Clinical Trial Protocol

Trial ID: VOMIT

Title of Trial

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

Investigational Medicinal Product:	Mirtazapine and Ondansetron
EudraCT No.:	2018-002285-39
Sponsor, Funder:	Ellen Christine Leth Løkkegaard
Central Laboratory:	
GCP-Monitor:	Stine Kjær Hovgaard
Ethical Committee number:	H-18047191
Clinicaltrials.gov number:	
Datatilsyn number:	VD-2018-144, I-suite: 6385
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Signatures

Sponsor:	**Name:** **Title:** **Department:** **Address:** **Telephone:** **E-mail:**	Ellen Christine Leth Løkkegaard MD, Professor, Consultant, Ph.D. Department of Obstetrics and Gynaecology Nordsjællands Hospital Dyrehavevej 29, 3400 Hillerød +45 48296249 Eloe0002@regionh.dk
	It is hereby declared that the trial will be performed according to the latest approved trial protocol, ICH-GCP Guidelines and local regulatory requirements and legislation Signature _____ Date _____	
Primary Investigator: **(Authorised to sign protocol and -ammendments)**	**Name:** **Title:** **Department:** **Address:** **Telephone:** **E-mail:**	Anne Ostenfeld MD, Ph.D.-student Department of Obstetrics and Gynaecology, Nordsjællands Hospital Dyrehavevej 29, 3400 Hillerød +45 20779758 anne.ostenfeld.02@regionh.dk
	Signature _____ Date _____	
Study Coordinator:	**Name:** **Title:** **Department:** **Address:** **Telephone:** **E-mail:**	Anne Ostenfeld MD, Ph.D.-student Department of Obstetrics and Gynaecology, Nordsjællands Hospital Dyrehavevej 29, 3400 Hillerød +45 20779758 anne.ostenfeld.02@regionh.dk
	Signature _____ Date _____	
Protocol Author:	**Name:** **Title:** **Department:** **Address:** **Telephone:** **E-mail:**	Anne Ostenfeld MD, Ph.D.-student Department of Obstetrics and Gynaecology, Nordsjællands Hospital Dyrehavevej 29, 3400 Hillerød +45 20779758 anne.ostenfeld.02@regionh.dk
	Signature _____ Date _____	

Advisors

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

Study Sites and Local Investigators

Hillerød Hospital:	**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
Aarhus Universitets-hospital:	**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
Aalborg Universitets-hospital:	**Name:**	Anne Margrethe Møller
	Title:	MD, Associate Professor, Consultant
	Department:	Department of Obstetrics and Gynaecology Aalborg Universitetshospital
	Address:	Reberbansgade 15, 9000 Aalborg
	Telephone:	
	E-mail:	margr@dadlnet.dk
Herlev Hospital:	**Name:**	Tina Bergmann Futtrup
	Title:	MD
	Department:	Department of Obstetrics and Gynaecology Herlev Hospital
	Address:	Herlev Ringvej 75, 2730 Herlev
	Telephone:	
	E-mail:	tina.bergmann.futtrup@regionh.dk
Hvidovre Hospital:	**Name:**	Benny Kirschner
	Title:	MD, Associate Professor, Consultant, Ph.D.
	Department:	Department of Obstetrics and Gynaecology Hvidovre Hospital
	Address:	Kettegård Alle 30, 2650 Hvidovre
	Telephone:	
	E-mail:	benny.kirschner@regionh.dk
Odense Universitets-hospital:	**Name:**	Lise Lotte Torvin Andersen
	Title:	MD, Associate Professor, Consultant
	Department:	Department of Obstetrics and Gynaecology Odense Universitetshospital
	Address:	J. B. Winsløws Vej 4, 5000 Odense C
	Telephone:	
	E-mail:	Lise.lotte.andersen@rsyd.dk
Rigshospitalet:	**Name:**	Øjvind Lidegaard
	Title:	MD, Professsor, Consultant
	Department:	Department of Obstetrics and Gynaecology Rigshospitalet
	Address:	Blegdamsvej 9, 2100 København Ø
	Telephone:	
	E-mail:	Oejvind.lidegaard@regionh.dk

Laboratories and Biobanks

Hillerød Hospital:	**Laboratory:** **Address:** **Biobank:**	Department of Biochemistry Nordsjællands Hospital Dyrehavevej 29, 3400 Hillerød Locked freezer in locked room 101-21 at Forskningsafdelingen
Aarhus Universitets-hospital:	**Laboratory:** **Address:** **Biobank:**	Department of Biochemistry Aarhus Universitetshospital Palle Juul-Jensens Blvd. 99, 8200 Aarhus N
Aalborg Universitets-hospital:	**Laboratory:** **Address:** **Biobank:**	Department of Biochemistry Aalborg Universitetshospital Reberbansgade 15, 9000 Aalborg
Herlev Hospital:	**Laboratory:** **Address:** **Biobank:**	Department of Biochemistry Herlev Hospital Herlev Ringvej 75, 2730 Herlev
Hvidovre Hospital:	**Laboratory:** **Address:** **Biobank:**	Department of Biochemistry Hvidovre Hospital Kettegård Alle 30, 2650 Hvidovre
Odense Universitets-hospital:	**Laboratory:** **Address:** **Biobank:**	Department of Biochemistry Odense Universitetshospital J. B. Winsløws Vej 4, 5000 Odense C
Rigshospitalet:	**Laboratory:** **Address:** **Biobank:**	Department of Biochemistry Rigshospitalet Blegdamsvej 9, 2100 København Ø

Plasma-Mirtazapine and plasma-ondansetron will be analysed at a separate laboratory after the trial is finished. This will be specified at a later time.

Contents

List of Abbreviations

AE	Adverse Event
BP	Blood Pressure
CGM	Continuous Glucose Monitor
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
SAP	Statistical Analysis Plan
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 Hyperemesis Gravidarum (**VOMIT**). A double-blind randomised 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 objectives are 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% of pre-pregnancy weight OR
  2. hospitalisation 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 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.

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.

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.

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 during the intervention.

- 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 (health-related quality of life).
- Modified 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.
- Pregnancy outcome (birth weight, gestational age, APGAR, umbilical cord pH, placenta weight, sex, hospitalisations on neonatal ward during the first month, congenital malformations, loss/termination of pregnancy).

