Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after Roux-en-Y gastric bypass and sleeve gastrectomy. (UPGRADE)

PROTOCOL TITLE

Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after Roux-en-Y gastric bypass and sleeve gastrectomy. (UPGRADE)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CEA	**Cost-effectiveness analysis**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GMP	**Good Manufacturing Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
iMCQ	**iMTA Medical Consumption Questionnaire**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
iPCQ	**iMTA Productivity Costs Questionnaire**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
QALY	**Quality adjusted life year**
RYGB	**Roux-en-Y gastric bypass**

(S)AE	**(Serious) Adverse Event**
SG	**Sleeve gastrectomy**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UDCA	**Ursodeoxycholic acid**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: The number of bariatric interventions for morbid obesity is rapidly increasing in the Netherlands. Rapid weight loss is a major risk factor for gallstone development. Approximately eleven percent of patients who underwent Roux-en-Y gastric bypass (RYGB) develop symptomatic gallstone disease. After sleeve gastrectomy similar incidences of symptomatic gallstone disease are reported. Gallstone disease can lead to severe complications and often requires hospitalization and surgery. Ursodeoxycholic acid (UDCA) prevents the formation of gallstones after bariatric surgery. However, randomized controlled trials with symptomatic gallstone disease as primary endpoint have not been conducted. Currently, major guidelines make no definite statement about postoperative UDCA prophylaxis and most bariatric centres do not prescribe UDCA.
Objective: This study is designed to provide evidence regarding the prophylactic use of UDCA in preventing symptomatic gallstone disease after RYGB or sleeve gastrectomy.
Study design: We will conduct a randomized, placebo-controlled, double-blind multicentre trial.
Study population: Patients aged 18-65 who are scheduled to undergo laparascopic RYGB or laparoscopic sleeve gastrectomy in the MC Slotervaart, OLVG West or MC Zuiderzee Lelystad. Exclusion criteria are prior bariatric or gallbladder surgery and symptomatic gallstone disease before bariatric surgery. Patients will receive a preoperative ultrasound, randomisation will be stratified for patients already having gallstones and for type of surgery.
Intervention: The intervention group will receive UDCA 900mg once daily (or 450mg twice daily) for six months. The placebo group will receive similar-looking placebo tablets.
Main study endpoints: The primary endpoint is the difference between the two groups in symptomatic gallstone disease within 24 months, defined as admission or hospital visit for symptomatic gallstone disease. Secondary endpoints consist of the development of gallstones or sludge on ultrasound at 24 months, presence of gallstones or sludge on ultrasound at 24 months, side-effects of UDCA, therapy compliance and cost-effectiveness, cost-utility and budget impact analyses
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Most of the procedures required for this study are similar to the current standard care. Additional measures include a gallbladder ultrasound preoperatively and after 24 months, the prescription of investigational product (UDCA or placebo) for 6 months, and several questionnaires that have to be filled in at 6 or 7 different time points. The risks of this study are minimal. UDCA has been used for several decades in the treatment of gallstone disease and other biliary diseases, and is known to have only few side effects and no serious side effects.

1. INTRODUCTION AND RATIONALE

The number of bariatric interventions for morbid obesity is rapidly increasing. Currently over 10000 interventions are performed annually in the Netherlands, compared to 8000 in 2013 and 5000 in 2011. [1-3] The laparoscopic Roux-en-Y gastric bypass (RYGB) is the bariatric intervention performed most often in the Netherlands as well as worldwide. However, in the past 5 years the sleeve gastrectomy (SG) is increasingly being performed, led by its technical simplicity and promising outcomes. At the moment, SG is the most performed bariatric surgery in the USA, Canada and Asia and the second most performed bariatric surgery in Europe and Latin America. [4] Rapid weight loss after bariatric surgery is a major risk factor for the development of gallstones. [5-7] Up to 40% of patients undergoing bariatric surgery who still have an intact gallbladder may develop gallstones. [7-12] Between 20-40% of the patients developing gallstones will become symptomatic. [7, 8, 13, 14] Overall, 8-15% of patients with an intact gallbladder undergoing bariatric surgery will develop symptomatic gallstone disease in the first two years after bariatric surgery. [8, 9, 15, 16] This number probably is an underestimation, because mentioned studies excluded patients with cholecystolithiasis prior to surgery, or performed concomitant cholecystectomy in these patients. This increased risk of gallstone formation was first described among patients undergoing RYGB. More recently, similar rates of gallstone disease are reported in patients who underwent SG. [10, 12, 17, 18] Two population-based studies from Sweden showed that patients who underwent bariatric surgery have a 5.5 fold increased risk of undergoing a cholecystectomy when compared to the general population, the incidence was highest between 7 and 24 months after bariatric surgery. [5, 19] The increased risk of gallstone development involves several determinants. Rapid weight loss leads to a change in cholesterol metabolism and consequently increases the concentration of cholesterol in the bile to a level at which not all cholesterol can be dissolved by the bile salts. The undissolved cholesterol is prone to crystallize into stones, especially in the presence of calcium and mucin, a glycoprotein that stimulates cholesterol crystal aggregation. [6, 20] The concentration of mucin in the bile increases 10-20 fold after bariatric surgery. The exact mechanism behind this increase is unknown. [20] The risk of gallstone formation is also increased by incomplete and slower emptying of the gallbladder, causing stasis of bile. [6]

