Statistical Analysis Plan (SAP)

Trial ID: VOMIT

Title of Trial

Validating the Effect of **O**ndansetron and **M**irtazapine **I**n **T**reating Hyperemesis Gravidarum. A Double-blind Randomized Placebo-Controlled Multicentre Trial.

Investigational Medicinal Product:	Mirtazapine and Ondansetron
EudraCT No.:	2018-002285-39
Sponsor, Funder:	Ellen Christine Leth Løkkegaard
Monitor:	Stine Kjær Hovgaard, GCP-unit
Ethical Committee number:	H-18047191
Clinicaltrials.gov number:	
Datatilsyn number:	VD-2018-144, I-suite: 6385
Date:	14.09.2018
Version:	1
Protocol Reference:	1

SAP revisions:

Signatures

Sponsor:	**Name:**	Ellen Christine Leth Løkkegaard
	Title:	MD, Head of Research, Associate Professor, Consultant, Ph.D.
	Department:	Department of Obstetrics and Gynaecology Nordsjællands Hospital
	Address:	Dyrehavevej 29, 3400 Hillerød
	Telephone:	+45 48296249
	E-mail:	Eloe0002@regionh.dk
	Signature	Date
Statistician:	**Name:**	Andreas Kryger Jensen
	Title:	Assistant Professor, PhD
	Department:	Department of Research Nordsjællands Hospital and Department of Biostatistics, Institute of Public Health, University of Copenhagen
	Address:	Øster Farimagsgade 5, 1014 Copenhagen K
	Telephone:	
	E-mail:	andreas.emil.kryger.jensen@regionh.dk
	Signature	Date
Chief investigator:	**Name:**	Anne Ostenfeld
	Title:	MD, Ph.D.-student
	Department:	Department of Obstetrics and Gynaecology Nordsjællands Hospital
	Address:	Dyrehavevej 29, 3400 Hillerød
	Telephone:	+45 20779758
	E-mail:	anne.ostenfeld.02@regionh.dk
	Signature	Date
SAP author:	**Name:**	Anne Ostenfeld
	Title:	MD, Ph.D.-student
	Department:	Department of Obstetrics and Gynaecology Nordsjællands Hospital
	Address:	Dyrehavevej 29, 3400 Hillerød
	Telephone:	+45 20779758
	E-mail:	anne.ostenfeld.02@regionh.dk
	Signature	Date

Roles and responsibilities:

