RECOVER-study

RAAS blockag**E** in SARS **COV-2** Critically ill pati**E**nts– a **R**andomized controlled trial

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2. List of Abbrivations

ACE-2	Angiotensin-Converting Enzyme 2
ACEi	Angiotensin Converting Enzyme inhibitors
AE	Adverse Events
ALAT	ALanine AminoTransferas
AR	Adverse Reaction
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
ASAT	ASpartatAminoTransferasAT-1
BMI	Body Mass Index
CNS	Central Nervous System
CRP	C-Reactive Protein
DSMC	Data and Safety monitoring Committee
eGFR	estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
IMP	Investigational Medical Product
MPA	Medical Product Agency
NA	NoreAdrenaline
NEWS2	National Early Earning Score 2
NT-pro-BNP	N-Terminal prohormone Brain Natriuretic Peptide
OR	Odds Ration
PCR	Positive Chain Reaction
PI	Principal Investigator
RAAS	Renin-Angiotensin-Aldosterone System
SAEs	Serious Adverse Events
SARs	Serious Adverse Reactions
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIR	Swedish Intensive Care Registry
SMPA	Swedish Medical Product Agency
SUSARs	Suspected Unexpected Serious Adverse Events

3. Abstract

Background: There is an ongoing pandemic of severe respiratory disease (Covid-19) caused by a novel Coronavirus (SARS-CoV-2) that was first detected in the Hubei Province in China in December, 2019 [1]. The first cases were observed in Sweden in January, 2020, and there is currently ongoing spread in all Swedish regions. Unfortunately, there is currently no available specific treatment for Covid-19. However, recognizing that the SARS-CoV-2 virus infects affected tissues through binding of the membrane-bound form of angiotensin-converting enzyme 2 (ACE2), several investigators have postulated that treatment with angiotensin converting enzyme inhibors (ACEi) or angiotensin receptor blockers (ARB) might lead to improvement in disease outcomes for Covid-19 patients [2, 3].

1. Methods: In this investigator-initiated randomized trial, we will test the hypothesis that treatment with the ARB losartan will decrease the risk of admission to intensive care or death for in-hospital patients treated for Covid-19. The study will be conducted using a pragmatic design as a head-on comparison of losartan and standard of care. Patients will be followed through the duration of their hospitalization, or for a maximum of 28 days. The primary outcome will be a composite of all-cause mortality or admission to intensive care unit (ICU). The secondary outcomes will be All-cause mortality at day 28 from randomization, occurrence of ICU admission during hospital stay, need for and duration of invasive mechanical ventilation, area under the curve for C-reactive protein (CRP), and National Early Warning score 2 (NEWS2) score.,. A total of 750 patients will be randomized in a 1:1 fashion using an online randomization system, with blocks of random size.

Trial registration: ISRCTN
Keywords: Covid-19, angiotensin receptor blocker, randomized clinical trial, renin-angiotensin-aldosterone system

4. Background and rationale

In late 2019, an outbreak of pneumonia caused by a novel coronavirus occurred in Wuhan, Hubei province China. The virus was offically named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). The ongoing pandemic of Covid-19, the disease caused by SARS-CoV-2, is one of the major health challenges of our time, with the potential of causing millions of deaths and putting huge strains on health care systems worldwide [1, 4].

Respiratory symptoms is the main clinical manifestation of Covid-19, but other organs, mainly the cardiovascular system, can also be affected in more severe cases. Patients with higher age, obesity and underlying cardiovascular diseases, such as hypertension, or renal failure and diabetes are at increased risk of a poor outcome [5]. Today, there is no specific treatment available, other then supportive care. It is therefore important to understand the underlying pathophysiological mechanisms that are triggered by the SARS-COV-2 virus, to guide timely and effective treatment, and ultimately reduce mortality.

The mechanism for SARS-CoV-2 infection is through binding to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2). The virus uses a surface glycoprotein called a "spike" to connect to ACE2 and enter the host cell [6]. The ACE2 membrane protein is present in most tissues [7], but is abundant in the type II alveolar cells of the lungs, which may explain why the respiratory system is especially affected. As the alveolar disease progresses, respiratory failure develops, which in the most severe cases leads to death [8].