Symptomatic gallstone disease can lead to severe complications such as cholecystitis, cholangitis, pancreatitis, and biliary colics. Acute (biliary) pancreatitis develops in 1% of all patients after bariatric surgery, compared to 0.017% in the general population. [21] In case of cholangitis, biliary pancreatitis or pain due to symptomatic bile duct stones, conventional endoscopic retrograde cholangiopancreatography (ERCP) cannot be performed after RYGB

due to the altered anatomy. Therefore more invasive procedures, such as an ERCP via double balloon enteroscopy or a surgically created gastrostomy, or percutaneous transhepatic drainage need to be performed in these patients. [22] The majority of patients with gallstone disease have milder disease and only suffer from biliary colics. These patients are treated with a laparoscopic cholecystectomy, which requires hospital admission and can be difficult due to adhesions caused by previous bariatric surgery. In general, the chance of conversion from laparoscopic to open cholecystectomy is up to three times higher after previous abdominal surgery. [23, 24] Conversion to open cholecystectomy increases the risk of postoperative complications and the hospital costs. [25] Another severe complication of cholecystectomy is bile leak due to bile duct injury (0.4-0.5%).[26, 27]

Several strategies have been proposed for the prevention of gallstone disease in patients undergoing bariatric surgery. Routine cholecystectomy during bariatric surgery has long been debated. Although some authors advocate routine cholecystectomy [28], this prolongs the duration of surgery and admission, increases the number of laparoscopy incisions required for surgery and carries a risk of complications, especially in this morbidly obese population. [29, 30] A selective approach in which all patients undergo pre-operative ultrasound and those with stones in the gallbladder undergo concomitant cholecystectomy, has been proven to lead to a higher morbidity and is therefore not recommended. [29, 31] A patient-based approach in which only patients at high risk of developing gallstone disease undergo treatment is not possible, as studies have failed to identify specific risk groups in the bariatric population at whom prophylactic treatment could be directed. [32-34] This is because the risk of gallstone development is very strongly correlated with the amount of weight loss. [33, 35] The amount of weight loss varies per patient and cannot be predicted beforehand. Other patient characteristics such as the traditional risk factors for gallstone formation play a minor role in this specific population.

An opportunity to medically prevent symptomatic gallstone disease during rapid weight loss is the administration of ursodeoxycholic acid (UDCA). UDCA is an orally taken bile acid that is known to prevent the formation of gallstones by increasing bile flow and reducing its lithogenicity. It is currently mainly used in chronic cholestatic diseases and is well tolerated with few side effects. A systematic review including 1447 patients in total showed that side effects were comparable to placebo. [36] Five randomised controlled trials have studied the use of UDCA for gallstone prophylaxis after different types of bariatric surgery (RYGB, gastric banding and vertical banded gastroplasty), the data of which has been pooled in two meta-analyses. [37, 38] In summary, UDCA for 3 to 6 months effectively prevents the formation of gallstones 24 months after bariatric surgery. The relative risk in an intention-to-

treat analysis was 0.43 (0.22-0.83) in favour of UDCA. [37, 38] However, the primary endpoint of all included studies consisted of the formation of gallstones on ultrasound and not symptoms of, or medical interventions for gallstones. Taking into account that 60-80% of patients with gallstones will remain asymptomatic [7, 8, 13], it is vital to choose a clinically relevant endpoint. Apart from the absence of a clinically relevant primary endpoint, most studies were underpowered and showed a high loss to follow-up. To date, there are only 3 studies who investigated and suggested the preventive effect of UDCA after SG. [10, 11, 39]

The current uncertainty about the use of postoperative gallstone prophylaxis is reflected in the different guidelines. Most recent guidelines for the postoperative treatment of bariatric patients such as the World Gastroenterology Organization guideline and the guideline by the Dutch Society for Surgery (Nederlandse Vereniging voor Heelkunde) do not cover postoperative gallstone prophylaxis. [40, 41] The 2013 guideline by the American Society of Metabolic and Bariatric Surgeons states that both prophylactic cholecystectomy and the postoperative use of ursodeoxycholic acid may be considered, but makes no definitive statement about either of the preventive strategies. [42] A survey among Dutch bariatric centres, performed by the MC Slotervaart, shows that none of the major centres perform prophylactic cholecystectomy, or prescribe UDCA prophylaxis.

2. OBJECTIVES

Primary objective

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

Secondary Objective(s)

Secondary objectives are the assessment of the health care efficiency of prophylactic use of UDCA and its budget impact.

3. STUDY DESIGN

We will conduct a multicentre, randomized, placebo-controlled, double-blind study of prophylactic use of UDCA versus placebo in bariatric surgery patients. The study population will consist of patients who are scheduled to undergo a RYGB or SG in the MC Slotervaart, OLVG West (formerly Sint Lucas Andreas hospital) and MC Zuiderzee Lelystad.

Approximately 10-15% of patients undergoing bariatric surgery already have asymptomatic gallstones. [13, 15] One study indicates that these patients do not have a higher risk of becoming symptomatic after bariatric surgery. [32] In current practice, these patients receive no extra treatment or prophylaxis after RYGB or SG. Therefore, these patients will also be included in this study. Before randomisation and surgery an ultrasound of the gallbladder will be performed by an experienced radiographer in all patients. Randomisation will be stratified for the presence of cholecystolithiasis and type of surgery.