Protocol author:	**Name:**	Anne Ostenfeld
	Title:	MD, Ph.D.-student
	Department:	Department of Obstetrics and Gynaecology Nordsjællands Hospital
	Address:	Dyrehavevej 29, 3400 Hillerød
	Telephone:	+45 20779758
	E-mail:	Anne.ostenfeld.02@regionh.dk
Head-advisor:	**Name:**	Ellen Christine Leth Løkkegaard
	Title:	MD, Professor, Consultant, Ph.D.
	Department:	Department of Obstetrics and Gynaecology Nordsjællands Hospital
	Address:	Dyrehavevej 29, 3400 Hillerød
	Telephone:	+45 48296249
	E-mail:	Eloe0002@regionh.dk
Co-advisor:	**Name:**	Tonny Studsgaard Petersen
	Title:	MD, Associate Professor, Consultant, Ph.D.
	Department:	Department of Clinical Pharmacology Bispebjerg Hospital
	Address:	Bispebjerg Bakke 23, 2400 København NV
	Telephone:	+45 38635855
	E-mail:	Tonny.studsgaard.petersen@regionh.dk
Co-advisor:	**Name:**	Hanne Brix Westergaard
	Title:	MD, Associate Professor, Consultant, Ph.D.
	Department:	Department of Obstetrics and Gynaecology Nordsjællands Hospital
	Address:	Dyrehavevej 29, 3400 Hillerød
	Telephone:	+45 48296364
	E-mail:	Hanne.brix.westergaard@regionh.dk
Co-advisor:	**Name:**	Lars Henning Petersen
	Title:	MD, Associate Professor, Consultant, Ph.D.
	Department:	Department of Obstetrics and Gynaecology Aarhus Universitetshospital
	Address:	Palle Juul-Jensens Blvd. 99, 8200 Aarhus N
	Telephone:	+45 50526512
	E-mail:	lhp@clin.au.dk
Co-advisor:	**Name:**	Jon Thor Trærup Andersen
	Title:	MD, Ph.D.
	Department:	Department of Clinical Pharmacology Bispebjerg Hospital
	Address:	Bispebjerg Bakke 23, 2400 København NV
	Telephone:	
	E-mail:	jon.thor.traerup.andersen@regionh.dk
Statistician:	**Name:**	Andreas Kryger Jensen
	Title:	Assistant Professor, PhD
	Department:	Department of Research Nordsjællands Hospital and Department of Biostatistics, Institute of Public Health, University of Copenhagen
	Address:	Øster Farimagsgade 5, 1014 Copenhagen K
	Telephone:	
	E-mail:	andreas.emil.kryger.jensen@regionh.dk
Monitor:	**Name:**	Stine Kjær Hovgaard
	Title:	GCP-coordinator, nurse
	Department:	Copenhagen University Hospital GCP-unit
	Address:	Bispebjerg Bakke 23, Byg. 51, 3. sal, 2400 Copenhagen NV
	Telephone:	+45 38635626
	E-mail:	Stine.hovgaard@regionh.dk

Contents

List of Abbreviations

AE	Adverse Event
BP	Blood Pressure
CRF	Case Report From
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form
GCP	Good Clinical Practice
HG	Hyperemesis gravidarum
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
NVP	Nausea and Vomiting of Pregnancy
MD	Medical Doctor
OD	Once Daily
PUQE	Pregnancy-Unique Quantification of Emesis and Nausea
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Protocol Synopsis / Summary

Title of trial:

Validating the Effect of **O**ndansetron and **M**irtazapine **I**n **T**reating Hyperemeis Gravidarum (**VOMIT**). A double-blind randomized placebo-controlled multicentre trial.

Objectives:

The primary objective is to compare the efficacy of mirtazapine versus placebo on nausea and vomiting in patients with hyperemesis gravidarum.
The secondary objective is to compare the efficacy of ondansetron versus placebo and mirtazapine versus ondansetron on nausea and vomiting in patients with hyperemesis gravidarum.

Trial design:

A double-blind randomized placebo-controlled multi-centre trial. The subjects will be randomised 1:1:1 to receive treatment with either mirtazapine, ondansetron or placebo. The intervention will last for 14 days.

Trial population:

We will include approximately 180 pregnant women with hyperemesis gravidarum, 60 in each group.

Main inclusion criteria:

- Pregnant with gestational age between 5+0 and 11+6
- Nausea and vomiting without other obvious reason
- PUQE-24 score ≥13 OR
  PUQE-24 score ≥7 AND
  1. weight loss >5% OR
  2. hospitalization due to nausea and vomiting of pregnancy
- Normal singleton pregnancy

Main exclusion criteria:

- Mola-, multiple- or non-vital pregnancy
- Congenital long QT-syndrome
- Ongoing treatment with antidepressant medication
- Not able to take medicine orally
- Not able to understand spoken and written Danish

Methods:

The trial is dimensioned to find a difference in Pregnancy-Unique Quantification of Emesis and Nausea (PUQE)-24 score of 2 with a power of 80% based on a standard deviation of 3 in change in PUQE-24 score, a type 1 error rate of 2,5% and 25% drop out.

Trial endpoints:

The coprimary endpoints are:

- change in PUQE-24 score from baseline to Day 2 (short term) in the mirtazapine group versus the placebo group.
- change in PUQE-24 score from baseline to day 14(+/-1) (long term) in the mirtazapine group versus the placebo group.

