Clinical trial results:
Oral Controlled Release Formulations to Patients with Gastrointestinal Dysfunction – Is the Release of Drug and the Absorption Impaired?

Summary

EudraCT number	2017-000732-34
Trial protocol	DK
Global end of trial date	22 May 2019

Results information

Result version number	v1 (current)
This version publication date	05 January 2021
First version publication date	05 January 2021

Trial information

Trial identification

Sponsor protocol code	ABOXY_2017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Data Protection Agency : 2017-125, The North Denmark Region Committee on Health Rese: N-20170039

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Mølleparkvej 4 , Aalborg, Denmark, 9000
Public contact	Louise Ladebo, Mech-Sense, Dept. Gastroenterology & Hepatology, Aalborg University Hospital, + 4597663520, l.ladebo@rn.dk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2019
Global end of trial reached?	Yes
Global end of trial date	22 May 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to investigate the impact of GI-pathophysiology on net absorption of oxycodone administered as immediate release formulations and two different types of CRFs in patients with gastrointestinal disorders and to compare results obtained in healthy volunteers.

Protection of trial subjects:

Not known.

Background therapy: -

Evidence for comparator:

Participants were given one of three drugs:
a) 10 mL Oxynorm 1mg/mL (oral solution, no dissolution parameter)
b) 20 mg Oxycodonhydrochlorid “Lannacher” (swellable matrix based controlled release formulation)
c) 20 mg Oxycodone Depot “Sandoz" (lipid based controlled release formulation)
in a randomized order.

Actual start date of recruitment	15 May 2017
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: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	37
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited by oral advertisement at lectures at Aalborg university, internal meetings at Aalborg University Hospital or Aalborg university, as well as, through www.forsøgsperson.dk, www.sundhed.dk, www.gb-foreningen.dk and relevant facebook groups.

Pre-assignment

Screening details:

Pre-screening by telefon of physical meeting with questions related to in- and exclusion criteria, followed by assessment by a medical doctor.

Period 1

Period 1 title	Baseline characteristics
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline characteristics

Arm description:

Baseline characteristics obtained at this visit.

Arm type	Baseline characteristics
Investigational medicinal product name	No product - just baseline measurements
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

No dosage or drug was given at baseline. This visit was exclusively for obtainment of baseline measurements for all participants.

The above was chosen, as the EudraCT system does not allow a baseline visit with a product being given.

Number of subjects in period 1	Baseline characteristics
Started	37
Completed	37

Period 2

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

Blinding implementation details:

Semi-double blinded. Treatment medication was administered by personnel not involved in the study. Drugs were not blinded, by participants did not know which tablet was which.
The individual treatment assignment for each participant was available in sealed envelopes (provided by the person who made the randomization list), stored in a secure area.

Arms

Are arms mutually exclusive?	No
Arm title	Oxynorm (oral solution)

Arm description:

Administration of 10 mL oxynorm. Blood sampling, muscle pressure and pupil diameter was assessed over 24 hours.

Arm type	Active comparator
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

10 mL of oral liquid oxycodone with 50 ml water.

Arm title	Lannacher, swellable matrix

Arm description:

Administration of 20 mg oxycodone from water swellable controlled release formulation. Blood sampling, muscle pressure and pupil diameter was assessed over 24 hours.

Arm type	Active comparator
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg of a prolonged-release oxycodone tablet (water-swellable matrix) was given with 240 ml water.

Arm title	Sandoz - lipid based CRF

Arm description:

Administration of 20 mg oxycodone from lipid based matrix, controlled release formulation. Blood sampling, muscle pressure and pupil diameter was assessed over 24 hours.

Arm type	Active comparator
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg of a prolonged-release oxycodone tablet (lipid matrix) was given with 240 ml water.

Number of subjects in period 2	Oxynorm (oral solution)	Lannacher, swellable matrix	Sandoz - lipid based CRF
Started	37	37	37
Completed	35	35	35
Not completed	2	2	2
Consent withdrawn by subject	1	1	1
Physician decision	-	1	1
Adverse event, non-fatal	1	-	-

Period 3

Period 3 title	Smartpill investigation
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Smartpill

Arm description:

Smartpill investigation. Measurement of segmental pH, motility index and transit time of the stomach, small intestine and colon.

Arm type	Smartpill investigation

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Smartpill
Started	35
Completed	35

Baseline characteristics

Reporting groups

Reporting group title	Baseline characteristics

Reporting group description: -

Reporting group values	Baseline characteristics	Total	
Number of subjects	37	37	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	37	37	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age of all			
Units: years			
median	42		
inter-quartile range (Q1-Q3)	31 to 53	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	16	16	

Subject analysis sets

Subject analysis set title	Healthy
Subject analysis set type	Per protocol

Subject analysis set description:
Healthy controls

Subject analysis set title	Roux-en-Y gastric bypass
Subject analysis set type	Per protocol

Subject analysis set description:
All Roux-en-Y gastric bypass

Reporting group values	Healthy	Roux-en-Y gastric bypass	
Number of subjects	15	22	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	

Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	15	22	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age of all			
Units: years			
median	31	49	
inter-quartile range (Q1-Q3)	26 to 35.75	35.5 to 58	
Gender categorical			
Units: Subjects			
Female	7	14	
Male	8	8	