UDCA will be prescribed as 900 mg once daily for six months. Patients are allowed to take one tablet of 450 mg twice daily if they prefer that. It is expected that UDCA use for longer than 6 months has no extra benefit. The risk of developing new gallstones is maximal in the period of rapid weight loss and decreases when the weight stabilizes. Seventy-five percent of the total weight loss resulting from RYGB and SG, is lost in the first six months. After these first six months, the weight loss decreases and eventually stops at 18-24 months after surgery. [43] Therefore the window of opportunity in preventing gallstone formation exists in the first 6 months after surgery. Less than 5% of the patients who have not formed gallstones at 6 months, will have developed gallstones at 12 or 18 months after surgery. [7] When the rapid weight loss stops, gallstones may even dissolve spontaneously in time. [44] In a retrospective study, 6 or 12 months of UDCA use made no difference in the preventive effect. [45]

The follow-up duration will be 24 months. Newly formed gallstones will typically become symptomatic in the first 6-18 months after formation. The mean time from surgery to the development of symptomatic gallstone disease is 10-11 months. [16, 33] The longer gallstones remain asymptomatic, the smaller the chance that they will ever become symptomatic. [46] A prospective cohort study including 984 patients showed that in all 80 patients who developed symptomatic gallstone disease, symptoms occurred in the first 29 months after surgery. None of the remaining patients underwent cholecystectomy in a follow-up period up to 144 months after bariatric surgery. [16] Therefore, a follow-up period longer

than 24 months is not expected to result in a significantly higher rate of symptomatic gallstone disease.

4. STUDY POPULATION

4.1. Population (base)

The study population consists of all patients planned for RYGB or SG in the three participating centres. In these centres, patients aged 18 - 65 are considered eligible for RYGB and SG.

4.2. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Scheduled to undergo Roux-en-Y gastric bypass or sleeve gastrectomy for morbid obesity
- An intact gallbladder

4.3. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Symptomatic gallstone disease already present before RYGB
- Prior bariatric surgery
- Prior gallbladder surgery
- Ascertained or presumptive hypersensitivity to active or excipient ingredients of UDCA.
- Inflammatory bowel disease and other conditions of the small intestine and liver which may interfere with enterohepatic circulation of bile salts (ileal resection and stoma, extra and intra-hepatic cholestasis, severe liver disease)
- Intake of investigational drug within the last 30 days before the screening

4.4. Sample size calculation

As discussed previously, 8-15% percent of patients with an intact gallbladder undergoing bariatric surgery will develop symptomatic gallstone disease in the first two years after surgery. To determine the prevalence in our population more accurately, we performed a

retrospective cohort study in our population. All 313 patients who underwent a RYGB in the MC Slotervaart from May to September 2012 were approached. (Unpublished data) The response rate was 93.9% (n = 294). Fifty-two patients (17.7%) had already undergone cholecystectomy prior to surgery. Of the remaining 242 patients, 26 (10.7%, 95% CI 7.4-15.3) developed symptomatic gallstone disease in the 24 months after surgery. Three of these patients had complicated gallstone disease, requiring multiple interventions and hospital admission of more than 14 days. We do not expect that the percentage of patients developing symptomatic gallstone disease after bariatric surgery has changed since 2012. Important baseline characteristics of potential influence, including Body Mass Index (BMI) at baseline, have remained constant over the years (2012: mean BMI 42.9 kg/m2, SD 5.58; 2015: mean BMI 43.0 kg/m2, SD 5.03). Secondly, the criteria (BMI >40 kg/m2 or a BMI >35 kg/m2 with obesity-related comorbidities) also have not changed and are unlikely to be changed in the nearby future. We further do not expect RYGB and SG to differ by amount of weight loss over time and we therefore assume a similar risk for patients of developing symptomatic gallstone disease.

It is estimated that UDCA gives a two- to threefold decrease in gallstone development when compared to placebo. [37, 38] We decided to calculate the power based on a two-fold reduction in gallstone disease, to minimize the risk of an underpowered study. Assuming a 50% reduction in symptomatic gallstone disease from 11 to 5.5%, a 2-sided 5% alpha, power of 80%, and 20% dropout, 980 patients in total are needed (Chi square test without correction for continuity).

About 20-25% of patients will already have undergone cholecystectomy or prior bariatric surgery. So, approximately 75% of patients will be eligible for inclusion. More than 1200 bariatric interventions are performed annually in the MC Slotervaart, and over 400 per year in each of the other centres. Therefore, we expect the inclusion to be finished within one year after the start of the study.

5. TREATMENT OF SUBJECTS

5.1. Investigational product/treatment

Ursodeoxycholic acid is an artificial bile acid that reduces the ratio of cholesterol to bile salts plus phospholipids in bile, causing desaturation of cholesterol saturated bile.
In this study it is prescribed as tablets of 450mg, 2 tablets once daily. Patients are allowed to take one tablet twice daily if they prefer that. The placebo will be similar in look but without active ingredients.

5.2. Use of co-intervention (if applicable)

Not applicable

5.3. Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1. Name and description of investigational product(s)

Ursodeoxycholic acid is an orally taken bile acid that reduces the cholesterol / bile acid ratio in the bile, thereby reducing the risk of gallstone formation.

The placebo will be similar in look but without active ingredients.

6.2. Summary of findings from non-clinical studies

See Summary of Product Characteristics, section 5.3.

6.3. Summary of findings from clinical studies

See Summary of Product Characteristics, sections 4.1 - 4.9.

6.4. Summary of known and potential risks and benefits

See Summary of Product Characteristics, section 4.3, 4.4 and 4.8

6.5. Description and justification of route of administration and dosage

UDCA will be prescribed as 900 mg once daily for six months. This dose was shown to be more effective in preventing gallstone formation than 300mg once daily. [38] Ideally, UDCA dosage is calculated based on body weight. However, as patients rapidly lose weight during the course of treatment, this would mean that the UDCA dose has to be adjusted on a weekly basis and is therefore not a feasible approach. By choosing 900mg daily as dose in this study, it is made sure that all patients receive the minimal therapeutic dose.

6.6. Dosages, dosage modifications and method of administration

Intervention treatment: Ursodeoxycholic acid 450mg, two tablets once daily.
Placebo treatment: Placebo tablet, two tablets once daily.

