20 mg). The following days (day 2-4) they received 15 mg oxycodone twice (daily dose 30 mg) to maintain a steady plasma concentration and to induce effects from prolonged opioid treatment (e.g. constipation). On day 6 they were treated with oxycodone 15 mg once (daily dose 15 mg).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered orally as film-coated tablets. Subjects were treated with a placebo tablet once a day orally (day 2-6). Placebo tablets were similar to naloxegol tablets only excluding the active ingredient.

Number of subjects in period 1	Oxycodone+Naloxegol	Oxycodone+Placebo
Started	13	12
Colonic transit time (MTS-2)	13	12
Completed	13	12

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Oxycodone+Naloxegol

Arm description:

Experimental model of opioid-induced bowel disorder (oxycodone) and active treatment (naloxegol)

Arm type	Experimental
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oxycodone was administered as an orally ingested tablet with prolonged release. Oxycodone treatment commenced of 10 mg twice on day 1 (daily dose 20 mg). The following days (day 2-4) they received 15 mg oxycodone twice (daily dose 30 mg) to maintain a steady plasma concentration and to induce effects from prolonged opioid treatment (e.g. constipation). On day 6 they were treated with oxycodone 15 mg once (daily dose 15 mg).

Investigational medicinal product name	Naloxegol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Naloxegol was administered orally as film-coated tablets. Subjects were treated with naloxegol 25 mg once a day orally (day 2-6).

Arm title	Oxycodone+Placebo

Arm description:

Experimental model of opioid-induced bowel disorder (oxycodone) and placebo matching naloxegol

Arm type	Placebo
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oxycodone was administered as an orally ingested tablet with prolonged release. Oxycodone treatment commenced of 10 mg twice on day 1 (daily dose 20 mg). The following days (day 2-4) they received 15 mg oxycodone twice (daily dose 30 mg) to maintain a steady plasma concentration and to induce effects from prolonged opioid treatment (e.g. constipation). On day 6 they were treated with oxycodone 15 mg once (daily dose 15 mg).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered orally as film-coated tablets. Subjects were treated with a placebo tablet once a day orally (day 2-6). Placebo tablets were similar to naloxegol tablets only excluding the active ingredient.

Number of subjects in period 2	Oxycodone+Naloxegol	Oxycodone+Placebo
Started	13	12
Colonic transit time (MTS-2)	12	12
Completed	12	12
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Period 1

Reporting group description: -

Reporting group values	Period 1	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	25.3		
standard deviation	± 6.2	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	25	25	

End points

End points reporting groups	
Reporting group title	Oxycodone+Naloxegol
Reporting group description: Experimental model of opioid-induced bowel disorder (oxycodone) and active treatment (naloxegol)	
Reporting group title	Oxycodone+Placebo
Reporting group description: Experimental model of opioid-induced bowel disorder (oxycodone) and placebo matching naloxegol	
Reporting group title	Oxycodone+Naloxegol
Reporting group description: Experimental model of opioid-induced bowel disorder (oxycodone) and active treatment (naloxegol)	
Reporting group title	Oxycodone+Placebo
Reporting group description: Experimental model of opioid-induced bowel disorder (oxycodone) and placebo matching naloxegol	

Primary: Colorectal transit time in Naloxegol group vs. placebo	
End point title	Colorectal transit time in Naloxegol group vs. placebo
End point description:	
End point type	Primary
End point timeframe: day 2	

End point values	Oxycodone+Naloxegol	Oxycodone+Placebo	Oxycodone+Naloxegol	Oxycodone+Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: hours				
median (full range (min-max))	45 (35.5 to 53)	59.7 (52 to 68.3)	45 (35.5 to 53)	59.7 (52 to 68.3)

Attachments (see zip file)	Transit time Naloxegol vs. Placebo/nalox.PNG

Statistical analyses	
Statistical analysis title	Wilcoxon signed rank sum test
Statistical analysis description: For transit time data, Wilcoxon signed rank sum test was used to compare total and segmental transit times during the two treatments.	
Comparison groups	Oxycodone+Naloxegol v Oxycodone+Placebo v Oxycodone+Naloxegol v Oxycodone+Placebo

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - P-values less than 0.05 were considered statistically significant

Primary: Total gastrointestinal transit time

End point title	Total gastrointestinal transit time

End point description:

End point type	Primary

End point timeframe:

day 2

End point values	Oxycodone+Naloxegol	Oxycodone+Placebo	Oxycodone+Naloxegol	Oxycodone+Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: hours				
median (full range (min-max))	56.8 (48 to 65.7)	71.3 (63 to 79.5)	56.8 (48 to 65.7)	71.3 (63 to 79.5)

Attachments (see zip file)	Transit time Naloxegol vs. Placebo/nalox.PNG

Statistical analyses

Statistical analysis title	Wilcoxon signed rank sum test

Statistical analysis description:

For transit time data, Wilcoxon signed rank sum test was used to compare total and segmental transit times during the two treatments.

Comparison groups	Oxycodone+Naloxegol v Oxycodone+Placebo v Oxycodone+Naloxegol v Oxycodone+Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - P-values less than 0.05 were considered statistically significant

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From time of informed consent until three days after period 2 has been concluded.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24

Reporting groups	
Reporting group title	Oxycodone+Naloxegol
Reporting group description: -	
Reporting group title	Oxycodone + placebo
Reporting group description: -	

Serious adverse events	Oxycodone+Naloxegol	Oxycodone + placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Oxycodone+Naloxegol	Oxycodone + placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)	23 / 24 (95.83%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 25 (36.00%)	14 / 24 (58.33%)	
occurrences (all)	9	14	
Headache			
subjects affected / exposed	10 / 25 (40.00%)	10 / 24 (41.67%)	
occurrences (all)	10	10	
Fatigue			
subjects affected / exposed	16 / 25 (64.00%)	17 / 24 (70.83%)	
occurrences (all)	16	17	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	13 / 25 (52.00%)	14 / 24 (58.33%)	
occurrences (all)	13	14	
Nausea			
subjects affected / exposed	10 / 25 (40.00%)	15 / 24 (62.50%)	
occurrences (all)	10	15	
Vomiting			
subjects affected / exposed	3 / 25 (12.00%)	4 / 24 (16.67%)	
occurrences (all)	3	4	
Abdominal pain			
subjects affected / exposed	3 / 25 (12.00%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Skin irritation	Additional description: Skin itch		
subjects affected / exposed	11 / 25 (44.00%)	12 / 24 (50.00%)	
occurrences (all)	11	12	
Metabolism and nutrition disorders			
Dry mouth			
subjects affected / exposed	10 / 25 (40.00%)	9 / 24 (37.50%)	
occurrences (all)	10	9	

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

None reported