Trial medication:

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

In the mirtazapine group, the ‘Morning’ medication will contain placebo and the ‘Bedtime’ medication will contain mirtazapine 15 mg.
In the ondansetron group both the ‘Morning’ and the ‘Bedtime’ medication will contain ondansetron 8 mg.
In the placebo group both the ‘Morning’ and the ‘Bedtime’ medication will contain placebo.
All subjects will be allowed to take metoclopramide as rescue medication, and IMP dosage increase will be possible on Day 7(+/-1) in case of insufficient effect

Trial schedule:

Planned first subject first visit:	February 2019
Planned last subject randomised:	February 2021
Planned last subject last visit:	February 2021
End of trial:	October 2021

2. Trial Schedule

	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 15-20	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, modified 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		
Pregnancy Outcome							x

1) Height only at screening

3. Background / Rationale

3.1 Disease background and current treatment modalities

Nausea and vomiting in pregnancy (NVP) is a common condition. However, in about 1,5% of pregnancies the symptoms are so severe that hospitalisation is required(1). The most severe cases are diagnosed hyperemesis gravidarum (HG). However, there is not international consensus on the diagnostic criteria of HG which might include weight loss, hospitalisation, ketonuria, etc(2). In the guideline from the Danish Society of Obstetrics and Gynaecology, HG is defined as a 'condition with severe nausea and vomiting (PUQE-score ≥13) that starts in early pregnancy and is accompanied by dehydration, electrolyte imbalance and nutrition deficits'(3). PUQE (Pregnancy-Unique Quantification of Emesis and Nausea) is a validated scoring system used to grade the severity of NVP within the last 24 hours. Total score ranges from 3 to 15 (see appendix 1)(4).
The condition is so physically, psychologically and socially invalidating that 27% of pregnant women with HG consider ending the pregnancy and 75% do not wish to become pregnant again(5).
Furthermore, HG can cause long term complications for mother and child. Maternal complications include deep vein thrombosis, Mallory Weiss syndrome, Wernicke's encephalopathy, rhabdomyolysis, lower quality of life, depression in pregnancy and post-partum anxiety and post-traumatic stress symptoms(5–10). In case of insufficient maternal weight gain (<7 kg) there is increased risk of adverse infant outcome including low birth weight, 5-minute APGAR <7, preterm delivery and perinatal death(11).
The frequency of hospitalisations caused by HG has been increasing in England(1) and the condition is associated with considerable socioeconomic loss because of sick leave and treatment costs. The weekly cost per woman with HG was estimated to C$ 653 (2005) in Canada(12), equivalent of DKK 4.000 (2017).
The aetiology of NVP is poorly understood, but there seems to be consensus that the condition is multifactorial.

The current treatment for NVP is divided into non-pharmacological and pharmacological initiatives. There are few clinical studies of good quality that examine the pharmacological treatment, and overall the quality of evidence is low(13–15).
The current guideline from the Danish Society of Obstetrics and Gynaecology recommends pyridoxine (vitamin B6), if necessary in combination with cyclizine (a sedating antihistamine), for mild cases where pharmacological treatment is indicated. In severe cases, where this has not had sufficient effect, metoclopramide or promethazine can be tried. As a third line of treatment the guideline recommends ondansetron or in rare cases after the 10th week of pregnancy glucocorticoids (3).

The use of ondansetron for NVP has been increasing. According to the Mini Sentinel Distributed Database from the USA, which covered 1,949,201 pregnant women and 2,432,489 live birth pregnancies, oral ondansetron use increased from 3.1% of pregnancies in 2006 to 19.7% in 2014(16). Extrapolated to all of the USA that is more than 750,000 pregnant women per year(17). In spite of the large number of exposed pregnant women it is still unclear if ondansetron poses a risk of congenital heart defects. Two studies have found a higher incidence of congenital heart defects in offspring of women who had been exposed to ondansetron in pregnancy, while three studies have not(18).
Another important consideration is that ondansetron has not been approved as treatment for NVP. Alarmingly, oral ondansetron has not been tested as treatment for NVP in one single placebo-controlled trial and there have only been two double-blinded randomised trials with active comparators.
In the first study 83 patients with NVP were randomised to treatment with either ondansetron 4 mg or metoclopramide 10 mg for two weeks. The first week the ondansetron and metoclopramide were administered 3 times daily. The second week of treatment administration was reduced to twice daily for 3 days and once daily for 4 days. The ondansetron group had a slightly lower VAS score on both nausea and vomiting compared to the metoclopramide group, but the difference was only statistically significant on day 3-4 for nausea and day 2-8 for vomiting(19).
The other study included 36 patients with NVP who were randomised to ondansetron 4 mg three times daily or doxylamine 12,5 mg and pyridoxine 25 mg daily three times daily for 5 days. The study found that ondansetron significantly reduced nausea with a median reduction of 51 on a VAS scale compared to a reduction of 20 for doxylamine-pyridoxine (p=0.02). Likewise the vomiting was reduced more with ondansetron than with doxylamine-pyridoxine (VAS scale reduction of 41 vs 17)(20).

In spite of the common use of the above-mentioned treatment modalities it is often not possible to reduce symptoms sufficiently. Consequently it is relevant to examine the effect of alternative treatment options(21). A promising candidate for pharmacologic treatment for HG is mirtazapine. It is primarily an antidepressant, but it also known to have antiemetic and appetite stimulating effects(22).
There are case reports on 23 pregnant women where mirtazapine has been effective on treatment resistant HG(see appendix 2)(21,23), but there has never been a clinical controlled trial with mirtazapine for NVP or HG.

There have, however, been clinical controlled trials where mirtazapine has been showed to prevent postoperative nausea(24,25), as well as case reports describing effect on other conditions associated with nausea and vomiting(26–31).