PUQE-score (Pregnancy-Unique Quantification of Emesis and Nausea) is a validated scoring system used to grade the severity of nausea and vomiting of pregnancy. It ranges 3-15.

Secondary endpoints include:

- Change in PUQE-24 score on short and long term in the ondansetron group versus the placebo group.
- Change in PUQE-24 score on short and long term in the mirtazapine group versus the ondansetron group.

- Area under the curve for PUQE-24 score day 1-14.
- PUQE well-being score.
- Number of daily vomiting episodes.
- Nausea VAS.
- NVPQOL (health-related quality of life for nausea and vomiting during pregnancy).
- HELP (hyperemesis level prediction).
- EQ-5D (a measure of health-related quality of life).
- 7 days PSQI (Pittsburg Sleep Quality Index)
- Patient satisfaction with treatment VAS.
- Patient consideration of termination of pregnancy.
- Occurrence of treatment failure.
- Use of rescue medication.
- Request for dosage increase.
- Days on sick leave.
- Amount of treatments with i.v.-fluids.
- Days of hospitalization.
- Weight change.
- Request for continuation of trial medication after end of intervention.
- Birth outcome (birth weight, gestational age, APGAR, umbilical cord pH, placenta weight, sex, hospitalizations on neonatal ward during the first month, congenital malformations).

Trial medication:

All trial medication will be provided by Glostrup Apotek in accordance with GMP. The investigational medicinal products(IMPs) will be similar in regard to appearance, smell and taste due to the IMPs being encapsulated in gelatine. Each subject will be given two containers one labelled ‘Daytime’ and one labelled ‘Bedtime’ to be administered orally in the morning and before bedtime for 14 days.

In the mirtazapine group, the ‘Daytime’ medication will contain placebo and the ‘Bedtime’ medication will contain mirtazapine 15 mg.
In the ondansetron group both the ‘Daytime’ and the ‘Bedtime’ medication will contain ondansetron 8 mg.
In the placebo group both the ‘Daytime’ and the ‘Bedtime’ medication will contain placebo.

Increase in dosage will be possible on Day 7(+/-1) in case of insufficient effect of medication during the first week.

Trial schedule:

Planned first subject first visit:	January 2019
Planned last subject randomised:	July 2020
Planned last subject last visit:	July 2020
End of trial:	January 2021

2. Flowchart

	Screening Day -2-0	Visit 1 Randomisation Day 0	Online questionnaire Day 1-14	Visit 2 Day 7(+/-1)	Visit 3 Day 14(+/-1)	Day 15-17	Postpartum
Informed Consent	x						
In- and Exclusion criteria	x	x		x	x		
Demography	x						
Medical History	x						
Previous and concomitant medication	x						
Changes in concomitant medication		x		x	x		
Vital signs (Height[1], weight, BP and pulse)	x	x		x	x		
Physical examination	x						
Ultrasound	x						
PUQE 24-score	x	x	x	x	x		
Nausea VAS, daily vomiting episodes		x	x	x	x		
Rescue medication			x	x	x		
NVPQOL, HELP, EQ-5D, PSQI		x		x	x		
Patient consideration of termination of pregnancy		x		x	x		
Patient satisfaction with treatment VAS				x	x		
Sick leave				x	x		
Hospitalization				x	x		
I.v. fluids				x	x		
Dosage increase				x			
Continuation of trial medication					x		
Side effects, adverse events			x	x	x	x	
Blood samples	x	x		x	x		
Urine sample	x						
ECG	x			x	x		
Randomisation		x					
Dispense of trial medication		x		x			
Drug accountability				x	x		
Birth Outcome							x

1) Height only at screening

3. Background

Refer to the Clinical Trial Protocol **3. Background/Rationale**.

4. Hypothesis

The hypothesis is that both mirtazapine and ondansetron reduce nausea and vomiting more than placebo in patients with hyperemesis gravidarum.

