Clinical trial results:
Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after Roux-en-Y gastric bypass and Sleeve Gastrectomy

Summary

EudraCT number	2016-003245-29
Trial protocol	NL
Global end of trial date	06 November 2020

Results information

Result version number	v1 (current)
This version publication date	21 May 2022
First version publication date	21 May 2022

Trial information

Trial identification

Sponsor protocol code	SA652013

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AMC
Sponsor organisation address	Meibergdreef, Amsterdam, Netherlands,
Public contact	Gastroenterology and Hepatology, Amsterdam UMC, locatie AMC, s.haal@amsterdamumc.nl
Scientific contact	Gastroenterology and Hepatology, Amsterdam UMC, locatie AMC, s.haal@amsterdamumc.nl

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	06 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 November 2020
Global end of trial reached?	Yes
Global end of trial date	06 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is designed to provide evidence regarding the prophylactic use of UDCA in preventing symptomatic gallstone disease after bariatric surgery.

Protection of trial subjects:

No specific protective measures were necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 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	Netherlands: 985
Worldwide total number of subjects	985
EEA total number of subjects	985

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)	985
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

- Between Jan 11, 2017, and Oct 22, 2018, participants were recruited.
- Participants were recruited in three hospitals.
- Study staff informed patients about the trial during the screening for bariatric surgery. If eligible for surgery, patients were asked to participate, and informed consent was obtained.

Pre-assignment

Screening details:

3272 patients were assessed for eligibility, of whom 985 were enrolled and randomised, 2287 were excluded (813 patients did not meet inclusion criteria, 1228 patients declined to participate, 246 patiens were included in another trial)

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Placebo tablets were identical in appearance to ursodeoxycholic acid tablets and each package was given a randomisation number to ensure masking.

Arms

Are arms mutually exclusive?	Yes
Arm title	UDCA

Arm description: -

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

Dosage and administration details:

Patients were given tablets of 450mg and were instructed to take 900mg daily.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Patients were instructed to take 2 tablets per day

Number of subjects in period 1[1]	UDCA	Placebo
Started	477	490
Completed	475	484
Not completed	2	6
Lost to follow-up	2	6

Notes:

[1] - 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: 13 randomly assigned patients did not receive the allocated treatment because the violated eligibility criteria and were thus excluded.

Baseline characteristics

Reporting groups	
Reporting group title	UDCA
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	UDCA	Placebo	Total
Number of subjects	477	490	967
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			
least squares mean	45.5	44.7	
standard deviation	± 11.2	± 11.0	-
Gender categorical Units: Subjects			
Female	381	391	772
Male	96	99	195

End points

End points reporting groups

Reporting group title	UDCA
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Sympomatic gallstone disease

End point title	Sympomatic gallstone disease
End point description:	
The primary endpoint was the proportion of patients with symptomatic gallstone disease within 24 months of follow-up. Symptomatic gallstone disease was defined as biliary disease (biliary pancreatitis, acute cholecystitis, choledocholithiasis, cholangitis, or biliary colic), for which a hospital visit or admission was required (see trial protocol for detailed definitions of biliary disease).	
End point type	Primary
End point timeframe:	
Within 24 months	

End point values	UDCA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	484		
Units: number	31	47		

Attachments (see zip file)	Primary endpoint.PNG

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
Proportions and relative risk (RR) with corresponding 95% CIs are presented for the primary endpoint with testing for significance based on the χ^2 test.	
Comparison groups	UDCA v Placebo
Number of subjects included in analysis	959
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.071
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.04

Secondary: Cholecystectomy

End point title	Cholecystectomy
End point description:	
End point type	Secondary
End point timeframe:	
Within 24 months	

End point values	UDCA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	484		
Units: number	25	44		

Attachments (see zip file)	Cholecystectomy.PNG

Statistical analyses

Statistical analysis title	Cholecystectomy
Comparison groups	UDCA v Placebo
Number of subjects included in analysis	959
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.022
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.93

Secondary: Presence of gallstones or sludge on postoperative ultrasonography

End point title	Presence of gallstones or sludge on postoperative ultrasonography

End point description:

End point type	Secondary

End point timeframe:
Within 24 months

End point values	UDCA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	415		
Units: Number	112	138		

Attachments (see zip file)	Presence of gallstones on ultrasonography.PNG

Statistical analyses

Statistical analysis title	Presence of gallstones
Comparison groups	UDCA v Placebo
Number of subjects included in analysis	834
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.04
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.99

Adverse events

Adverse events information

Timeframe for reporting adverse events:

- AEs until 30 days after the trialemedication was discontinued.
- SAEs until the end of follow-up.