Angiotensin-converting enzyme (ACE) and ACE2 serves two opposing physiological functions. ACE convertes angiotensin I to angiotensin II, with subsequent physiological actions leading to constriction of blood vessels, elevating blood pressure. ACE2, on the other hand, inactivates angiotensin II thereby serving as a negative regulator of the renin–angiotensin system. In addition, ACE2 degrades angiotensin II to angiotensin (1-7) wich opposes the effects of Angiotensin II. The loss of ACE2 receptors due to internalisation and decreased expression may explain some of the various negative health effects observed in COVID-19 patients, e.g. aggravated cardiovascular disease, kidney failure, brainstem reflex malfunction and pulmonary hypertension [9].

It has been shown that treatment with angiotensin receptor inhibitors (ARB) increases the expression of ACE2 and it has been suggested that the shifted balance towards the ACE2 signal pathway is responsible for the benefits of AT-1 inhibitor treatment in diabetes, hypertension, heart failure and kidney disease. It has repeteadly been shown in experimental studies that renin–angiotensin–aldosterone system (RAAS) blockade stimulates ACE2 expression in most organs such as kidney, heart, CNS and lungtissue [2, 8].

Increasing ACE2 expression, with the use of angiotensin II receptor blocker medications, could therefore be protective in COVID 19 patients by preventing the development of acute respiratory distress syndrome (ARDS) thus averting both morbidity (e.g., admission to intensive care unit [ICU] or mechanical ventilation) and mortality [10, 11]. A recent published retrospective study in China showed that among hospitalized COVID-19 patients with hypertension, inpatient use of ACEI/ARB was associated with lower risk of all-cause mortality compared with ACEI/ARB non-users [3].

Increasing ACE2 expression, with the use of angiotensin II receptor blocker medications, could therefore be protective in COVID 19 patients by preventing the development of acute respiratory distress syndrome (ARDS) thus averting both morbidity (e.g., admission to intensive care unit [ICU] or mechanical ventilation) and mortality [7, 8]. Liu et al showed that patients with COVID-19 infection had increased angiotensin II concentration in blood and that it correlated with their lung injury (12)

Recent published retrospective study in China showed that among hospitalized COVID-19 patients with hypertension, inpatient use of ACEI/ARB was associated with lower risk of all-cause mortality compared with ACEI/ARB non-users (3,7% vs 9,8%) [13]. A study, performed in the United Kingdom, reports that patients with hypertension and ACE inhibitors or ARB had a trend of beneficial effect on mortality or transfer to an ICU (OR 0,63(CI 0,47-0,84,p<0,01) (14).

5. Risk-benefit analysis

The potential benefit of treatment with ARB in patients with Covid-19 could be a milder form of the disease with reduced inflammation and coagulopathy. This might lead to less need for intensive care, mechanical ventilation and reduced mortality.
The main potential risks to treat patients with Covid-19 with ARB are hypotension, impaired kidney function and hyperkalemia. In case of hypotension there might be a risk of dizziness and falls. To reduce the risks for the patients, we have strict inclusion and exclusion criteria. The patients will be closely monitored for side effects. The treatment will be modified or discontinued according to specified criteria (6.4.2-3).
Our estimation is thus that the study can be performed with low risk for the patients and might yield important knowledge about possible treatment of patients with Covid-19.

6. Study design

This is an academic, investigator-initiated, open-label, pragmatic, phase IV randomized controlled trial. The study has been designed in response to the rapidly developing COVID-19 epidemic. We estimate to include 750 patients, 375 of whom randomized to receive losartan in addition to standard-of-care, and 375 randomized to receive standard-of-care alone. The active-treatment arm will receive the ARB losartan in a dosage titrated with regards to blood pressure and renal function up to a maximum of 100 mg once daily. The control arm will receive standard care treatment. If blood pressure medication is deemed necessary in the control arm a non-ACEi or ARB medication will be chosen.

6.1 Objectives

To test if treatment with the ARB losartan can decrease the risk of intensive care unit admission or death in hospital-treated patients with confirmed COVID-19. The aim is also to evaluate safety and feasibility of this intervention.

6.2. Sites and Participants

6.2.1 Study setting

All hospitals in the Stockholm region treating adult patients with COVID-19.