5. Objectives

5.1 Primary objective

The primary objective is to compare the efficacy of mirtazapine versus placebo on nausea and vomiting in patients with HG.

5.2 Secondary objectives

The secondary objective is to compare the efficacy of ondansetron versus placebo and of mirtazapine versus ondansetron on nausea and vomiting in patients with hyperemesis gravidarum.

6. Study Methods

6.1 Trial Design

A double-blinded randomized placebo-controlled multi-centre trial.

180 subjects will be randomised 1:1:1 to receive treatment with either

a) Mirtazapine oral tablet 15 mg at bedtime and placebo oral tablet morning,
b) Ondansetron oral tablet 8 mg morning and ondansetron oral tablet 8 mg at bedtime, or
c) Placebo oral tablet morning and at bedtime.

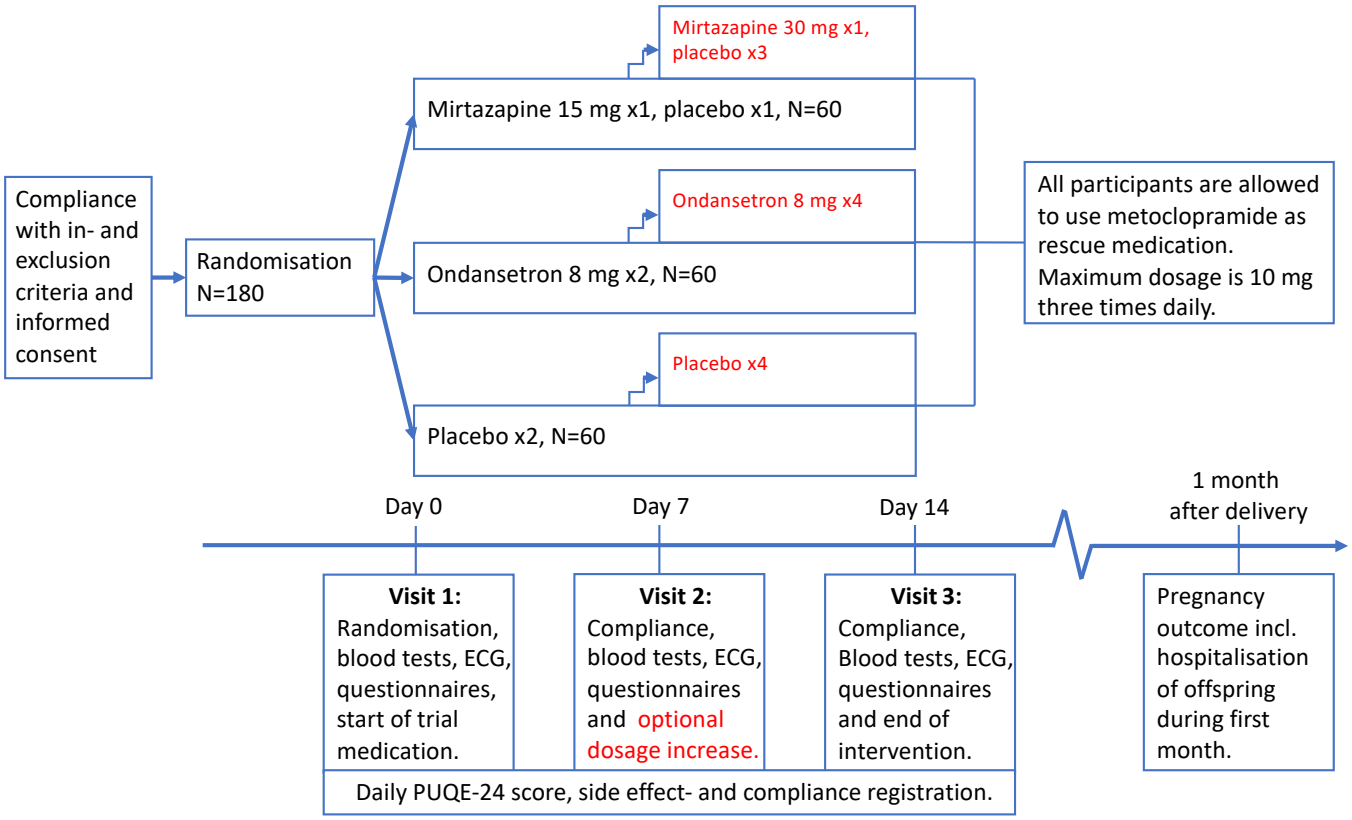
The trial subjects will receive treatment for 14 days.