6.7. Preparation and labelling of Investigational Medicinal Product

Production of the placebo, preparation, randomisation and labelling is performed in accordance with GMP and GCP guidelines by the pharmacy of the MC Slotervaart, which is licensed in Good Manufacturing Practice and has ample experience with randomised clinical trials.

6.8. Drug accountability

Ursodeoxycholic acid will be delivered by Zambon BV to the pharmacy of the MC Slotervaart. The MC Slotervaart pharmacy will repack the ursodeoxycholic acid into the correct dose per patient and label the packages with the randomisation numbers and other information required by GMP.

The placebo tablets are produced by the pharmacy of the MC Slotervaart in accordance with GMP guidelines, packed in the correct dosage and labelled with the randomisation numbers. The pharmacy of the MC Slotervaart will distribute the investigational products to the local pharmacies.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1. Study parameters/endpoints

Endpoint adjudication will be done by the investigators when they are blinded. All primary endpoints will be reviewed by a blinded independent endpoint adjudication committee.

8.1.1. Main study parameter/endpoint

The primary endpoint of this study is symptomatic gallstone disease within 24 months, defined as hospital admission or hospital visit for symptomatic gallstone disease. Hospital visit is a condition, because all patients with noteworthy symptoms will eventually visit the hospital. Mild and self-limiting complaints are not a large burden to the health care system or to the patient, and usually gallstone involvement is not objectified in these patients.

Symptomatic gallstone disease is defined as biliary disease (biliary pancreatitis, acute cholecystitis, choledocholithiasis, cholangitis, or biliairy colics).

Acute pancreatitis is diagnosed when at least two of the three following features are present: 1. Upper abdominal pain; 2. Serum lipase or amylase levels above three times the upper level of normal; 3. Characteristic findings of acute pancreatitis on cross-sectional abdominal imaging. [47] Biliary pancreatitis is diagnosed when one of the following definitions is present 1. Gallstones and/or sludge diagnosed on imaging (transabdominal or endoscopic ultrasound or computed tomography); 2. In the absence of gallstones and/or sludge, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old); 3. The following laboratory abnormality: alanine aminotransferase (ALT) level >2 times higher than normal values, with ALT >aspartate aminotransferase.

Acute cholecystitis is defined according to the 2007 Tokyo classification. There must be at least one local sign of inflammation: 1. Murphy's sign; 2. Right upper quadrant mass/pain/tenderness. And at least one systemic sign of inflammation: 1. Fever; 2. Elevated C-reactive protein; 3. Elevated white blood cell count. Positive imaging findings characteristic of acute cholecystitis confirm the diagnosis in case of clinical suspicion.

Biliary colics are defined as upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes with gallstones or sludge visible on abdominal imaging, according to the Rome criteria.

Choledocholithiasis is defined as the presence of stones in the extrahepatic bile ducts as proven by clinical imaging OR clinical suspicion based on abnormal liver function tests in combination with upper abdominal pain for which an ERCP or PTC was indicated.

Cholangitis is diagnosed according to the diagnostic criteria of the updated Tokyo Guidelines (TG13). Suspected diagnosis: One item in A + one item in either B or C.
A. Systemic inflammation
A-1. Fever and/or shaking chills (BT >38 °C)
A-2. Laboratory data: evidence of inflammatory response (abnormal white blood cell count, increase of serum C-reactive protein levels, and other changes indicating inflammation)
B. Cholestasis
B-1. Jaundice (T-Bil ≥ 34 μmol/L)
B-2. Laboratory data: abnormal liver function tests (increased serum alkaline phosphatase, gamma-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase levels >1.5x higher than the upper limit of normal value)
C. Imaging
C-1. Biliary dilatation
C-2. Evidence of the etiology on imaging (stricture, stone, stent etc.)

8.1.2. Secondary study parameters/endpoints

Secondary endpoints are:

1. The development of gallstones or sludge on ultrasound at 24 months (window 18-30 months) in the gallstone negative group.
2. Presence of gallstones or sludge on ultrasound at 24 months (window 18-30 months)
3. Number of cholecystectomies in the intervention and the placebo group.
4. Side-effects of UDCA.
5. Therapy compliance.
6. Quality of life, cost-effectiveness, cost-utility and budget impact analyses.

8.1.3. Other study parameters

Other study parameters include characteristics such as age, sex, weight, height, Body mass Index, comorbidities, medical history, medication use, weight loss after surgery and complications.

8.2. Randomisation, blinding and treatment allocation

After the investigator has determined the patient is eligible for inclusion, and the patients has given informed consent, a gallbladder ultrasound is performed by an experienced radiographer, either a radiologist, radiography assistant or a trained physician. Randomisation is stratified for the presence of gallstones and type of surgery. Patients are randomised to receive either UDCA 900 mg once daily (or 450mg twice daily) or placebo in a 1:1 ratio. Randomisation will be performed using a computerized randomisation program (ALEA), which is validated for use in GCP trials. Each randomized subject is given a randomisation number. This number is written on the (digital) prescription that is transferred to the pharmacy and corresponds to a certain package of investigational product, whether this package contains placebo or ursodeoxycholic acid is known only by the pharmacist. This way blinding of the investigators and patients is assured. In case of a suspected unexpected serious adverse reaction (SUSAR) treatment with the investigational product is discontinued and the deblinding procedure is initiated.