End points

End points reporting groups

Reporting group title	Baseline characteristics
Reporting group description:	
Baseline characteristics obtained at this visit.	
Reporting group title	Oxynorm (oral solution)
Reporting group description:	
Administration of 10 mL oxynorm. Blood sampling, muscle pressure and pupil diameter was assessed over 24 hours.	
Reporting group title	Lannacher, swellable matrix
Reporting group description:	
Administration of 20 mg oxycodone from water swellable controlled release formulation. Blood sampling, muscle pressure and pupil diameter was assessed over 24 hours.	
Reporting group title	Sandoz - lipid based CRF
Reporting group description:	
Administration of 20 mg oxycodone from lipid based matrix, controlled release formulation. Blood sampling, muscle pressure and pupil diameter was assessed over 24 hours.	
Reporting group title	Smartpill
Reporting group description:	
Smartpill investigation. Measurement of segmental pH, motility index and transit time of the stomach, small intestine and colon.	
Subject analysis set title	Healthy
Subject analysis set type	Per protocol
Subject analysis set description:	
Healthy controls	
Subject analysis set title	Roux-en-Y gastric bypass
Subject analysis set type	Per protocol
Subject analysis set description:	
All Roux-en-Y gastric bypass	

Primary: Primary endpoint

End point title	Primary endpoint
End point description:	
The primary endpoint was if there were any differences in bioavailability between the two oral controlled release tablets in patients with a Roux-en-Y gastric bypass.	
End point type	Primary
End point timeframe:	
First patient first visit to last patient last visit	

End point values	Lannacher, swellable matrix	Sandoz - lipid based CRF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	20[2]		
Units: unitless				
number (not applicable)	114	114		

Notes:

[1] - Only Roux-en-y individuals

[2] - Only Roux-en-Y individuals

Statistical analyses

Statistical analysis title	PKPD

Statistical analysis description:

PKPD modelling was used to determine differences in bioavailability of the two controlled release formulations.

Comparison groups	Lannacher, swellable matrix v Sandoz - lipid based CRF
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05
Method	Non-linear mixed effects
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1000

Notes:

[3] - PKPD modelling

Secondary: Secondary endpoint

End point title	Secondary endpoint

End point description:

The secondary endpoint was if there was any different in bioavailability between healthy volunteers and patients with Roux-en-Y gastric bypass.

End point type	Secondary

End point timeframe:

First patient first visit, last patient last visit

End point values	Healthy	Roux-en-Y gastric bypass		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	21[4]		
Units: unitless				
number (not applicable)	100	114		

Notes:

[4] - All patients who received oxycodone

Statistical analyses

Statistical analysis title	PKPD modelling

Statistical analysis description:	
PKPD modelling	
Comparison groups	Healthy v Roux-en-Y gastric bypass
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.05
Method	Mixed models analysis

Notes:

[5] - PKPD modelling

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first patient first visit to last patient last visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

Reporting groups	
Reporting group title	Oxynorm (arm 1)
Reporting group description: How many experienced side-effects.	
Reporting group title	Lannacher (arm 2)
Reporting group description: Number experiencing side-effects	
Reporting group title	Sandoz (arm 3)
Reporting group description: Number experiencing side-effects	

Serious adverse events	Oxynorm (arm 1)	Lannacher (arm 2)	Sandoz (arm 3)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 35 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Allergic oedema	Additional description: Quickes edema. Potential drug-drug interaction.		
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Oxynorm (arm 1)	Lannacher (arm 2)	Sandoz (arm 3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 36 (97.22%)	33 / 35 (94.29%)	34 / 35 (97.14%)
Cardiac disorders			
Palpitations			

subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 36 (33.33%)	11 / 35 (31.43%)	14 / 35 (40.00%)
occurrences (all)	12	11	14
Dizziness			
subjects affected / exposed	19 / 36 (52.78%)	22 / 35 (62.86%)	20 / 35 (57.14%)
occurrences (all)	19	22	20
Sedation			
subjects affected / exposed	32 / 36 (88.89%)	31 / 35 (88.57%)	30 / 35 (85.71%)
occurrences (all)	32	31	30
Immune system disorders			
Itching skin			
subjects affected / exposed	7 / 36 (19.44%)	8 / 35 (22.86%)	12 / 35 (34.29%)
occurrences (all)	7	8	12
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 36 (30.56%)	13 / 35 (37.14%)	11 / 35 (31.43%)
occurrences (all)	11	13	11
Vomiting			
subjects affected / exposed	7 / 36 (19.44%)	3 / 35 (8.57%)	4 / 35 (11.43%)
occurrences (all)	7	3	4
Dry mouth			
subjects affected / exposed	22 / 36 (61.11%)	18 / 35 (51.43%)	22 / 35 (62.86%)
occurrences (all)	22	18	22
Stomach ache			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	6 / 35 (17.14%)
occurrences (all)	3	3	6
Constipation			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	2 / 35 (5.71%)
occurrences (all)	2	1	2
Skin and subcutaneous tissue disorders			
Sweating			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	4 / 35 (11.43%)
occurrences (all)	3	3	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2019	The study was not completed in patients with diabetes nor short bowel as described in the protocol, as the study was very extensive

Notes:

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.

The number of gastric bypass participants was reduced from 30 to 20, as it was judged satisfactory.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31597014