A dosage increase will be optional on Day 7(+/-1). If desired the subject will then receive treatment with either

a) Mirtazapine oral tablet 30 mg at bedtime and placebo oral tablet morning, noon and late afternoon
b) Ondansetron oral tablet 8 mg morning, noon, late afternoon and at bedtime
c) Placebo oral tablet morning, noon, late afternoon and at bedtime

Data for the primary endpoint PUQE-24 score will be collected by the subjects completing online questionnaires related to their daily symptoms.

Figure 1 – Trial Design



6.2 Randomization

Subjects will be randomised in a 1:1:1 ratio and stratified by site.
Randomisation will be performed using REDCap to create a numbered randomisation list. After identification of an eligible patient, the subject will be assigned a randomisation number.
The randomisation list will not be accessible to trial personnel involved in the conduct of the trial during the intervention. A printed version of the randomisation list will be kept by a third party to ensure the possibility of unblinding in case REDCap unexpectedly becomes inaccessible.

6.3 Blinding

A double-blind set-up will be used. Mirtazapine, ondansetron and the matching placebo will be similar in appearance and will be packaged identically to maintain the treatment blind. Neither the sponsor, the subject, nor the investigational site staff will know which treatment the subject is receiving.
In case a subject desires to continue the IMP after the intervention, the randomization code for that particular subject can be broken. Thus, for unblinded subjects data collected after unblinding (AEs 0-5 days after the intervention and birth outcome) will not be blinded for the subjects or the clinicians, but the statistician will remain blinded.
Furthermore, the randomisation code for a particular subject can be broken during the intervention in a medical emergency or if knowledge of the IMP is necessary for the optimal treatment of the subject.
Whenever a randomisation code is broken, the person breaking the randomisation code must record the time, date and reason as well as his/her initials in the source documents. The sponsor and investigator must be notified immediately after randomisation code break if this happens because of an emergency during the intervention. No matter the reason for unblinding the subject must be discontinued from the trial (birth outcome will still be collected).

6.4 Sample size

The trial is dimensioned to find a difference of 2 in PUQE-24 score change from baseline to Day 2 (short term) and/or from baseline to Day 14(+/-1)(long term) between the mirtazapine group and the placebo group with 80% power based on a standard deviation (SD) of change of PUQE-24 score of 3, a type 1 error rate of 2,5% and 25% drop-out. The reason for the 2,5% type 1 error rate is that we want to test 2 hypotheses; effect of mirtazapine versus placebo short and long term on HG.
Thus, we will have to include 57 subjects in each of the 3 groups, which we round up to 60 subjects, equivalent of 180 subjects all together.
A SD of 3 is a conservative estimate based on the placebo-controlled trial with doxylamine-pyridoxine(1,2).

6.5 Framework

Two-sided equality test with the null hypothesis is that the expected difference of the effects of mirtazapine and placebo is zero.

6.6 Interim analysis

There are no planned interim analyses.

6.7 Early termination of the trial

The Sponsor reserves the right to terminate the trial under the following conditions:

- Safety concerns
- If an interim statistical analysis shows that the trial has no scientific value or too low power

If the trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or sponsor should promptly inform the pertinent ethics committee and regulatory authorities.