Mirtazapine is primarily an adrenergic alpha2-receptor antagonist that increases the release of noradrenalin. This leads to increased stimulation of the serotonergic neurons causing increased serotonin release. However, a closer look at the pharmacologic profile of mirtazapine reveals mechanisms of action similar to those of other drugs used to treat HG and NVP. Like ondansetron and metoclopramide, it is an antagonist on the serotonin 5HT3-receptor in the chemoreceptor trigger zone. This action contributes to the antiemetic effect. It also acts as an antagonist on the 5HT2A- and 5HT2C-receptors and on the histamine H1-receptor (as do promethazine and cyclizine). Thus, the antiemetic and appetite stimulating effects of mirtazapine are pharmacologically well explained.
A Danish register-study on 614 mirtazapine exposed pregnant women did not find an association between 1st trimester exposure and major congenital malformations(32). This is in accordance with a systematic review from 2016 including 390 women exposed to mirtazapine in pregnancy and/or lactation, which did not find an increase in major malformations(33).
According to janusinfo.se Swedish data on 602 mirtazapine exposed pregnant women found 16 cases of malformations where 12-13 cases were expected(34). Thus, they expected an incidence of malformations of 1,99- 2,16%. This background incidence of major congenital malformations is remarkably lower than the 3.49% found in the Danish study based on 966,372 births(32). Thus, the Swedish study might underestimate the background incidence of congenital malformations. Disregarding this, janusinfo.se concludes that the incidence of malformations in the mirtazapine exposed pregnancies was not alarmingly high and that no specific group of malformations was overrepresented(34).
A European study with a cohort of 357 mirtazapine exposed pregnant women found a (non-statistically significant) higher incidence of congenital malformations when compared to non-exposed pregnancies. However, the incidence in the mirtazapine exposed pregnancies was similar to that of SSRI exposed pregnancies(35). This increased incidence has been explained by underlying disease (confounding by indication (likely depression or anxiety)) in a Danish study(36).
Data on other pregnancy outcomes such as pregnancy loss, preterm birth and neonatal symptoms is inconclusive, but show risks similar to those of SSRI-exposed(33,35). Again, this might be explained by confounding by indication.
In summary, there is data on 1963 mirtazapine exposed pregnant women worldwide suggesting that mirtazapine is safe in pregnancy. However it is not officially recommended due to insufficient data(37).

3.2 Trial rationale

The existing treatment options for NVP and HG are not profoundly evidence based and in Denmark no drugs are approved as treatment on these indications. Furthermore, the current treatment options are often not sufficiently effective. Thus, a trial investigating the effect of pharmacologic treatment for NVP and HG is warranted.

There is a need for a clinical placebo-controlled trial to clarify the effect of mirtazapine, primarily, and secondarily ondansetron as treatment for HG. To date there have been no placebo-controlled trials with mirtazapine or oral ondansetron as treatment for HG, even though a considerable placebo-effect is reported in the few existing placebo-controlled trials with other treatment modalities for NVP(38–40).
Currently there are no planned or ongoing placebo-controlled trials with mirtazapine or ondansetron investigating the effect of these drugs on HG(41,42). The data on ondansetron gained from a such trial will make it possible to include ondansetron as comparator to mirtazapine in a possible future confirmatory phase three trial with mirtazapine as treatment for HG.
Due to the category of patients, i.e. pregnant women that do not usually participate in clinical trials, and mirtazapine and ondansetron being older drugs that are no longer protected by patents, it is unlikely at trial will be sponsored by the pharmaceutical industry.

3.3 Benefit-risk assessments and ethical considerations

The individual subjects may not necessarily benefit from participation in the trial, but the trial medication might alleviate NVP symptoms. The information gained from the trial may affect future recommendations on treatment for HG and NVP and thus help patients in the future.
Pregnant women are not regularly included in medical trials and our main concern has been an assessment on whether the trial medications are safe to use in early pregnancy. Neither mirtazapine or ondansetron use in

early pregnancy pose a significantly increased risk for the mother or unborn child. Based on the number of exposed pregnant women for both trial medications, we think that they can be used in early pregnancy(43). Despite the absence of placebo-controlled trials, ondansetron is currently being used for NVP in Denmark and many other countries. It is often used in the most severe cases and is recommended as third line treatment in the current Danish national guideline for hyperemesis. It is most likely the medication to be offered to our patient population were they not to participate in the trial. We find it substantially less concerning to enroll patients in a clinically controlled trial where efficacy and side effects are collected systematically, than to continue treating patients with the current treatment options without availability of such data.
Another ethical consideration has been randomizing patients to ineffective treatment. By making the trial three-armed we 'spare' a placebo-group and as a consequence only one third, as opposed to half, of the patient population will receive ineffective treatment. It should be noted, that the placebo-group will not be treated with ineffective medication alone, as all groups will be allowed to use metoclopramide as rescue medication.

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 objectives are to compare the efficacy of ondansetron versus placebo and of mirtazapine versus ondansetron on nausea and vomiting in patients with HG.

5.3 Primary 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.

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

5.4 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-5L (health-related quality of life) from baseline to Day 7(+/-1) and baseline to Day 14(+/-1) in the three different groups.
- Change in modified 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.
- 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.
- Amount of treatments with i.v.-fluids during the intervention in the three different groups.
- Number of days of hospitalisations 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.
- Pregnancy outcome (birth weight, gestational age, APGAR, umbilical cord pH, placenta weight, sex, hospitalizations on neonatal ward during the first month post-partum, congenital malformations, loss/termination of pregnancy). 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.

6. Trial design

6.1 Summary of trial design

A double-blinded randomised 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 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 dosage increase is 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

