Clinical trial results:
A novel approach to assess gastrointestinal adverse effects of opioids

Summary

EudraCT number	2013-001540-60
Trial protocol	DK
Global end of trial date	26 September 2017

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	MULTIPAIN6-2013

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Mølleparkvej 4, Aalborg, Denmark, 9000
Public contact	Dept. Gastroenterology & Hepatology, Mech-Sense, Aalborg University Hospital, 45 99326243,
Scientific contact	Dept. Gastroenterology & Hepatology, Mech-Sense, Aalborg University Hospital, 45 99326243,

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	Interim
Date of interim/final analysis	05 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2017
Global end of trial reached?	Yes
Global end of trial date	26 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to develop and validate a model capable of assessing gastrointestinal adverse effects of opioid treatment: opioid induced bowel dysfunction (OIBD) in healthy volunteers (substudy 1a and 1b).

Protection of trial subjects:

Daily inquiries during the study periods aimed at detecting any positive/euphoric experiences from the study medication. If so, the subject was withdrawn from the study immediately.
All subjects were also 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 had developed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2013
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	Denmark: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	50
From 65 to 84 years	12

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy volunteers will be recruited through an already established database and posters and flyers distributed and hung at the Aalborg University Hospital and Aalborg University. Chronic pancreatitis patients will be recruited from Aalborg University Hospital, Outpatient Clinic for chronic pancreatitis

Pre-assignment

Screening details:

Following informed consent, the subjects undervent a screening session. A medical doctor examined the subject, and they were screened to fulfil all inclusion and exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Substudy 1b_Oxycodone arm

Arm description:

Substudy 1b_Oxycodone arm

Arm type	Experimental
Investigational medicinal product name	OxyContin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

5 to 10 milligrams (mg) twice daily

Arm title	Substudy 1b_Placebo arm

Arm description:

Substudy 1b_Placebo arm

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

Dosage and administration details:

Placebo tablets for OxyCodone

Number of subjects in period 1	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm
Started	25	25
Completed	25	25

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

Arms	
Are arms mutually exclusive?	No
Arm title	Substudy 2a_OxyContin+Movicol arm

Arm description:

Substudy 2a_OxyContin+Movicol arm

Arm type	Active comparator
Investigational medicinal product name	OxyContin+Movicol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder, Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

OxyContin 5 to 10 mg twice daily + Movicol(macrogol 3350) 1 sachet (13,125 g) twice daily

Arm title	Substudy 2a_Targin+Placebo for Movicol arm

Arm description:

Substudy 2a_Targin+Placebo for Movicol arm

Arm type	Experimental
Investigational medicinal product name	Targin+Placebo for Movicol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder, Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Targin (Oxycodon/naloxone) 5/2,5 to 10/5 mg twice daily + Placebo powder for Movicol (macrogol 3350) 1 sachet (13,125 g) twice daily

Number of subjects in period 2	Substudy 2a_OxyContin+Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Started	20	20
Completed	20	20

Period 3	
Period 3 title	Substudy 2b
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Substudy 2b_Chronic Pancreatitis

Arm description:

Substudy 2b_Chronic Pancreatitis - exploratory study in patients suffering from chronic pancreatitis.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Substudy 2b_Chronic Pancreatitis
Started	28
Completed	28

Baseline characteristics

Reporting groups[1]	
Reporting group title	Substudy 1b
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: As this trial included three substudies, not all subjects participated in the baseline period (period 1/substudy 1b)

Reporting group values	Substudy 1b	Total	
Number of subjects	25	25	
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)	25	25	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	25	25	

End points

End points reporting groups

Reporting group title	Substudy 1b_Oxycodone arm
Reporting group description: Substudy 1b_Oxycodone arm	
Reporting group title	Substudy 1b_Placebo arm
Reporting group description: Substudy 1b_Placebo arm	
Reporting group title	Substudy 2a_OxyContin+Movicol arm
Reporting group description: Substudy 2a_OxyContin+Movicol arm	
Reporting group title	Substudy 2a_Targin+Placebo for Movicol arm
Reporting group description: Substudy 2a_Targin+Placebo for Movicol arm	
Reporting group title	Substudy 2b_Chronic Pancreatitis
Reporting group description: Substudy 2b_Chronic Pancreatitis - exploratory study in patients suffering from chronic pancreatitis.	