6.8 Timing of final analysis

Final analysis of all endpoints will be performed after the last patient has finished the intervention. All endpoints except birth outcome will be analysed shortly after the last subject has finished the intervention. Analysis of birth outcome will be performed one month after the last patient has given birth. This will allow for registration of possible hospitalization of the new-born.

6.9 Timing of outcome assessments

Baseline characteristics will be assessed on Day 0.
PUQE-24 score, daily vomiting episodes, nausea VAS, administration of IMP and rescue medication and possible side effects will be registered daily by subjects via online questionnaires.
NVPQOL, HELP, EQ-5D, PSQI, patient satisfaction with treatment, patient consideration of termination of pregnancy, number of days on sick leave, amount of treatments with i.v.-fluids, number of days of hospitalisations and weight change will be registered via online questionnaires at Visit 1, 2 and 3.
Request for continuation of trial medication will be registered via online questionnaire at Visit 3.
The visits on Day 7(Visit 2) and Day 14(Visit 3) can be scheduled for day 6-8 and day 13-15 respectively.
Possible treatment failure will be registered when it occurs.
Birth outcome will be registered one month after delivery.

7. Statistical Principles

7.1 Confidence intervals and *P* values

We aim for a p-value of 0.025 for each of the two primary outcomes. This will give a total type 1 error rate of 5% for the hypothesis.
Results will be reported with 95% confidence intervals.

7.2 Adherence and protocol deviations

Adherence to intervention will be monitored at Visit 2 and 3 and via online questionnaires. Adherence will be presented as part of the results.
Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major." Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments, and therefore, would result in a patient being excluded from the per protocol population. Major deviations will be identified and finalized prior to database lock and documented. Examples of major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are outlined below. Complete details will be included in a separate Protocol Deviation Plan, which will be appended to the final version of this SAP.

7.3 Major Protocol Deviation Population Exclusions

Randomized but did not take any study medication: Exclude from statistical analyses and per protocol analyses
Consumed the incorrect study medication per randomization scheme: Exclude from per protocol analyses
Major Protocol Violations: Exclude from per protocol analyses
Non-compliant (< 80% compliant with intended study medication): Exclude from per protocol analyses
Took prohibited medication that impacts efficacy: Exclude from per protocol analyses.

7.4 Analysis populations

The primary analyses will be performed on all subjects randomized in the trial (intention to treat). Sensitivity analyses will be performed on the per protocol population.

8. Trial Population

8.1 Screening data

Possible subjects are pregnant women suffering with HG.
We will collect data on all patients who were assessed for eligibility as to describe the representativeness of the trial population. If patients do not wish to be enrolled in the trial, the reason will be registered.

8.2 Eligibility

Inclusion criteria:

- Written informed consent obtained before any trial related procedures are performed
- Female age >18 years
- Pregnant woman with gestational age between 5+0 and 11+6
- Nausea and vomiting without other obvious reason
- PUQE-24 score ≥13 OR

PUQE-24 score ≥7 AND
1. weight loss >5% OR
2. hospitalization due to nausea and vomiting of pregnancy

Compliance with this criterion on any given day within 3 days prior to screening (possibly not compliant with this criterion on day of randomization)

- Singleton pregnancy
- The subject must be willing and able to comply with trial protocol

Exclusion criteria:

- Mola pregnancy, multiple gestation or non-vital pregnancy
- Nausea and vomiting of other aetiology than NVP
- Allergic to selective 5-HT3-receptor antagonists
- Ongoing treatment with antidepressant medication
- Pre-existing diagnosis of chronic kidney disease, diabetes type 1 or 2, significant cardiac disease (incl. long QT syndrome), epilepsy, HIV. In case of other pre-existing conditions subjects might be excluded based on individual assessment by an MD
- Elevated liver enzymes (ALAT/ASAT >150)
- Elevated creatinine (>100)
- ECG showing long QT-syndrome (QTc >460msek)
- Alcoholism; subject drinks more than recommended by health authorities
- Not able to take medicine orally
- Not able to understand spoken and written Danish
- Participation in another investigational drug trial within current pregnancy

8.3 Recruitment

We will report number of subjects assessed for eligibility, number and reasons for exclusion, and number of subjects randomised to each group.