8.3. Study procedures

The majority of patients is first informed about the study during the screening procedure for bariatric surgery, this procedure generally takes 1-3 months. After the screening procedure is finished, patients have an appointment with the surgeon in which the result of the screening is discussed and, when patients are considered eligible for bariatric surgery, they are put on the waiting list. At this time, the patient is also asked to give informed consent for this study, either by the surgeon, nurse practitioner or by the PhD-student. A minority of patients is informed about the study after the screening procedure when they are already put on the waiting list for RYGB or SG. These patients sign the informed consent form at the day of surgery. The ultrasound of the gallbladder has to be performed in the period between informed consent and surgery. At the time of writing (September 2016) this period takes approximately 8 weeks. It is the intention to perform the ultrasound concurrently with a hospital visit for regular care during this period. The result of the gallbladder ultrasound is blinded, to prevent “nocebo-effect”. It is likely that patients who are told they have gallstones are more prone to attribute abdominal symptoms to these gallstones. Knowledge of the presence of gallstones might therefore influence the number of cholecystectomies performed.

Patients are generally admitted for one day after surgery. When they go home they receive the study medication together with the standard prescription for pantoprazole and

the instructions to start multivitamins. In the MC Slotervaart and OLVG West, patients receive the study medication for the first 10 weeks. Patients who undergo surgery in the OLVG West, but who are not part of the Nederlandse Obesitas Kliniek (NOK) Amsterdam (e.g; NOK Nieuwegein or NOK Beverwijk) receive the study medication for the entire treatment period (26 weeks). In the MC Zuiderzee, patients also receive the study medication for the entire treatment period. Study medication has to be started as soon as possible, preferably within two weeks after surgery, but eight weeks the latest. A maximum mid-term break of four weeks was allowed during the treatment course.

The follow-up schedule for data collection in the study includes 5 visits. To facilitate visit compliance in the three centres we established time windows. The first follow-up visit is ideally scheduled at 6 weeks, the window for the first visit opens at the start of week 4 and closes at the end of week 8. The second visit is scheduled at 16 weeks, with a corresponding window of 14-18 weeks. The third visit is scheduled at 6 months, corresponding window: 5-9 months. The fourth visit is scheduled at 12 months, corresponding window: 10-15 months. The last visit is scheduled at 24 months, corresponding window: at least after 24 months.

The follow-up schedule for this study is very similar to the regular follow-up schedule in the three centres. Therefore, there is no need for extra study-related hospital visits. However, the implementation of the study follow-up schedule slightly differs between the 3 centres, because of the differences in regular care.

Regular care in the MC Slotervaart includes follow-up appointments at 2 and 6 weeks, 4, 6, 12 and 24 months. In the OLVG West regular follow-up care is conducted by an independent clinic: de Nederlandse Obsitas Kliniek. The study follow-up will be performed by the study staff. Patients will be called by telephone at 6 weeks, 4 months, 6, 12 and 24 months. In the first year after RYGB or SG, regular care in the MC Zuiderzee includes 3 follow-up appointments with the surgeon or nurse practitioner and 3-4 appointments with the dietician. In the second year, there are 2 regular follow-up appointments with the surgeon or nurse practitioner and 2 appointment with the dietician. If the regular visits do not correspond with the time windows of the study follow-up visits patients will be called by telephone.

The follow-up schedule for this study was almost not affected by the unexpected bankruptcy of two participating centers, the MC Slotervaart and MC Zuiderzee. The entire bariatric department of the MC Slotervaart is transferred to the Spaarne Gasthuis and

regular follow up care is restarted. In case patients did (or will) not visit the outpatient clinic for regular follow up, patients are called by telephone to guarantee study follow up. Before the bankruptcy, we also phoned patients in case they missed their regular follow-up appointment in the outpatient clinic of the MC Slotervaart. The entire bariatric department of the MC Zuiderzee is transferred to the Flevoziekenhuis (date: 1-3-2019). In the Flevoziekenhuis, the regular care and study follow up schedule will not be changed because it will be conducted according to the schedule of the former MC Zuiderzee. According to protocol, if these regular visits do not correspond with the time windows of the study follow-up visits patients will be called by telephone.

At each follow-up appointment, patients are asked for symptoms of, or manifestations of gallstone disease (such as a cholecystectomy performed in another hospital). In case of suspected gallstone disease, the clinician follows the standard protocol. Patients are asked for side effects of the study drug at the 6-week, 4 and 6-month appointment and for therapy compliance at the 6-month appointment.

In case the patient reaches the primary endpoint (i.e. develops symptomatic gallstone disease) in the first 6 months after surgery, the study medication will be discontinued.

In regular care, postoperative diarrhoea is treated with generous intake of fluids and antidiarrheal drugs when necessary. In case of diarrhoea (defined according to the WHO as the passage of three or more loose or liquid stools per day) that is considered burdensome by the patient, does not respond to regular treatment, persists for longer than one week and is possibly related to the study drug, the study drug dose can be halved to 450mg once daily. If the diarrhoea still persists after one week of follow-up, the study drug can be discontinued.

At the 6-week appointment, new study medication is collected by patients at the pharmacy in case they only received the first part of the study medication when they were discharged. Six to eight months after surgery, the patients discontinues the use of the study drug. The patients are asked to return the package material of the study drug that was taken together with any leftovers of the study drug at the 6-month visit. These are used to determine therapy compliance (see below).

At the 24-month appointment, the gallbladder ultrasound is repeated to evaluate the presence of gallstones (window 18-30 months).

A schedule of the procedures in regular care and the extra procedures for this study is shown in Appendix: Flowchart.

Therapy compliance

Therapy compliance is measured in three ways. Patients are asked at the 6-months follow-up appointment to indicate how many days per week they took their study medication and this is scored in the file. Secondly, a pill count is performed by the clinician. This is an efficacious method to determine therapy compliance in clinical trials.[48] Patients are asked to return the package material of the medication that was taken at the 6-months follow-up visit. The number of pills left in the package is then counted by the clinician. Furthermore, patients have to fill in a questionnaire about study medication adherence 6 weeks and 6 months after surgery. The questionnaire is administered via (e-)mail. Good therapy compliance was defined as a minimum of 300 pills taken within a timeframe of 6-8 months after surgery.