Adverse event reporting additional description:

We only recorded the AE if there was a reasonable suspicion of the AE being an effect of the trial medication and in case the AE was graded at least as moderately severe or mildly severe lasting longer than 1 week. We only recorded SAEs that occurred after the start of the trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Safety - UDCA
Reporting group description: -	
Reporting group title	Safety - placebo

Reporting group description: -

Serious adverse events	Safety - UDCA	Safety - placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 444 (13.96%)	76 / 453 (16.78%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	4 / 444 (0.90%)	7 / 453 (1.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal			

conditions			
Unintended pregnancy			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
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			
Dyspnoea			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contusion			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 444 (0.23%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic leak			
subjects affected / exposed	0 / 444 (0.00%)	2 / 453 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 444 (0.23%)	4 / 453 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding tube user	Additional description: Dislocated feeding tube		
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 444 (0.23%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	0 / 444 (0.00%)	2 / 453 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	1 / 444 (0.23%)	3 / 453 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drain of cerebral subdural space	Additional description: Dysfunctional external ventriculair drain		
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder	Additional description: Functional		
subjects affected / exposed	1 / 444 (0.23%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 444 (2.93%)	15 / 453 (3.31%)	
occurrences causally related to treatment / all	0 / 13	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic complication			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic stenosis			
subjects affected / exposed	2 / 444 (0.45%)	4 / 453 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer perforation			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 444 (0.23%)	5 / 453 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 444 (0.23%)	5 / 453 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	3 / 444 (0.68%)	6 / 453 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			

subjects affected / exposed	3 / 444 (0.68%)	4 / 453 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal stenosis			
subjects affected / exposed	1 / 444 (0.23%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal hernia			
subjects affected / exposed	9 / 444 (2.03%)	5 / 453 (1.10%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Pancreatitis			
subjects affected / exposed	1 / 444 (0.23%)	2 / 453 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 444 (0.45%)	4 / 453 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder disorder			
subjects affected / exposed	4 / 444 (0.90%)	4 / 453 (0.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct stenosis			
subjects affected / exposed	0 / 444 (0.00%)	2 / 453 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	3 / 444 (0.68%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 444 (0.68%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			

subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 444 (0.45%)	3 / 453 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	4 / 444 (0.90%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 444 (0.23%)	0 / 453 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 444 (0.00%)	1 / 453 (0.22%)	
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: 5 %

Non-serious adverse events	Safety - UDCA	Safety - placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 444 (1.35%)	4 / 453 (0.88%)	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	4 / 444 (0.90%) 4	2 / 453 (0.44%) 2	
Skin and subcutaneous tissue disorders Skin rash subjects affected / exposed occurrences (all)	2 / 444 (0.45%) 2	2 / 453 (0.44%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2017	- Addition of the definitions "choledocholithiasis" and "cholangitis" - Clarification of the instructions reporting (serious) adverse events - Clarification of monitoring drug safety by an independent reviewer
23 March 2017	- Change of principal investigator participating hospital (OLVG West) - Clarification of the definition "choledocholithiasis" - Clarification of the management of postoperative diarrhea
19 April 2017	- Appointment of a blinded endpoint adjudication committee - Clarification of study procedures: timing of obtaining informed consent and performance of study follow-up - Change in the timing of the administration of study questionnaires
03 May 2017	- Addition of time windows for study follow-up visits - Clarification of the performance of study follow-up visits
04 July 2017	- Change in inclusion criteria; sleeve gastrectomy was added - Change in stratification strategy; type of surgery was added
10 November 2017	- Addition of a questionnaire regarding trial medication adherence
21 December 2018	- Change of sponsor; Amsterdam UMC, location AMC became the sponsor after the bankruptcy of the MC Slotervaart - Replacement of MC Slotervaart as participating hospital by Spaarne Gasthuis - Clarification that after the bankruptcy, the study follow-up was guaranteed by telephone until the ethics committee and board of directors at each (new) participating hospital approved local conduct of the trial
13 March 2019	- Replacement of MC Zuiderzee as participating hospital by Flevoziekenhuis
31 December 2019	- Clarification of study procedures and secondary study endpoints

Notes:

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/34715031