8.4 Withdrawal/follow-up

Number, time and reason for discontinuation (withdrawal from intervention), lost-to-follow-up and final number analysed will be reported. Discontinued subjects and lost-to-follow-up will not be replaced.

8.5 Baseline patient characteristics

Baseline characteristics to be summarized in Table 1:
- History of HG in previous pregnancy
- Maternal age

- Weight, kg
- BMI, kg/m2
- Gestational age at randomisation, w+d
- PUQE-24 score at randomisation
- NVPQOL at randomisation
- HELP score at randomisation
- EQ-5D at randomisation
- 7 days PSQI at randomisation

9. Analysis

9.1 Outcome definitions

Primary endpoint:
The coprimary endpoints are:

- Change in PUQE-24 score from baseline to Day 2 (short term)
- Change in PUQE-24 score from baseline to Day 14(+/-1) (long term) in the mirtazapine group versus the placebo group.

The change in PUQE-24 score is calculated as baseline score minus Day 2 score and baseline score minus Day 14(+/-1) score, respectively. Baseline values will be recorded at randomisation.
The null hypothesis will be rejected if we find a difference of 2 or more on either short or long term or both.

PUQE-24 score (Pregnancy-Unique Quantification of Emesis and Nausea) is a validated scoring system used to grade the severity of NVP. PUQE-24 score consists of three elements:

1) number of hours with nausea within the last 24 hours (from none at all to more than 6 hours),
2) number of vomiting episodes in the last 24 hours (from 0 to >6 times), and
3) number of retching episodes without vomiting within the last 24 hours (from 0 to >6 times).

Each element gives a sub-score from 1 to 5 points and the total score is calculated by adding the three sub-scores giving a total score ranging from 3 to 15.
The condition is graded as mild if the score is 3-6, moderate with a score of 7-12 and severe if the score is 13-15(3). See Appendix 1.

Secondary endpoints:

- Change in PUQE-24 score from baseline to Day 2 in the ondansetron group versus the placebo group.
- Change in PUQE-24 score from baseline to Day 14(+/-1) in the ondansetron group versus the placebo group.
- Change in PUQE-24 score from baseline to Day 2 in the mirtazapine group versus the ondansetron group.
- Change in PUQE-24 score from baseline to Day 14(+/-1) in the mirtazapine group versus the ondansetron group.
- Area under the curve for PUQE-24 score during the intervention in the three different groups.
- Change in PUQE well-being score during the intervention in the three different groups.
- Change in daily nausea VAS during the intervention in the three different groups.
- Change in number of daily vomiting episodes during the intervention in the three different groups.
- Change in NVPQOL (health-related quality of life for nausea and vomiting during pregnancy) from baseline to Day 7(+/-1) and baseline to Day 14(+/-1) in the three different groups.
- Change in HELP score (hyperemesis level prediction) from baseline to Day 7(+/-1) and baseline to Day 14(+/-1) in the three different groups.
- Change in EQ-5D (health-related quality of life) from baseline to Day 7(+/-1) and baseline to Day 14(+/-1) in the three different groups.
- Change in past 7 days PSQI (Pittsburg Sleep Quality Index) from baseline to Day 7(+/-1) and baseline to Day 14(+/-1) in the three different groups.
- Patient satisfaction with treatment VAS on Day 7(+/-1) and Day 14(+/-1) in the three different groups.