Study site(s):

- Södersjukhuset
- Karolinska Universitetssjukhuset
- Danderyds sjukhus
- St Görans sjukhus
- Norrtälje sjukhus
- Södertälje sjukhus

6.2.2 Eligibility criteria

Awake (≥GCS 14) adult (>18 years of age) patients, admitted to hospital for confirmed COVID-19 infection.

6.2.3 Inclusion Criteria

1. Positive PCR laboratory test for SARS-CoV-2.
2. Age >18 years.
3. Admitted for in hospital care no more than 48 hours earlier.
4. GCS≥14

6.2.4 Exclusion Criteria

1. Admitted to ICU prior to randomization.
2. Current treatment with blood pressure lowering agent, affecting the RAAS system (i.e. Angiotensin Converting Enzyme inhibitor (ACEi), Angiotensin Receptor Blocker (ARB), Aldosteron antagonist or Renin inhibitor).
3. Patients with heart condition eg. heart failure with reduced ejection fraction, EF<40%, who has an evidence based indication for ACE inhibitors or Angiotensin receptor blockers.
4. Prior serious adverse reaction to an ARB or ACEi.
5. Systolic blood pressure below 120 mmHg or symptomatic hypotension. Blood pressure will be taken in supine position after 5 minutes rest with manual or automatic blood pressure manometers
6. Estimated Glomerular Filtration Rate (eGFR) of < 50ml/min/1.73 m2.
7. Potassium > 5 mEq/L.
8. Women of childbearing potential (a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy) will be excluded unless a negative pregnancy test can be provided. Post-menopausal women (postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.) may be included.
9. Women who are breastfeeding will be excluded.
10. Known renal artery stenosis.
11. Severe hepatic failure (i.e. ALAT/ASAT > 5x normal upper limit)
12. Volume depletion, chock or new onset of acute kidney injury that, in the opinion of the investigator, would preclude administration of ARB/ACE-inhibitors.

13. Any condition or therapy which would make the participant unsuitable for the study, according to the investigators opinion.
14. Inability to provide informed consent.
15. Moribund or palliative patients deemed unlike to survive hospital stay or who cannot make an informed decision for participations (e.g. non-adults or patients with dementia).

6.3 Study procedure

6.3.1 Recruitment strategy

The study will include adult patients treated as inpatients for laboratory-confirmed COVID-19 at hospitals in Stockholm, Sweden. Patients will be identified among admitted patients, daily, by participating clinicians and investigators. The goal, in this pragmatic trial, is to include patients who are as representative as possible to the wider group of patients with COVID-19. Therefore, the eligibility, inclusion and exclusion criteria are kept at a minimum and will strive to only exclude patients who are not suitable for participation from a safety perspective (e.g. patients with hypotension, pregnant patients, patients with estimated Glomerular Filtration Rate (eGFR) of < 50 ml/min/1.73 m2 or
potassium > 5 mEq/L. Blood pressure will be taken in supine position after 5 minutes rest with manual or automatic blood pressure manometers. If the patient has hypertension but has not taken his/her blood pressure medication the patient will be given his ordinary medication if not contraindicated. The patient might then be included after 24 hours if the blood pressure is >130 mm Hg systolic and he is not on an ACE inhibitor or Angiotensin receptor blocker. .
NSAID and potassium saving diuretics will be stopped at inclusion if possible. Creatinine and potassium will be monitored daily in all patients.

6.3.2 Consent and randomization process

After identifying patients who are likely to be eligible for participation, they will be approached either by one of the investigators of the trial or by participating clinicians. Patients will be informed both orally and in writing and will be asked to provide written informed consent. The patients will be provided with information about the trial, its rationale and possible safety risks. See appendix.

For patients who provide written consent for participation, we will randomize them to either the active arm or the comparison arm. Randomization will be performed either by one of the participating clinicians or one of the investigators. It will be done using an online, secure randomization system, accessible only by investigators or select clinician participants. As the trial is non-blinded, the participating patients will then be informed about their allocated treatment arm.