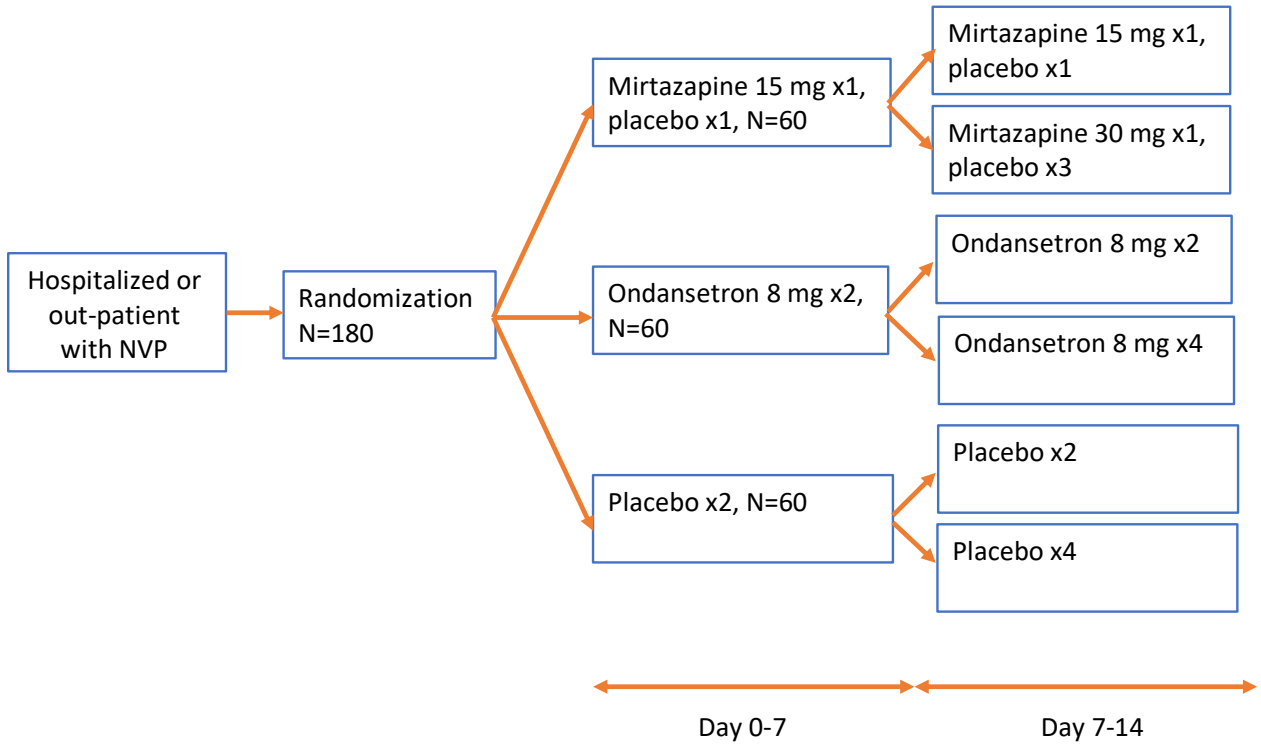
b) Ondansetron oral tablet 8 mg morning, noon, late afternoon and at bedtime

c) Placebo oral tablet morning, noon, late afternoon and at bedtime

If dosage increase is not desired the treatment from Day 0-7 will remain unchanged until Day 14.

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

Figure 1 - Trial design



6.2 Discussion of Design

The existing clinical studies on treatment for NVP generally have two arms; an IMP is tested against placebo or an active comparator. In designing this study with three arms, we can compare both mirtazapine and ondansetron to placebo and thus spare a placebo group. Furthermore, we can gain data on mirtazapine compared to an active comparator (ondansetron).

The intervention will last 14 days which is also seen in other clinical trials on treatment of NVP(39). This is estimated to be sufficient time to observe the effect of the intervention. An effect is expected within days after initiating treatment, thus at the visit on Day 7 a potential effect will have reached a stable level. If the treatment is not sufficiently effective it will be possible to increase the dosage of the IMPs.

In the national guideline on HG ondansetron 8 mg is to be administered twice daily with optional increase to a maximum total dosage of 32 mg per day. By allowing an increase in administration to exactly that our intervention will reflect current practice.

In most of the case reports on mirtazapine as treatment for HG, dosages of up to 15 mg daily have been effective. However, in a few cases the patients were started on mirtazapine 30 mg daily. Thus, to not disregard a possible effect due to inadequate dosage, we consider it relevant to make dosage increase to 30 mg daily optional.

The option of dosage increase might also ensure that the subjects stay in the trial even if they do not experience the desired symptom relief during the first week. However, there is still a concern that due to drop-outs and missing data the dataset may be incomplete at the end of the trial. As a consequence, we risk that a potential clinically significant effect of an IMP might not be shown as statistically significant. To minimize this risk, we will have two primary endpoints: a change in PUQE-score from baseline to Day 2 and from baseline to Day 14(+/-1). In this manner, we will be able to show a potential effect on Day 2, even if we do not have sufficient data to show it at the end of the intervention (Day 14). Furthermore, we have added 'treatment failure' as a secondary outcome, and subjects will be prompted to indicate if insufficient symptom relief was the reason for drop-out.

According to the Danish guideline, diagnosis of HG requires a PUQE-24 score ≥13. However, patients with a PUQE-24 score ≥13 are often not able to tolerate oral tablets and would therefore not be able to participate in this trial. Thus, subjects can be included in the trial with PUQE-24 score <13. The inclusion criterion on severity of NVP is PUQE-24 score ≥13 OR PUQE-24 score ≥7 AND weight loss >5% of pre-pregnancy weight and/or

hospitalisation due to nausea and vomiting of pregnancy. This is in accordance with other randomised controlled trials on HG where weight loss and hospitalisation often are seen as definition items(2).

6.3 Patient Involvement

Development of the study protocol and the final trial design has been supported by patient representatives as well as leading HG researches from Amsterdam. Patient representatives from the Danish and English patient organisations have provided valuable input to the protocol, specifically on outcome measures, feasibility of the study and ethical considerations.

6.4 Trial Schedule

Planned first subject first visit	February 2019
Planned last subject randomised	February 2021
Planned last subject last visit:	February 2021
End of trial	October 2021

7. Trial population

The trial population will consist of pregnant women with HG both out-patient and hospitalised patients.

If a patient at the time of referral to hospital is in a condition where treatment with intravenous antiemetics (ondansetron or other) is indicated, such treatment will be initiated. If and when the patient's clinical condition improves sufficiently for a transfer to orally administered antiemetics, the patient can then be enrolled in the trial.

Subjects meeting all of the inclusion criteria listed and none of the exclusion criteria will be considered eligible for the trial.

7.1 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% of pre-pregnancy weight and/or
  2. hospitalisation 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

7.2 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 U/l)
- Elevated creatinine (>100 µmol/l)
- ECG showing long QT-syndrome (QTc >460msek)
- Weekly alcohol intake >2 units of alcohol
- Not able to take medicine orally
- Not able to understand spoken and/or written Danish
- Participation in another investigational drug trial within current pregnancy

7.3 Recruiting

Eligible subjects, either out-patient or hospitalised, will be identified by medical professionals (MD, nurse or midwife) involved in their treatment. The subjects will be asked if they are interested in hearing more about the trial. If they accept they will be informed about the trial by either that same medical professional or specific trial personnel. Consent from an eligible subject must be obtained before any transfer of information on the subject from a medical professional involved in the treatment to trial personnel.