Quality of life, cost-effectiveness, cost-utility and budget impact analyses.

Participating patients are monitored regarding use of health care, quality of life and health utility, productivity loss and out-of-pocket expenses. The primary outcomes of these analyses will be the costs per patient without poor outcome (defined as symptomatic gallstone disease), and costs per quality adjusted life year (QALY). A budget impact analysis from a governmental and health insurer perspective will be performed, describing the financial consequences of prophylactic use of UDCA and reduced numbers of surgical interventions for the extramural medication budget and budget for specialized health care. If >10% of all included patients received SG, then an exploratory subgroup analysis of differences in QALYs and costs will be performed to assess the need for extrapolation scenarios that account for the potential future growth in popularity of SG among patients.

Preoperatively, 3, 6, 12, 18 and 24 months after surgery, patients have to fill in three questionnaires: the EQ-5D-5L for quality of life and the Medical Consumption Questionnaire (MCQ) and Productivity Cost Questionnaire (PCQ) for the economic evaluations. The questionnaires are administered via (e-)mail. In case patients do not have an (e)mail-address, the patients are called to fill in the questionnaire or it can be filled in at a regular follow-up appointment. The iPCQ and iMCQ have been slightly adjusted for this study in order to be more specific for the study population and procedure. To give one example, the question about visits to a speech therapist was removed from the iMCQ, as this is not a relevant endpoint when it comes to gallstone disease. In the original validated version of the iMCQ and iPCQ the authors explicitly permitted these kind

of changes to the questionnaires without limiting the validity. The versions of the questionnaires that will be administered are available in the appendix: Questionnaires.

Furthermore, the SF-36 or the RAND-36 (almost identical to the SF-36), which are also questionnaires concerning quality of life, are already administered in current practice. The results of the SF-36/RAND-36 and EQ-5D-5L will be combined for the secondary endpoint quality of life.

8.4. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5. Replacement of individual subjects after withdrawal

When patients withdraw after randomisation, they will not be replaced, except for patients who decided for SG and discarded RYGB prior to this protocol amendment. In the power analysis, a 20% correction for dropout is included to ensure enough statistical power even when a relatively high number of patients drops out.

8.6. Follow-up of subjects withdrawn from treatment

Subjects withdrawn from treatment will be asked to give permission for receiving the follow up schedule for this study, as the follow up schedule for this study is very similar to the regular follow up schedule.

8.7. Premature termination of the study

It is unlikely the study has to be terminated prematurely. In case this does happen, distribution of the study drug is discontinued and patients will receive follow-up according to the regular follow-up schedule.

9. SAFETY REPORTING

9.1. Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended

pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2. AEs, SAEs and SUSARs

9.2.1. Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events, reported by the subject or observed by the investigators, meeting all of the following criteria will be recorded:

- Severity: moderately severe, or mildly severe lasting longer than one week.
- Causality: there needs to be a reasonable suspicion of the AE being an effect of the intervention. This includes the following adverse events: diarrhoea, abdominal pain, and skin rash. For the record, AEs will be registered and reported if they occurred within 30 days of the last dose of study medication.

9.2.2. Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

SAE's after bariatric surgery are relatively common. Short-term complications of the RYGB such as staple line leakage, infection, bleeding and thrombo-embolic events have a combined prevalence of 5%. [49] The mortality of primary RYGB is 0.03% in the MC Slotervaart, and at least <0.2% in experienced centres. [50] Similarly, the overall mortality rate of SG is 0.3%. [51, 52] In the first two years after RYGB, the most prevalent complications apart from gallstone disease are internal herniation, marginal ulcers and stenosis with a combined prevalence of 1-5%. [53-55] The most common complications of SG include bleeding, gastric leaks and gastroesophageal reflux disease. [51, 56-59] Since

980 patients will be included in this study, it is expected that SAEs will occur in about 50 patients. Given the expected high prevalence, SAEs will be registered and reported in the annual safety report, instead of expedited reporting. For the record, only SAE's that occurred after start of the study medication will be registered and reported. They will be reported till the end of study.

9.2.3. Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report. Local investigators will report all SUSARs to the coordinating investigator. The coordinating investigator is responsible for reporting SUSARs to the sponsor.

When deblinding is considered necessary by the clinicians involved in the treatment of the patient, the study coordinator is notified. The pharmacist and the coordinating investigator will decide whether it is necessary to break the randomisation code. If so, the independent physician can break the code and discuss the results with the attending clinician of the patient. This way, blinding of the investigators is not disrupted.

9.3. Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.
- A list of all SAEs in the past year.

9.4. Follow-up of adverse events

All (S)AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5. [Data Safety Monitoring Board (DSMB) / Safety Committee]

Due to the design of the study an interim analysis is not feasible. Patients will develop symptomatic gallstone disease at a mean time of 11 months after surgery. As inclusion is

scheduled to take approximately 12 months, an interim analysis for effect or futility will have no consequences for the number of patients that has to be included.

However, a DSMB could be useful for monitoring of the safety of the drug. As UDCA has been prescribed in clinical practice for several decades and there have never been any serious safety concerns with UDCA, we have chosen not to install a formal DSMB. However, dr. AJ Bredenoord, gastroenterologist and member of the medical ethics committee of the Academic Medical Center, will function as independent reviewer regarding drug safety. When 50% of the total number of patients has finished the six months of UDCA, the independent reviewer will be informed about all SAE's. To prevent deblinding of the researchers, the Clinical Research Unit will provide the reviewer with the allocation code directly without involvement of the researchers.