6.3.3 Patient treatment, monitoring and follow-up process

After randomization, patients allocated to the active arm will immediately begin treatment according to the dosing scheme under section 0). Treatment and follow-up will be continued throughout the first 28 days after randomization. All participating patients (both in the active and control arms) will be monitored closely during their hospitalization, with daily laboratory testing

and at least twice-daily vital sign checkups. The purpose of frequent testing and checkups is to ensure the safety of the intervention and the ascertainment of secondary outcomes. Adverse events will be recorded continuously.

For the follow-up we will extract data from a range of local data sources. See section 0, below.

6.4 Interventions

6.4.1 Intervention description: Active treatment arm

Patients will be receiving open label Losartan in a dosage titrated with regards to blood pressure and renal function up to a maximum of 100 mg once daily. Active treatment with Losartan will continue until death or discharge from hospital, or for a maximum of 28 days post randomization.

The starting dose will be 25mg for patients with systolic blood pressure of 120-130mmHg at randomization and 50mg for patients with systolic blood pressure of >140mmHg.

6.4.2 Criteria for modifying allocated intervention

Treatment dose with study drug will be decreased to half dose if:

1. Increase in creatinine by more than 50% from baseline
2. Potassium increase to > 5mEq/L
3. Symptomatic hypotension/orthostatism or a high clinical risk of fall injury.

The dose can be doubled on Day 3 (i.e. from 25 mg to 50 mg if the systolic blood pressure >120 or from 50 mg to 100 mg if the systolic blood pressure >130) and a creatinine below 1.5 times baseline value.

6.4.3 Criteria for discontinuing allocated intervention

Treatment with study drug will be discontinued in the event of occurrence of:

1. Systolic blood pressure<100 mmHg despite adequate volume repletion
2. Potassium > 5,5 mEq/L
3. Angioedema or allergic reactions
4. Patient preferences to opt out
5. Acute Kidney Injury (>1,5 increase from baseline Creatinine, or reduced urine output <0,5ml/Kg/hour the last six hours)
6. The patient admitted to an ICU and treated with mechanical ventilation
7. Any serious adverse reaction

In addition, patients in both the active and control arms can freely withdraw their consent from participation at any point during the trial.

6.4.4 Intervention description: Control arm

The control arm will receive standard care treatment. If blood pressure medication is warranted according to existing guidelines a non ACEi or ARB medication should be chosen.

6.5 Outcomes

6.5.1 Primary outcome

Time to first occurrence of composite endpoint of admission to intensive care unit, or death, within 28 days of randomization.

6.5.2 Secondary outcomes

In addition to the primary outcome, we will also investigate differences in the occurrence of five secondary outcomes:

1. All-cause mortality at day 28 from randomization.
2. Occurrence of ICU admission during hospital stay.
3. Need for and duration of invasive mechanical ventilation.
4. Peak level and area under the curve during hospitalization for National Early Warning score 2 (NEWS2) score.
5. Peak level and area under the curve during hospitalization for CRP score.

6.5.3 Safety Outcomes

Safety outcomes in the trial are:

Adverse events:

1. Occurrence of acute kidney injury (defined as a 50% decline in estimated GFR relative to baseline, or decrease of more than 30 ml/min/1.73m^2)
2. Hypotension requiring vasopressors.
3. Symptomatic hypotension
4. Mild allergic reaction or mild angioedema
5. Falls with no subsequent treatment needed
6. Hyperkalemia, with serum-potassium > 5.0 mmol/L
7. All incidents and side-effects will be registered.

Serious adverse events

1. Occurrence of Acute Kidney Injury with anuria>12 h or need for dialysis during hospital stay
2. Falls resulting in injury requiring subsequent treatment such as surgery, fracture immobilization, Intracranial hemorrhage
3. Allergic reaction with difficulty to breath or angioedema
4. Serum-potassium > 7.0 mmol/L
5. Acute respiratory distress syndrome requiring mechanical ventilation
6. Myocardial infarction
7. Cardiac arrest
8. Pulmonary embolism
9. Deep venous thrombosis
10. Systemic inflammatory response syndrome
11. Pneumonia
12. Sepsis
13. Stroke
14. Unexpected admission to intensive care unit.

6.5.4 Other variables for in between group comparisons

1. Length of hospital stay.
2. Peak level and area under the curve during hospitalization for inflammatory biomarkers, including CRP, D-dimer and Ferritin, and for cardiac markers, including Troponin T, and NT pro BNP.
3. Need for continuous renal replacement therapy.
4. Need for and duration of non-invasive mechanical ventilation or high-flow nasal cannula oxygenation.
5. Occurrence of venous thromboembolism.