7.4 Discontinuation

Subjects will be informed about the possibility of discontinuing the trial at any time. We will encourage the subjects to inform the investigator as soon as they have decided to discontinue the trial and last administration of trial medication will be registered. In case of discontinuation we will ask the subject to indicate a reason for the discontinuation which will be registered. If the reason for discontinuation is treatment failure, time of treatment failure will be registered.
Subjects will be discontinued from the trial in case of icterus or mania or if they comply with an exclusion criterion.
Subjects may be unblinded at discontinuation if this is necessary to make clinical decisions about their future treatment. Subjects will be encouraged to fill out daily online questionnaires on possible side effects until three days after last administration of trial medication.
Birth outcome will be registered on all subjects including dropouts unless subjects withdraw consent.
Data on treatment effect (NVP symptoms) collected before discontinuation will be evaluated and dropouts will not be replaced by new subjects.
All discontinued subjects will have to return the trial medication.

8. Randomisation, treatment blinding / unblinding and sample size

8.1 Randomisation

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 and will subsequently receive trial medication corresponding to the randomisation number.

8.2 Blinding

A double-blind set-up will be used. Mirtazapine, ondansetron and placebo will be similar in appearance, smell and taste and will be packaged identically to maintain the treatment blind.
Information on type of trial medication corresponding to each randomisation number will be kept by Glostrup Apotek and thus will not be accessible to trial personnel involved in the conduct of the trial during the intervention. Neither the sponsor, the subject, nor the investigational site staff will know which treatment the subject is receiving.
If a subject desires to continue the IMP after the intervention, the randomisation code for that particular subject can be broken. Thus, for unblinded subjects data collected after unblinding (side effects and AEs 0-3 days after the intervention and birth outcome) will not be blinded for the subjects or the clinicians, but the statistician will remain blinded.
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.
To break the randomisation code the investigational staff must call Glostrup Apotek which is available at all times of day and night.
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 (side effects and AEs 0-3 days after the intervention and birth outcome will still be collected).

8.3 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.
An SD of 3 is a conservative estimate based on the placebo-controlled trial with doxylamine-pyridoxine(39).

9. Trial Products

9.1 Administration of Trial Products

Each subject will be randomly assigned to receive mirtazapine (IMP1), ondansetron (IMP2) or placebo. Please refer to figure 1 on page 17 for a visual on the trial design.
Trial medication will be provided by Glostrup Apotek in accordance with GMP. IMP1, IMP2 and placebo will be similar in appearance, smell and taste due to the IMPs being encapsulated in gelatine. In the placebo group the medication will be an empty gelatine capsule.

At Visit 1 on Day 0 each subject will receive two containers with sufficient medication for 10 days. One container will be labelled ‘Morning’ and one will be labelled ‘Bedtime’ to be administered orally in the morning and at bedtime for the first week (until Visit 2 on Day 7(+/-1)). Administration will start at bedtime of Day 0.
Thus, during the first week of intervention there will be two administrations of trial medication daily.
At Visit 2, two new containers with sufficient medication for 10 days will be administered. If dosage increase is not desired administration will proceed unchanged.
If a dosage increase is desired the number of daily administrations will go from two to four. One container will then be labelled ‘Morning, noon and afternoon’ and will be administered orally in the morning, at noon and late afternoon or early evening. The other container labelled ‘Bedtime’ will be administered only at bedtime.

In case a subject vomits within 45 minutes after administration of trial medication the subject will have to administer a new dosage as described in the folder ‘Praktisk information om forsøgsmedicinen’.
If a subject runs out of trial medication before the next visit due to extra administrations because of vomiting, the subject must contact the investigator as described in the folder ‘Praktisk information om forsøgsmedicinen’.

The folder ‘Praktisk information om forsøgsmedicinen’ will be handed out with the trial medication. Patients are encouraged to register time of administration and possible vomiting episodes within 45 minutes after administration in the folder.

9.2 Mirtazapine: IMP1

In the mirtazapine group, the 'Morning' medication will contain placebo and the 'Bedtime' medication dispensed at Visit 1 will contain mirtazapine 15 mg. Thus, the subjects in this group will initially receive treatment with

Placebo oral tablet in the morning and
Mirtazapine 15 mg oral tablet at bedtime.

The medication dispensed at Visit 2 on day 7(+/-1) will be the same and administration will remain unchanged in week 2 if dosage increase is not desired.
If dosage increase is desired at Visit 2 the 'Morning, noon and afternoon/evening' medication will be unchanged and still contain placebo. However, the 'Bedtime' medication dispensed will contain mirtazapine 30 mg as opposed to 15 mg in week 1. Thus, the treatment in the second week will be

Placebo oral tablet in the morning, at noon and late afternoon/early evening and
Mirtazapine 30 mg oral tablet at bedtime.

Mirtazapine is an antidepressant known to have antiemetic and appetite-stimulating effect. It is an alfa2-receptor antagonist, an antagonist on several serotonin-receptors ($5HT_{2A}$, $5HT_{2C}$ and $5HT_3$) and on one histamine-receptor (H_1).
Recommended dosage is 15-30 mg daily initially and 15-45 mg daily as maintenance dosage, preferably administered once daily before bedtime.
Peak plasma-concentration is reached within 2 hours after oral administration. Elimination half-life is 20-40hours and time to reach steady state is 3-4 days.

Side effects:

>10% :	Increased appetite, weight gain, dry mouth, headache, sedation and somnolence.
1-10%:	Diarrhea, obstipation, vomiting, orthostatic hypotension, peripheral edema, arthralgia, myalgia, back pain, abnormal dreams, anxiety, drowsiness, confusion, dizziness, tremor and rash.
0,1-1%:	Hypotension, agitation, hallucinations, mania, motoric unrest, paresthesia, syncope.
0,01-0,1%:	Pancreatitis, aggressiveness, myoclonia.
Not known:	Edema, eosinophilia, bone marrow depression, hyponatremia, rhabdomyolysis, dysarthria, oral paresthesia, serotonin syndrome, suicidal thoughts or behavior, bullous dermatitis, erythema multiforme, Stevens-Johnsons syndrome, toxic epidermal necrolysis, urine-retention.(37)

There is data on 1963 mirtazapine-exposed pregnant women without higher incidence of congenital malformations(32–35).