10. STATISTICAL ANALYSIS

10.1. Primary study parameter(s)

The primary endpoint is the difference in symptomatic gallstone disease between the placebo and the UDCA group within 24 months of follow-up. The analysis will be performed as intention-to-treat. For missing data a multiple imputation approach will be selected (and justified) that best fits the observed missing data pattern at the time of analysis. A sensitivity analysis will be performed for which only cases with complete follow-up will be analyzed. The difference in symptomatic gallstone disease will be compared using the chi-square test.

10.2. Secondary study parameter(s)

The secondary endpoints development of gallstones or sludge on ultrasound at 24 months (window 18-30 months) in the gallstone negative group; presence of gallstones or sludge on ultrasound at 24 months (window 18-30 months), number of cholecystectomies in the intervention and the placebo group; side-effects of UDCA; and therapy compliance; are all binary variables that can be analyzed using chi-square testing.

Quality of life, cost-effectiveness, cost-utility and budget impact analyses.

General considerations

The economic evaluation of prophylactic UDCA use after bariatric surgery will be performed as cost-effectiveness and cost-utility analyses from a societal perspective with the costs per patient without symptomatic gallstone disease and the costs per quality adjusted life year (QALY) as primary economic outcomes respectively. The cost-effectiveness analysis (CEA) closely relates to the clinical outcome parameter and may be used for prioritization or bench marking of treatment strategies in the fields of gastroenterology and surgery. The cost-utility analysis allows for priority setting during health care policy making across patient groups, interventions and health care settings. The comparator for prophylactic use of UDCA will be placebo treatment. The time horizon will be 2 years after surgery, which equals the length of the follow-up period that is clinically relevant. Considering this length, health effects and costs in the second year of follow-up will be discounted against base rates of respectively 1.5% and 4%. Because gallstone development and treatment will take place well within the first 24 months following bariatric surgery without longer lasting effects, a lifetime horizon is not

opportune here. Incremental cost-effectiveness ratios will be calculated as the extra costs per additional patient without symptomatic gallstone disease and as the extra costs per QALY gained. Sampling variability will be accounted for by bias-corrected and accelerated non-parametric bootstrapping. Results will be reported along with their 95% confidence intervals and displayed graphically with cost-effectiveness (CE) planes and with cost-effectiveness acceptability curves for societal willingness-to-pay (per QALY) levels up to 100,000 euros. One-way and multi-way sensitivity analyses will be done for unit costs of UDCA (minus 5% and 10%), plausible ranges (plus or minus 10%) in unit costs of biliary complications, for international differences in utility weights (see below), and for different discounting rates (effects: 0%, 1.5%; costs: 0%, 3.5%, 4%). Explorative subgroup analyses will be performed for patients with or without cholecystolithiasis, for type of surgery, and for distinct treatment centres. If the CE-plane precludes dominance of one intervention over the other, we will subsequently perform value-of-information analysis and identify the parameters on which additional data should be collected, by calculating the expected value of (partial) perfect information.

Cost analysis: components, data source, unit costing

Medical, patient and employer costs will be included in the evaluation. The medical costs cover the costs of (1) diagnosis (ultrasound, CT-scanning), (2) admission for and treatment with cholecystectomy, (3) admissions other than for cholecystectomy (for example pancreatitis, choledocholithiasis, biliary colics), and (4) treatment other than with cholecystectomy (for example ERCP, percutaneous transhepatic drainage). The evaluation will NOT include the research costs of the placebo compound; placebo treatment is no real option in daily practice and including the costs of the placebo compound would only let prophylactic UDCA treatment look more efficient than it actually is. The patient costs include the expenses for over-the-counter medication, non-reimbursable dietaries, and health care related travel. The employer costs reflect losses of productivity resulting from absenteism and presenteism. Use of health care resources will be retrieved from the clinical report forms and patients' hospital records. Because patients receive bariatric surgery to begin with, their health care demand will very much be hospital or medical specialist oriented and just a shortened version of the iMTA Medical Consumption Questionnaire (iMCQ) will disseminated half-yearly to gather data on out-of-hospital health care resources. Productivity losses from absenteism and presenteism will half-yearly be gathered with the iMTA Productivity Costs Questionnaire (iPCQ). Questions on actual out-of-pocket expenses by patients will be added to the iPCQ. Unit costing of health care resources will be derived from the most recent national health care costing guideline for (pharmaco-)economic evaluations at the time of analysis

in 2018. Productivity losses will be based on the friction cost method, again taking the most recent estimate in 2018 for the length of the friction period as reference. All costs will be expressed in Euros for the base year 2018. Unit costs borne in other calendar years will be price indexed (based on general yearly consumer price indices).

Patient outcome analysis

The relevant patient outcomes for this modelling study are all biliary complications (see before). The SF-36/RAND-36 is already administered preoperatively, 1 year after surgery and 2 years after surgery in the standard treatment protocol of all three centers. In addition, the validated EQ-5D-5L will be used to gather information on patients' health states at baseline, 3 and 6 months and subsequently at half-yearly intervals. Based on the EQ-5D-5L scoring profiles, health utilities will be derived from readily available cross-walk value sets from the www.euroqol.org website. Subsequently, QALYs will be quantified as the area under the curve for health utilities over time following interpolation between successive measurements.