6.5.5 Pre-defined subgroups

1. Sex (Male vs Female)
2. Age (<50, 50-75, vs >75 years)
3. BMI (<25, 25-30, vs >30)
4. Presence of hypertension at baseline (yes, vs no)
5. Diabetes (yes, vs no)
6. GFR at admission (40-60, vs >60)

7. Safety and adverse event management

7.1 Definitions

7.1.1Adverse events (AE)

An AE is: “Any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research, which does not necessarily have a causal relationship with the research”.

7.1.2 Adverse reactions (AR)

An AR is defined as any untoward and unintended response to the study Investigational Medical Product (IMP), i.e. losartan (intervention)where a causal relationship cannot be ruled out.

7.1.3 Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Events (SUSARs).

An AE or AR is considered serious if it:

1. Results in death
2. Is immediately life-threatening
3. Requires hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability or incapacity
5. Is a congenital anomaly or birth defect
6. Is an important medical condition

A SAE is not thought to be causally related to the research.
A SAR is thought to be related but is expected.
SUSARs are SARs that are unexpected i.e their nature or severity is not consistent with the Summary of Product Characteristics.
The term ‘severity’ is used here to describe the intensity of a specific event, as in mild (without impact on daily activities), intermediate(some impact on daily activities), and severe (considerable impact on daily activities) This has to be distinguished from the term ‘serious’.

7.2 Reporting of SAEs and SUSARs

Upon encountering serious adverse events, and a report will be sent within 24 hours by the Investigator to the sponsor. The investigator and the sponsor will evaluate if there could be a causal relationship between the IMP and the SAE. If so, the IMP will be discontinued.

All reports of SAE will be reviewed by the Primary Investigator and the Sponsor. All unexpected SAE and where a causal relationship with the IMP cannot be ruled out
will be notified to the Ethics Committee, SMPA within 7 days of in accordance with regulatory requirements. Reports of SAE/SAR/SUSAR will also be reviewed by the Data Safety Monitoring Committee (DSMC) at their regular meetings, or more frequently if requested by the DSMC Chair.

The frequency of occurrence of expected events (see above) will be the main emphasis of the planned interim analysis. In preparation for this analysis, we will collect data on the occurrence of all adverse events as well as the primary outcomes and assess their frequency with regards to the allocated treatment.
Substantial changes in the protocol (or in other documentation included in the trial application) will be submitted for approval by the MPA before implementation.

7.2.1 End of the trial

The trial will end when the last data has been entered into the study database, which is expected to happen within 1 month of termination of follow-up of the last randomized patients. The trial will be stopped prematurely if:

1. Mandated by the DSMC
2. Mandated by the Ethics Committee
3. Mandated by the SMPA
4. The trial Steering Committee

The Ethics Committee and SMPA will be notified in writing if the trial has been concluded or terminated early within 15 days

7.3 Concurrent treatment with other drugs

The participation patients will also receive other drugs, with no restrictions. These will include antibiotics, anti-viral therapy, anesthesia drugs, other blood pressure lowering agents, intravenous fluids, according to clinical praxis and looking of medical interactions or contra indications.
Based upon an updated critical appraisal of the literature, the RECOVER Management Committee endorses and encourages co-enrolment in the RECOVER trial. Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment.

8. Sample size, follow-up and statistical analysis plan

8.1 Sample size for primary hypothesis

A power calculation was performed using a simulation approach, based on Chi-squared tests. Based on experience with Covid-19 patients, we estimated the occurrence of the primary outcome

to 30%, and hypothesized a reduction in the occurrence of the primary outcome of 33% (i.e. to 20%). Moreover, we postulated a dropout rate in the active arm of the trial of 15%. With an alpha-level of 0.05, the power analyses indicated that we would need to randomize 750 patients to achieve 80% power with an intention-to-treat analysis. Power will be higher for the secondary outcomes.

8.2 Sequence generation:

Online electronic system, with computer generated random numbers. Simple 1:1 allocation in blocks of random length from 2-6.