9.3 Ondansetron: IMP2

In the ondansetron group both the 'Morning' and the 'Bedtime' medication dispensed at Visit 1 on Day 0 will contain ondansetron 8 mg. Consequentially the subjects in this group will initially receive

Ondansetron 8 mg oral tablet in the morning and at bedtime.

If dosage increase is desired on at Visit 2 on Day 7(+/-1) the medication dosage in the dispensed medication will remain unchanged, but with the two added administrations the treatment regimen will be

Ondansetron 8 mg oral tablet in the morning, at noon, in late afternoon/early evening and at bedtime.

Ondansetron is an antiemetic. It works as a serotonin antagonist by binding selectively to the $5HT_3$-receptors in the chemo-receptors of the trigger zone thus reducing nausea and vomiting.
Recommended dosage depends is 8 mg every 12 hours.
Peak plasma-concentration is reached within 1,5 hours after oral administration, and elimination half-life is about 3 hours.

Side effects:

>10%:	Headache.
1-10%:	Blushing, sensation of heat, obstipation.
0,1-1%:	Affected liver, arrhythmia, bradycardia, hypotension, extrapyramidal symptoms.
0,01-0,1%:	QT-interval prolongation, allergic reactions, anaphylactic reaction, visual disturbances (primarily seen in i.v. administration)
<0,01%:	Toxic epidermal necrolysis, passing blindness (primarily seen in i.v. administration).(45)

Obstipation is a common side effect to ondansetron and this will be emphasised at randomisation and in the folder 'Praktisk information om forsøgsmedicinen'. Patients will be encouraged to administer a laxative (we recommend magnesium) if they experience any signs of constipation.

In spite of the large number of ondansetron-exposed pregnant women it is still unclear whether ondansetron caused a higher incidence of congenital heart defects. Two studies have found a higher incidence of congenital heart defects, while three studies have not(18). However, ondansetron is frequently used for HG in Denmark and other countries.

9.4 Placebo

In the placebo group both the 'Morning' and the 'Bedtime' medication dispensed at Visit 1 on Day 0 will contain placebo. Consequentially the subjects in this group will initially receive

Placebo oral tablet in the morning and at bedtime.

If dosage increase is desired on at Visit 2 on Day 7(+/-1) the medication will still be placebo, but with the added administrations the treatment regimen will be

Placebo oral tablet in the morning, at noon, in late afternoon/early evening and at bedtime.

9.5 Rescue Medication: Metoclopramide

All three groups will receive metoclopramide which they are allowed to use as rescue medication. In case of insufficient symptom relief, subjects are allowed to administer

Metoclopramide 10 mg oral tablet or i.v. max x 3 daily.

Subjects will be asked to register administered rescue medication in the daily online questionnaires.

Metoclopramide is an antiemetic that increases gastrointestinal motility. It is a competitive dopamine(D_2)-receptor antagonist and in high concentrations it also works as a $5HT_3$-receptor antagonist. Furthermore, it inhibits the chemo-receptors of the trigger zone and thus reduces nausea and vomiting.
Recommended dosage is 10 mg max x3 daily.
Peak plasma-concentration is reached within 1 hour after oral administration, and elimination half-life is 3-5 hours.

Side effects:

>10%:	Drowsiness.
1-10%:	Weakness, diarrhea, dry mouth, hypotension, akathisia, depression, extrapyramidal symptoms, parkinsonism.
0,1-1%:	Bradycardia, hyperprolactinemia, loss of consciousness, dyskinesia, dystonia, hallucinations, hypersensitivity, amenorrhea.
0,01-0,1%:	Confusion, cramps.
Not Known:	AV-bloc, QT-interval prolongation, cardiac arrest, hypertension, vascular collapse, methemoglobinemia, gynecomastia, malignant neuroleptica syndrome, suicidal behavior, syncope, tardive dyskinesia, allergic reactions.(46)

Subjects will be thoroughly instructed to stop administrations of metoclopramide if they experience extrapyramidal symptoms.

9.6 Thiamine

All subjects will receive treatment with thiamine during the trial as to minimize the risk of developing Wernicke's encephalopathy. If the subject is hospitalised thiamine 100 mg i.v. will be administered daily. Out-patient participants will take 1 oral tablet Apovit B-combin stærk daily which contains B1 15 mg, B2 15 mg and B6 15 mg.

9.7 IMP Management and accountability

At each study site, there will be an IMP accountability log that will contain

- Amount received at the study site
- Date of delivery
- Expiration date
- Amount accessible at the study site
- Date and initials of the person updating the log

There will be an accountability log on subject level to ensure traceability and compliance. This log will contain

- Subject ID

- Expiration date
- Amount dispensed
- Dispensed by: date and initials
- Amount returned by subject
- Excess medication received by

The subjects will be instructed to keep a log of administered IMP and rescue medication as described in the folder 'Praktisk information om forsøgsmedicinen'. They will be asked to return any unused medication.
The local investigators are responsible for keeping the accountability log up to date at centre level as well as on subject level.

IMP management and accountability will be monitored by the GCP-unit throughout the trial.

10. Procedures

10.1 Visit Schedule

Visit ID	Procedures to be performed at the visit
Screening Visit Day -2-0	Obtain written informed consent for the trial before any other trial procedures are performed Assess compliance with inclusion and exclusion criteria Obtain demographic data Record medical history Record use of relevant previous medications and concomitant medication Record PUQE-24 score Record pre-pregnancy weight Measure weight Measure height Measure vital signs Perform physical examination Perform ultrasound scan to confirm gestational age and singleton pregnancy, if there is no record of such in the medical journal from within 4 four weeks prior to visit Collect blood samples Record ECG to rule out long QT-syndrome Schedule date for next visit.
Visit 1 (Randomisation) Day 0 Baseline values recorded	Re-assess compliance with inclusion and exclusion criteria Record changes to concomitant medication Record PUQE-24 score Record nausea VAS Record number of daily vomiting Record EQ-5D, NVPQOL, HELP and modified PSQI Record possible patient consideration of termination of pregnancy Measure weight Measure vital signs Collect blood samples Randomise the subject Instruct the subject on how to use the IMP Dispense IMP, rescue medication and B-kombin to the subject (sufficient medication for 10 days) Schedule date for next visit
Visit 2 Day 7	Re-assess compliance with inclusion and exclusion criteria Record changes to concomitant medication and including rescue medication Record PUQE-24 score Record nausea VAS Record number of daily vomiting Record EQ-5D, NVPQOL, HELP and modified PSQI