Primary: Gastric emptying

End point title	Gastric emptying
End point description:	
End point type	Primary
End point timeframe: For each arm in period 1 and 2 and 3 (NB! Only one arm in period 3)	

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[1]	0[2]	19	19
Units: hour				
median (inter-quartile range (Q1-Q3))	(to)	(to)	3.2 (2.3 to 4.9)	3.5 (2.6 to 6.8)

Notes:

[1] - Not possible to evaluate gastric emptying for this substudy due to technical issues.

[2] - Not possible to evaluate gastric emptying for this substudy due to technical issues.

End point values	Substudy 2b_Chronic Pancreatitis			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: hour				
median (inter-quartile range (Q1-Q3))	(to)			

Notes:
[3] - Data yet to be analysed for this substudy

Statistical analyses

Statistical analysis title	Comparison of transit time between treatments
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.334
Method	Wilcoxon (Mann-Whitney)

Primary: Small intestinal transit

End point title	Small intestinal transit

End point description:

End point type	Primary

End point timeframe:
For each arm in period 1 and 2 and 3 (NB! Only one arm in period 3)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	19	19	19
Units: hour				
median (inter-quartile range (Q1-Q3))	5.3 (1.5 to 9.6)	3.7 (1.9 to 10.0)	5.8 (4.6 to 8.1)	5.3 (4.7 to 6.3)

End point values	Substudy 2b_Chronic Pancreatitis			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: hour				
median (inter-quartile range (Q1-Q3))	(to)			

Notes:
[4] - Data yet to be analysed

Statistical analyses

Statistical analysis title	Comparison of transit time between treatments
Comparison groups	Substudy 1b_Placebo arm v Substudy 1b_Oxycodone arm
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.147
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison of transit time between treatments
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.091
Method	Wilcoxon (Mann-Whitney)

Primary: Colorectal transit time

End point title	Colorectal transit time

End point description:

End point type	Primary

End point timeframe:

For each arm in period 1 and 2 and 3 (NB! Only one arm in period 3)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	19	19	19
Units: hour				
median (inter-quartile range (Q1-Q3))	38.6 (5.6 to 88.6)	18.6 (7.0 to 82.2)	38.2 (30.9 to 61.2)	39.6 (26.6 to 74.3)

End point values	Substudy 2b_Chronic Pancreatitis			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: hour				

median (inter-quartile range (Q1-Q3))	(to)			

Notes:

[5] - Data yet to be analysed

Statistical analyses

Statistical analysis title	Comparison of transit time between treatments
Comparison groups	Substudy 1b_Oxycodone arm v Substudy 1b_Placebo arm
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison of transit time between treatments
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.872
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in fecal volume ascending colon (day 5-baseline)

End point title	Change in fecal volume ascending colon (day 5-baseline)

End point description:

End point type	Secondary

End point timeframe:

For each arm in period 1 and 2 (This endpoint was only assessed in healthy volunteers and thus NOT a part of substudy 3/period 3 in chronic pancreatitis patients)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	12	12
Units: millilitre(s)				
arithmetic mean (confidence interval 95%)	77 (29 to 124)	49 (17 to 81)	54 (23 to 85)	26 (1 to 51)

Statistical analyses

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 1b_Oxycodone arm v Substudy 1b_Placebo arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.005
Method	ANOVA

Notes:

[6] - Test if significant change in fecal volume from day 1 to day 5 within same period/treatment

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 1b_Placebo arm v Substudy 1b_Oxycodone arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03
Method	ANOVA

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005
Method	Mixed models analysis

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 2a_Targin+Placebo for Movicol arm v Substudy 2a_OxyContin+Movicol arm
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.156
Method	Mixed models analysis

Secondary: Change in fecal volume transverse colon (day 5-baseline)	
End point title	Change in fecal volume transverse colon (day 5-baseline)

End point description:

End point type	Secondary

End point timeframe:

For each arm in period 1 and 2 (This endpoint was only assessed in healthy volunteers and thus NOT a part of substudy 3/period 3 in chronic pancreatitis patients)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	12	12
Units: millilitre(s)				
arithmetic mean (confidence interval 95%)	49 (17 to 81)	-6 (-28 to 16)	87 (40 to 134)	48 (11 to 85)

Statistical analyses

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 1b_Oxycodone arm v Substudy 1b_Placebo arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005
Method	ANOVA

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 1b_Placebo arm v Substudy 1b_Oxycodone arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.57
Method	ANOVA

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.006
Method	Mixed models analysis

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 2a_Targin+Placebo for Movicol arm v Substudy 2a_OxyContin+Movicol arm
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.161
Method	Mixed models analysis

