ASAC TRIAL
Scandinavian Livermet Study

ACETYLSALICYLIC ACID AS SECONDARY PREVENTION IN COLORECTAL CANCER (ASAC TRIAL)

A multi-centre, double-blinded, randomized, placebo-controlled clinical intervention trial with ASA in patients undergoing liver resection for CRC metastasis

Protocol Identification Number: ASA-CRCLM-2014

EudraCT Number: 2014-003601-15

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- CONFIDENTIAL -

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SIGNATURE PAGE

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A multi-centre, double-blinded, randomized, placebo-controlled clinical intervention trial with ASA in patients undergoing liver resection for CRC metastasis

Protocol ID no: ASA-CRCLM-2014

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ClnicalTrials.gov Identifier: NCT03326791

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Elin Henriksen	Head of department, OUS	Sponsor		20.10.2017
Bjørn Atle Bjørnbeth	MD PhD	Principal investigator (PI)		20.10.2017
Kjetil Tasken	Professor, MD PhD	Co-PI		20.10.2017
Sheraz Yaqub	MD PhD	Coordinating investigator		20.10.2017

SIGNATURE PAGE – PRINCIPAL INVESTIGATOR

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Bjørn Atle Bjørnbeth	MD PhD	Principal investigator (PI)		20.10.2017
Kjetil Tasken	Professor, MD PhD	Co-PI		20.10.2017

PROTOCOL SYNOPSIS

Acetylsalicylic acid as secondary prevention in colorectal cancer (ASAC trial)
A multi-centre, double-blinded, randomized, placebo-controlled clinical intervention trial with ASA in patients undergoing liver resection for CRC metastasis

Sponsor	Oslo University Hospital, Elin Henriksen
Phase and study type	Phase II, multicentre, randomized, placebo-controlled, group sequential clinical intervention trial
Investigational Medical Product (IMP) (including active comparator and placebo) :	Trombyl 160 mg (Pfizer); Active ingredient: Acetylsalicylic acid (ASA) Comparator: Placebo (by ClinStorage AB, Sweden)
Centres:	**NORWAY:** Oslo University Hospital (Oslo) Stavanger University Hospital (Stavanger) Haukeland University Hospital (Bergen) St.Olavs Hospital (Trondheim) University Hospital of Northern Norway (Tromsø) **SWEDEN:** Sahlgrenska University Hospital (Gothenburg) Karolinska University Hospital (Stockholm) Linköping University Hospital (Linköping) Lund University Hospital (Lund) Uppsala University Hospital (Uppsala) **DENMARK:** Rigshospitalet University Hospital (Copenhagen) Aarhus University Hospital (Aarhus)
Study Period:	Estimated date of first patient enrolled: November 2017 Anticipated recruitment period: 3 years Estimated date of last patient completed: October 2023
Treatment Duration:	36 months (3 years) or until disease recurrence
Follow-up:	The patients will be followed in the outpatient clinics according to the National Guidelines for treatment of colorectal liver metastases with clinical control and CT of the chest and abdomen at 4, 8, 12, 18, 24, 30 and 36 months to investigate for any disease recurrence and register challenges regarding the study drug. The total study duration is 36 months.
Objectives	Primary objective: To determine whether treatment with 160 mg ASA (Trombyl) once daily for 3 years can improve Disease Free Survival (DFS) in patients treated with resection for CRCLM, compared with placebo Secondary objectives:

- To determine the effect of 160 mg ASA on Time to Recurrence (TTR) and Overall Survival (OS) compared to placebo
- To determine the effect of 160 mg ASA on Health-related Quality of Life (HRQOL) outcome measures. The related endpoints will be the eight RAND 36-Item Health Survey 1.0 (SF-36) dimension scores as well as physical and mental health summary measures, and the EQ-5D index value

Exploratory objectives:

- To determine whether 160 mg ASA can improve DFS and OS in patients with mutations in PIK3CA and KRAS
- To determine the cost-effectiveness of 160 mg ASA compared to placebo
- Direct medical-care costs, Quality-Adjusted Life-Years (QUALYs) and life-years gained

Efficacy endpoints:

Primary endpoint: Time from randomisation to disease recurrence or death by any cause (DFS)

Secondary endpoints:

- Time from randomisation to disease recurrence (TTR)
- Time from randomisation to death by any cause (OS)
- HRQOL outcome measures
  - SF36
  - EQ-5D health surveys

Study Design:

This is a multicentre, randomized, blinded, placebo-controlled, group-sequential trial. There will be an interim analysis when approximately half of the planned primary events (disease recurrence) have occurred. The study may be stopped for efficacy at this interim analysis.

Main Inclusion Criteria:

All patients undergoing radical liver resection for CRCLM as a part of a curative intent (macroscopic surgical free resection margin, R0 or R1) or combined with radiofrequency or microwave ablation technique:

- First time CRCLM (synchronous or metachronous), or
- Recurrence of CRCLM (not previously included in this trial)

Main Exclusion Criteria:

- Concomitant use of ASA or other anticoagulants or platelet inhibitors such as warfarin or klopidogrel
- Inherited or acquired coagulopathy (haemophilia)
- Blood platelets (thrombocytes) < 100 x 10^9/L
- Severe heart
- Kidney failure

- Pregnancy
- Ongoing regular use of corticosteroids, NSAIDs
- Contraindication listed on the Summary of Product Characteristics (SmPC) of Trombyl:
    - Hypersensitivity/allergies to ASA or NSAIDs
    - Previous severe gastrointestinal haemorrhage/peptic ulcer due to ASA/NSAID
    - Active peptic ulcer
- Need to use medications contraindicated according to SmPC of Trombyl from Swedish Medicines Agency

Sample Size:	Up to 800 patients will be randomized to 2 study arms; Arm#1 receiving ASA 160 mg once daily until recurrent disease or a total period of 3 years; Arm#2 Placebo. The final sample size is conditional on the efficacy evaluation of the interim analysis.
Efficacy Assessments:	At each study visit, the patients will be assessed by CT scan or MRI for disease recurrence. Death by any cause will be recorded at time of event.
Safety Assessments:	Safety will be monitored by laboratory assessments (haematology and biochemistry), collection of AEs, physical examination and evaluation of performance status using WHO/ECOG performance status scale at every visit.
Other Assessments:	Molecular profiling of the tumours (both primary and metastases) to assess for gene alterations like mutations in PIK3CA (exon 9 and exon 20) or KRAS will be recorded as well as immune profile of the tumours and used to stratify the material. The study subjects will complete a short-form health survey SF-36 and EQ-5D on at every visit.
Statistical Methods	Patients will be randomised to 160 mg ASA or placebo in a 1:1 ratio. The null hypothesis for the comparison of DFS, and for the secondary endpoints, is that there is no difference between the treatment arms; the alternative hypothesis is that a difference exists. All tests will be two-sided. Superiority of 160 mg ASA will be demonstrated only if the nominal p-value from the appropriate two-sided test is less than the significance level of 0.01 at the interim analysis and 0.0456 at the final analysis, and the efficacy estimate is in favour of the ASA arm. The primary efficacy endpoint, time from randomisation to disease recurrence or death by any cause, as well as all time-to-event secondary endpoints will be analysed using a stratified log-rank test accounting for the stratification factor (study centre), and the treatment effect will be estimated using the Cox proportional hazards regression model stratified by study centre. A subgroup analysis will be performed to assess the interaction effect between ASA and the mutations in PIK3CA and KRAS. The analysis will be performed on primary and secondary time-to-event endpoints using a stratified Cox proportional model with an ASA/mutation in PIK3CA/KRAS mutation interaction term.