Visit ID	Procedures to be performed at the visit
	Record patient satisfaction with treatment VAS Record possible patient consideration of termination of pregnancy Record sick leave Record possible hospitalization Record possible administration of i.v. fluids Record side effects Assess AEs occurring since the last visit Record use of rescue medication Record desire for dosage increase Measure weight Measure vital signs Record ECG Collect blood samples Collect used IMP and rescue medication and perform drug accountability and compliance check Dispense IMP, rescue medication and B-kombin to the subject (sufficient medication for 10 days) Schedule date for next visit
Visit 3 Day 14	Re-assess compliance with inclusion and exclusion criteria Record changes to concomitant medication including rescue medication Record PUQE-24 score Record nausea VAS Record number of daily vomiting Record EQ-5D, NVPQOL, HELP and modified PSQI Record patient satisfaction with treatment VAS Record possible patient consideration of termination of pregnancy Record sick leave Record possible hospitalization Record possible administration of i.v. fluids Record side effects Assess AEs occurring since the last visit Record use of rescue medication Record desire to continue trial medication Measure weight Measure vital signs Record ECG Collect blood samples Collect used IMP and rescue medication and perform drug accountability and compliance check If continuous treatment is desired the subject will be unblinded
Pregnancy Outcome obtained from Medical Journal	Record gestational age at birth or loss/termination of pregnancy Record APGAR Record gender Record birth weight Record umbilical cord pH Record placenta weight Record possible congenital malformations and hospitalization at neonatal ward during the first month post-partum

10.2 Trial Procedures

This section outlines the trial procedures that will be performed during the trial. For further details on the specific timing of the procedures please refer to the visit schedule in above.

The tasks listed below must be performed by a physician or an appropriately trained nurse or midwife to whom the local investigator has delegated the tasks:

- Obtainment of informed consent
- Evaluation of in- and exclusion criteria
- Physical examination
- Assessment of AEs/SAEs
- Assessment of ECG and other laboratory results
- Decision to break the randomisation code for individual subjects (See **7.3 Discontinuation** and **8.2 Blinding**)

10.3 Informed Consent

The written informed consent must be obtained (i.e. signed and dated by the subject) before any trial activities are performed.

Each subject must be informed that participation in the trial is voluntary and that he/she may withdraw from the trial at any time during the course of the trial and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

Subjects meeting the inclusion criteria for the trial will be given thorough verbal and written information about the trial. This information will be given by a trial authorized physician, nurse or midwife directly affiliated with the trial. Information must take place in an undisturbed room. The subject will be given time to ask questions and allowed sufficient time (minimum 24 hours) to consider the trial before deciding whether to participate.

If subjects so desire, they may make a later appointment with the site investigator after having reviewed the written information about the trial, at which they can meet and discuss participation in the trial. Such a meeting must take place in an undisturbed room and the subject may bring a family member or friend to aid the decision-making. After this meeting, the subject may deliberate on trial participation for up to seven days.

The subjects will be informed of any potential risks associated with the trial.

It is the responsibility of the principal investigator or a sub-investigator to obtain the written informed consent from the subject.

After completion of trial, all participating subjects will be informed of the overall results. Information of individual data and the interpretation hereof will be provided by the investigator. The individual subject's right not to know of own data will be respected.

10.4 Future contact

When subjects are asked to consent to participation in the trial, they will be asked specifically if they can accept possible future contact for the purpose of further research regarding HG. The answer to this question will be recorded on the informed consent form as well as on the e-CRF. Subjects will be able to participate in the trial without giving consent to future contact and they can withdraw their consent at any time.

10.5 Consent for long-term storage of blood samples in a biobank

Subjects will also be asked specifically if they can accept the storage of their samples within a biobank. The answer to this question will be recorded on the informed consent form as well as on the e-CRF. Subjects will be able to participate in the trial without giving consent to long-term storage of blood samples. Subjects may withdraw this consent at any time, and any samples stored in the biobank will then be destroyed.

10.6 Access the offspring's medical journal

In order to register possible congenital malformations and/or hospitalizations of the offspring during the first month after delivery we will ask consent from both parents (forældremyndighedsindehaver(e)) to access the offspring's medical journal. Access to the offspring's medical journal is solely a safety measure and there will be no intervention on the newborn.

If the co-parent is present at screening or trial visits he/she will be informed verbally and in writing then and there. If the co-parent is not present, the trial subject will be asked if there is a future co-parent and if confirmatory, written information on the trial may be given to the trial subject who can pass it on to the co-parent. The co-parent will be offered to make an appointment with the site investigator after having reviewed the written information on the trial. Such a meeting must take place in an undisturbed room. If the co-parent prefers

verbal information on the trial may be given over the phone. The co-parent will be given time to ask questions and allowed sufficient time (minimum 24 hours) to consider whether to consent.

The co-parent may sign the consent form at home and it may be brought to the trial personnel by the trial subject.

10.7 Subject ID number

All subjects enrolled must be identifiable throughout the trial. This will be done by using subject number allocated to the subject at Visit 1 (the screening visit).

10.8 Demography

The following data will be recorded directly in REDCap:

- Date of birth
- Phone number
- E-mail address
- Occupation
- Pre-pregnancy weight
- Gestational age
- Parity
- Possible previous NVP or HG
- Date of initiation of current hospital contact
- PUQE-24 score leading up to current hospital contact

10.9 Medical history and concomitant disease

Medical history is a medical event that the subject has experienced in the past. Only medical history considered relevant by the Investigator should be reported.

Concomitant disease is any illness that is present at the start of the trial (i.e. at the screening visit or found as a result of the screening procedure)

This will be recorded directly in the e-CRF.

10.10 Concomitant and previous medication

All medication taken during current pregnancy will be recorded, as will concomitant medication. Concomitant medication is any medication, other than trial products, which is taken after signing the Informed Consent.