Secondary: Change in fecal volume descending colon (day 5-baseline)

End point title	Change in fecal volume descending colon (day 5-baseline)

End point description:

End point type	Secondary

End point timeframe:

For each arm in period 1 and 2 (This endpoint was only assessed in healthy volunteers and thus NOT a part of substudy 3/period 3 in chronic pancreatitis patients)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	12	12
Units: millilitre(s)				
arithmetic mean (confidence interval 95%)	25 (3 to 47)	-12 (-24 to 0)	70 (35 to 105)	38 (0 to 76)

Statistical analyses

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 1b_Oxycodone arm v Substudy 1b_Placebo arm

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.08
Method	ANOVA

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 1b_Placebo arm v Substudy 1b_Oxycodone arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.07
Method	ANOVA

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.022
Method	Mixed models analysis

Statistical analysis title	Change in fecal volume from day 1 to day 5
Comparison groups	Substudy 2a_Targin+Placebo for Movicol arm v Substudy 2a_OxyContin+Movicol arm
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.384
Method	Mixed models analysis

Secondary: Sphincter function (FLIP)

End point title	Sphincter function (FLIP)

End point description:

End point type	Secondary

End point timeframe:

For each arm in period 1 and 2 (This endpoint was only assessed in healthy volunteers and thus NOT a part of substudy 3/period 3 in chronic pancreatitis patients)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	20	20
Units: pressure-strain elastic modulus				
number (not applicable)	3	4	6	6

Statistical analyses

Statistical analysis title	Change in anal canal distensibility
Comparison groups	Substudy 1b_Oxycodone arm v Substudy 1b_Placebo arm
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Mixed models analysis

Statistical analysis title	Change in anal canal distensibility
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Mixed models analysis

Secondary: Gut secretion - short circuit current

End point title	Gut secretion - short circuit current

End point description:

End point type	Secondary

End point timeframe:

For each arm in period 1 (This endpoint was ONLY evaluated in healthy volunteers in period 1, and due to the results during period 1/substudy 1b this endpoint was dropped in period 2 and 3, substudy 2a and 2b, respectively)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: microampere per sqauare centimeter				
arithmetic mean (confidence interval 95%)	12 (9 to 15)	7 (5 to 9)		

Statistical analyses

Statistical analysis title	Change in SCC from day 1 to day 5
Comparison groups	Substudy 1b_Oxycodone arm v Substudy 1b_Placebo arm
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change in SCC from day 1 to day 5
Comparison groups	Substudy 1b_Placebo arm v Substudy 1b_Oxycodone arm
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.47
Method	Wilcoxon (Mann-Whitney)

Secondary: Subjective assessment - Bowel Function Index

End point title	Subjective assessment - Bowel Function Index

End point description:

End point type	Secondary

End point timeframe:

For each arm in period 1 and 2 (This endpoint was only assessed in healthy volunteers and thus NOT a part of substudy 3/period 3 in chronic pancreatitis patients)

End point values	Substudy 1b_Oxycodone arm	Substudy 1b_Placebo arm	Substudy 2a_OxyContin +Movicol arm	Substudy 2a_Targin+Placebo for Movicol arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	20	20
Units: score	34	3	23	22

Statistical analyses

Statistical analysis title	Change in BFI score between treatments
Comparison groups	Substudy 1b_Placebo arm v Substudy 1b_Oxycodone arm
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided

Statistical analysis title	Change in BFI score between treatments
Comparison groups	Substudy 2a_OxyContin+Movicol arm v Substudy 2a_Targin+Placebo for Movicol arm
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.666
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2013-08-08 to 2017-09-26	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Period 1, 2 and 3 (all study periods)

Reporting group description: -

Serious adverse events	Period 1, 2 and 3 (all study periods)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Period 1, 2 and 3 (all study periods)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)		
Surgical and medical procedures			
Hematoma	Additional description: Minor hematoma at site for blood sampling		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Lightheadness and nausea after administration			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			

Skin irritation from abdominal belt for transit time evaluation subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2		
Musculoskeletal and connective tissue disorders Mild pain in right wrist during study period subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29291613

http://www.ncbi.nlm.nih.gov/pubmed/26811503

http://www.ncbi.nlm.nih.gov/pubmed/28986667

http://www.ncbi.nlm.nih.gov/pubmed/26795566

http://www.ncbi.nlm.nih.gov/pubmed/26610166