8.3 Data collection and management

8.3.1 Plans for assessment and collection of outcomes

The study will collect necessary variables and outcomes from the following:

1. Local electronic medical record systems (Take Care, Clinisoft, or comparable systems depending on local practice)
2. Local hospital quality databases
3. Swedish intensive care register (SIR)
4. Local laboratory information management system
5. Swedish tax authorities (for ascertainment of date of death), as well as Swedish Death Certificate Registers.

All linkages will be done using national registration numbers to ensure validity.

8.4 Data management

All data from the study will be kept in a database within the firewalls of Södersjukhuset and Karolinska Institutet. After all data collection has been completed, the database will be pseudonymized before data analysis. Access to stored information will be restricted to authorized personnel only. No documentation or data will be in paper form. Electronic data will be stored in a secure area of the computer with access restricted to staff working on the trial. All databases containing identifiable information will be password protected. All data processing and management will be compliant with the General Data Protection Regulation (GDPR).
Data will be stored for 10 years after termination for the study.

8.5 Confidentiality

All personal data will be pseudonymized and keys will be held separate. No data will be presented on individual level. Only aggregated data on group level will be presented.

8.6 Statistical methods

8.6.1 Statistical methods for primary outcome

The main analysis will be done using intention to treat comparisons. Here, comparisons for the occurrence of the composite primary outcome will be done using unadjusted Cox proportional hazards regression, resulting in hazard ratios (with 95% confidence limits) comparing the active arm to the control arm. The Cox regression models will not account for any other factors than the randomized allocation. In addition to hazard ratios, we will compute absolute risk differences, with 95% confidence limits. These will be computed using the Kaplan-Meier method with log-rank tests.

8.6.2 Statistical methods for secondary outcomes

Analyses for the four secondary outcomes will use different statistical approaches. Differences between the two arms in the occurrence of "All-cause mortality at day 28 from randomization", "ICU admission during hospital stay" and "Need for invasive mechanical ventilation" will be assessed the same two-pronged approach as the primary outcome (i.e. using unadjusted Cox regression and the Kaplan-Meier method with log-rank tests).

Differences between the two arms in the "duration of invasive mechanical ventilation" will be assessed by comparing the number of ventilator-free hours during the study period, using the non-parametric Wilcoxon test. Wilcoxon test will also be used to assess differences in the Peak level and area under the curve of National Early Warning score 2 (NEWS2) score".

8.6.3 Per protocol analyses for primary outcome

In addition to the primary analyses, which will be done according to the intention-to-treat approach, we will also perform per protocol analyses comparing the different attained doses of the study group to patients who did not receive the study drug, either because they were randomized to the control group or due to non-adherence/compliance. The per protocol analyses will be performed for the primary outcome only and will likely also be done using Cox regression, accounting for maximum attained dose of losartan. The per protocol analyses will adjust for a number of confounding variables, including blood pressure at randomization, and comorbidity. In the event that non-compliance is dependent on measurable side-effects (e.g. hypotension, or electrolyte disturbances), we may employ an alternative, causal-inference approach using a marginal structural model.

8.7 Interim analyses

The trial will be monitored by an independent Data Safety Monitoring Committee (DSMC) that will receive unblinded summaries of data for an interim analysis scheduled at 250 patients. The DSMC will review the accumulating data for early, convincing evidence of benefit (i.e. with regards to the primary outcome) or harm. Early stopping for efficacy reasons and for the four major safety outcomes will be considered if the differences are seen between the groups according to the Peto-Haybittle stopping rule with a p-value <0.001.

8.8 Good Clinical Practice (GCP) and Helsinki declaration

The study will be conducting according to the protocol, GCP, and the latest revision of the declaration of Helsinki, as well as in accordance with current legal framework for clinical trials [15].

8.9 Quality control and quality assurance

The study will be monitored by GCP certified research nurse in a different clinic. The monitor will have access to all the source data. It is the task of the principal investigators to train all participating personnel. Investigators will provide access to source data during audits, at review by Data and Safety monitoring Committee (DSMC) and ethics committee and at regulatory inspections.

9. Steering committee

Anders Hedman (PI)
Carl-Johan Treutiger (Co-PI)
Jacob Hollenberg
Gustaf Edgren
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10. Protocol signatures

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