Budget impact analysis

The mid term budget impact (up to four calendar years) of standard prescription of UDCA after bariatric surgery will be assessed from governmental, insurer and hospital care provider perspectives, in accordance with a recent ISPOR-guideline42 and upcoming Dutch BIA manual. The governmental perspective is chosen to help setting priorities in health care optimization and further includes an impact assessment on budgets for (i) specialist medical care and (ii) extramural drugs (State budget 2016, premium financed health care expenditures). The insurer perspective is chosen to assess the net financial consequences of standard prescription of UDCA rather than the current clinical practice. Budget impact analyses may guide reimbursement decisions and may influence price and volume negotiations between insurer and health care provider and between health policy makers and the pharmaceutical industry (as the price of UDCA tablets has recently increased). The hospital care provider perspective is chosen to assess the consequences of a reduced number of biliary complications on returns and on returns per employed or contracted surgeon and gastro-enterologist. In this study, the budget impact analyses will be prevalence-based, meaning that the yearly estimates include the UDCA drug costs and the hospital care expenditures of patients with biliary complications. The analyses will further be patient- rather than episode-based, covering the health care costs observed during the full 2 years of follow-up.

Cost analysis

For the budget impact analysis the actual financing model of health care in the Netherlands at the time of analysis will frame the costing approach. Principally, the extra expenses for UDCA will be revenued separately from the reimbursement of treatment costs of biliary complications through DOT-charges. In case of impact assessments concerning premium financed health care and from the insurer perspective, existing (ranges in) charges at the time of analysis will be used. Unit costs derived from the hospital ledger as well as charges will be used to assess the budget impact for participating hospitals. To determine the real revenues, distinct diffusion scenarios of prophylactic UDCA during bariatric surgery will be sketched. These include immediate or gradual, full or partial implementation scenarios. The time horizon will be four calendar years and results will be reported in millions of Euros per calendar year for all perspectives taken.

10.3. Interim analysis

No interim analysis will be performed as this is not feasible due to the methodology of the study (see also section 9.5).

10.4. Regulation statement

This study will be conducted in accordance with the principles of the Declaration of Helsinki (latest version, October 2013) and in accordance with the regulations in the Medical Research Involving Human Subjects Act (WMO).

10.5. Recruitment and consent

The majority of patients is first informed about the study during the screening procedure for bariatric surgery, this procedure generally takes 1-3 months. This will be done both by written information (information letter in the screening envelope; information poster in the waiting room) and orally by the treating physicians during the scheduled appointments. After the screening procedure is finished, patients have an appointment with the surgeon in which the result of the screening is discussed and, when patients are considered eligible for bariatric surgery, they are put on the waiting list. At this time, the patient is also asked to give informed consent for this study, either by the surgeon, nurse practitioner or by the PhD-student. If patients require more time to decide, the informed consent can be obtained at any time between the appointment with the surgeon and the operation. At the time of writing (September 2016) this period takes approximately 8 weeks. A minority of patients is informed about the study after the screening procedure when they are already put on the waiting list for bariatric surgery. These patients sign the informed consent form at the day of surgery.

10.6. Objection by minors or incapacitated subjects

No minors or incapacitated subjects will be included, as only adults over 18 years old who are deemed mentally fit after screening by a psychologist are eligible for bariatric surgery in the participating centres.

10.7. Benefits and risks assessment, group relatedness

Participation might be beneficial for patients receiving ursodeoxycholic acid, as the hypothesis of this study is that UDCA will decrease the risk of symptomatic gallstone disease by at least 50%. Risks of this study are minimal, as UDCA has few side effects and no serious side effects. However, there is a chance of incidental findings at the gallbladder ultrasound (see chapter 12.2). There are no subgroups that are expected to have a higher chance of benefit or risk from this study.

10.8. Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.9. Incentives

Not applicable.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1. Handling and storage of data and documents

For this study, the PhD-student and independent monitor will have access to the electronic patient files of the participating patients in all participating centers in order to collect data. An electronic Case Record Form will be developed using the program CastorEDC. This is a validated program for GCP studies. For initial data collection, standardized written forms will be used where possible. Patient data will be coded after collection to ensure subject privacy. The key to decode the patient data is accessible only by the PhD-student and the principal investigators.

Methodological and data management support is provided by the clinical research unit (CRU) of the AMC. The AMC implemented a SOP for research data management. This guides, amongst others, data stewardship, control on the (software) applications and adherence to the AMC policy for privacy and security. Data storage falls under the central IT-regime. In the AMC the quality of data storage is standardized.

11.2. Monitoring and Quality Assurance

Monitoring will be done by an independent monitor provided by the CRU of the AMC. Because the study was classified as very low risk, monitoring will consist of an initiation visit to all participating sites, and an annual visit to each site after initiation. The monitor will focus on the quality of data collection for the primary endpoint and patient safety. A monitoring plan is currently developed by the monitor.

11.3. Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4. Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5. Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.6. Public disclosure and publication policy

The trial results will be published open access in a peer reviewed scientific journal. The funding parties have no influence on the content or timing of the publication. The trial and protocol will be registered in a public trial registry before inclusion of the first patient. After the end of the study, raw data will be made available on request as is stipulated by ZonMW for all ZonMW-funded research. The requests will be discussed by the principal investigator and project leader.

12. STRUCTURED RISK ANALYSIS

12.1. Potential issues of concern

See 12.2

12.2. Synthesis

Chapter 12.1 was skipped because UDCA is used within the indication of dissolution of gallstones or prevention of gallstone formation. There is ample experience with UDCA in clinical practice. It is well tolerated with few side effects. A systematic review including 1447 patients in total showed that side effects were comparable to placebo. [36]
The main risk arising from the study procedures is the chance of incidental findings at gallbladder ultrasound. The aim of the ultrasound is to only visualize the gallbladder, thereby minimizing other incidental findings. The prevalence of gallbladder polyps varies widely, but generally the prevalence of gallbladder polyps > 6 mm in size is less than 1% in the general population. [60] The risk of malignancy is negligible in asymptomatic patients with a gallbladder polyp smaller than 6 mm. [61] Patients with an incidental finding of a gallbladder polyp larger than 6 mm require a repeat ultrasound after 6 months and will be referred to their general practitioner for follow-up.

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