- Change in patient consideration of termination of pregnancy from baseline to Day 7(+/-1) and baseline to Day 14(+/-1) in the three different groups.
- Frequency of and time to treatment failure in the three different groups.
- Frequency of request for dosage increase in the three different groups.
- Average daily use of rescue medication during the intervention in the three different groups.
- Number of days of sick leave during the intervention in the three different groups.
- Number of treatments with i.v.-fluids during the intervention in the three different groups.
- Number of days of hospitalizations during the intervention in the three different groups.
- Weight change in kg from baseline to Day 7(+/-1) and baseline to Day 14(+/-1) in the three different groups.
- Frequency of request for continuation of trial medication after end of intervention in the three different groups.
- Birth outcome (birth weight, gestational age, APGAR, umbilical cord pH, placenta weight, sex, hospitalizations on neonatal ward during the first month post-partum). This endpoint will not be double blind on all patients since patients can be unblinded after end of the intervention. The statistician will remain blinded.

9.2 Analysis methods

The primary analysis will consist of a linear mixed effects model taking the full longitudinal design into account. The model will be adjusted for site (categorical variable) due to the stratified design. Subjects will be included in the analysis irrespectively of their adherence to the protocol. The treatment effect for the primary outcome will be presented as the average difference between the mirtazapine and placebo groups in PUQE-24 score change from baseline to day 2 and from baseline to day 14. These comparisons will be based on the standard errors from the linear mixed model. Sensitivity analyses will be performed using multiple imputation where the imputation model will include all available baseline variables.

The statistician performing the analyses will remain blinded until the analyses results are closed.

9.3 Missing data

Missing data will be addressed by the mixed model analysis method and their influence will be assessed by the imputation analysis.

9.4 Harms

Refer to the Clinical Trial Protocol **10. Assessment of Safety** for information on definitions of adverse events (AEs) and how they will be reported.

9.5 Statistical software

R will be used for the statistical analysis.

10. References

1. Koren G, Clark S, Hankins GD V, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: A randomized placebo controlled trial. Am J Obstet Gynecol [Internet]. 2010;203(6):571.e1-571.e7. Available from: http://dx.doi.org/10.1016/j.ajog.2010.07.030
2. FDA. Center for Drug Evaluation and Statistical Review (S) - Tecfidera [Internet]. 2013. p. 1–5. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/021876Orig1s000StatR.pdf
3. EQ-5D. EQ-5D [Internet]. Available from: https://euroqol.org/eq-5d-instruments/
4. Axelsson P, Zikkenheimer M, Futtrup TB, Buchgreitz L, Westergaard HB, Martinsen AW, et al. Hyperemesis

Gravidarum - Guideline - DSOG [Internet]. 2013. Available from:
http://gynobsguideline.dk/sandbjerg/Hyperemesisgravidarum.pdf

Appendix 1

PUQE-score (Pregnancy Unique Quantification of Emesis and Nausea- score)

Marker det svar, der bedst beskriver dine symptomer de sidste 24 timer				
1. Hvor lang tid har du følt dig forkvalmet, i løbet af de sidste 24 timer?				
Slet ikke	≤ 1 time	2-3 timer	4-6 timer	> 6 timer
(1)	(2)	(3)	(4)	(5)
2. Hvor mange gange har du kastet op, i løbet af de sidste 24 timer?				
Ingen opkastninger	1-2 gange	3-4 gange	5-6 gange	≥ 7 gange
(1)	(2)	(3)	(4)	(5)
3. Har du haft opkastningsbevægelser (uden at der kommer noget med op), i løbet af de sidste 24 timer?				
Nej	1-2 gange	3-4 gange	5-6 gange	≥ 7 gange
(1)	(2)	(3)	(4)	(5)

PUQE-24 score: Mild ≤ 6, Moderat = 7-12, Svær = 13-15.

På en skala fra 0 til 10 hvordan vil du vurdere dit generelle **velbefindende**? ____
0 (værst tænkelig), 10 (så godt, som du havde det før, du blev gravid)

Dansk oversættelse af: Ebrahimi et al. Nausea and Vomiting of Pregnancy: Using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) Scale. J Obstet Gynaecol Can. September 2009;31(9):803-7 (4)