At each visit the Investigator or delegate should ask the subject about use of concomitant medication including rescue medication. All concomitant medication and changes hereto must be documented in the subject's medical records and directly in the e-CRF.

10.11 Vital signs and weight

Blood pressure (BP) and pulse will be measured after 10 minutes sitting rest twice on the left arm with an automatic device.

Weight and height will be measured according to local procedures.

This will be recorded directly in the e-CRF.

10.12 Physical Examination

A physical examination will be performed by the investigator or a delegate according to local procedures.

Significant findings that are present at screening must be recorded as medical history in the e-CRF. Significant findings found at the following visits, which meet the definition of an AE, must be recorded on an AE page in the e-CRF.

10.13 Ultrasound scan

An ultrasound scan will be performed by the investigator or a delegate trained to do so. The purpose of the ultrasound scan is to determine gestational age and confirm singleton pregnancy.
If the medical journal holds records that an ultrasound scan has been performed within 4 weeks prior to screening visit, a confirmatory ultrasound is not necessary. The ultrasound confirmed gestational age will be recorded in the e-CRF. It will also be recorded whether the it was obtained from the medical journal or recorded directly in the e-CRF based on an ultrasound scan performed by the investigator or a delegate.

10.14 ECG

An ECG will be recorded according to local procedures with the purpose of identifying possible subjects with long QT-syndrome and potential QT prolongation during the study. Subjects with long QT syndrome cannot be enrolled in the trial. In case of QT prolongation onset during the trial subjects must be discontinued, QT, QTc and pulse will be recorded in the e-CRF.

10.15 Laboratory Tests

Blood samples will be taken using standard venepuncture techniques. Altogether approximately 25 ml blood will be drawn from each subject.

The following laboratory variables will be measured:

Haematology:

Erythrocytes, haemoglobin, haematocrit, leukocytes, neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

Blood chemistry:

Creatinine, urea, sodium, potassium, calcium, alanine aminotransferase (ALAT), albumin, bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), C-reactive protein (CRP), thyroid stimulation hormone (TSH), T3 and T4.

The clinical laboratory values will be reported to the investigator or a delegate by the laboratory and he/she must review them for significance.

These blood samples are taken as standard part of monitoring patients suffering from HG in order to identify possible electrolyte derangement or other conditions causing symptoms similar to HG. Specifically relevant to this trial are ALAT, ASAT and creatinine since subjects might be excluded from the trial if these are elevated.

Plasma-mirtazapine and -ondansetron will be measured in the mirtazapine- and ondansetron-groups, after the last subject has been unblinded. The purpose of this analysis is explorative.

Biobank:
Blood samples will be stored at -80^0 C, so that subsequent analysis of newly discovered relevant markers can be performed without further discomfort to the patient. The blood samples will be stored for 10 years and will then be destroyed.

10.16 Questionnaires

Questionnaires on PUQE-24 score, nausea VAS, number of daily vomiting episodes, EQ-5D-5L (health related quality of life), NVPQOL (nausea and vomiting of pregnancy quality of life), HELP (hyperemesis level prediction), modified PSQI (Pittsburg sleep quality index), patient satisfaction with treatment VAS, possible patient consideration of termination of pregnancy and possible side effects and AEs, sick leave, hospitalisation and amount of i.v. fluids will be filled out online directly in the e-CRF by subjects at Visit 1, 2 and 3.
Subjects will daily fill out online questionnaires directly in the e-CRF on PUQE-24 score, nausea VAS, number of daily vomiting episodes, time of IMP-administration (and possible re-administration) use of rescue medication as well as possible side effects and AEs during the trial.
Subjects will be prompted to continue daily online registration of possible side effects and AEs until five days after end of intervention.

10.17 Treatment failure

Treatment failure will be registered if a subject decides to discontinue the trial because of insufficient symptom relief. Time of treatment failure will be registered directly in the e-CRF by the investigator or a delegate.

10.18 Electronic medical record

The electronic medical record will be viewed in the process of recruiting subjects and assessing compliance with in- and exclusion criteria. The subjects will have to confirm compliance with these criteria prior to starting the trial. Furthermore the medical record will be accessed to obtain pregnancy outcome.

The following data will be obtained from the subject's electronic medical record and entered in the e-CRF:
Prior to enrolment:

- Record of possible ultrasound to confirm gestational age and singleton pregnancy
- Record of PUQE-24 score
- 5HT3-receptor allergy
- Pre-existing diagnosis of cronic disease

Postpartum:

- Pregnancy outcome: gestational age at birth or loss/termination of pregnancy, APGAR, gender, birth weight, placenta weight, umbilical cord pH, mode of delivery. Pregnancy outcome is a safety measure to ensure the identification of any serious adverse events.

Record of possible congenital malformations or hospitalization of the new-born at neonatal ward during the first month post-partum will be obtained from offspring's electronic medical record and entered in the e-CRF. This outcome is a safety measure to ensure the identification of any serious adverse events.

11. Assessment of Safety

Information about Adverse Events (AEs), whether reported by the subject, discovered by the investigator by reviewing dialy records, detected through physical examination, laboratory test or other means, must be collected and recorded on the AE form and followed up as appropriate.

Evaluation of AEs including severity, causality, outcome and seriousness assessments must be performed by a physician.

Any AE occurring from the time the informed consent was signed by the subject and until five days after Visit 3 must be recorded and reported on an AE page in the e-CRF.

Standardised report forms for AEs and SAEs will be provided as part of the e-CRF.

11.1 Definitions – Adverse Event (AE)

An AE is any untoward medical occurrence in a subject administered a medicinal product/device even if it does not necessarily have a causal relationship with this treatment.

The following events should not be recorded as AEs:

- A pre-planned procedure, e.g. a surgical intervention, unless the condition for which the procedure was planned has worsened since the informed consent form was signed.
- Pre-existing conditions documented as medical history. Any worsening in severity or frequency of a pre-existing condition during the clinical trial period must be regarded as an AE.

11.2 Definitions – Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

A serious adverse event/reaction is an experience that at any dose results in any of the following:

- Results in death
- Is life-threatening - this refers to an event in which the subject was at risk of death at the time of the event
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect
- Is judged medical important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above)

11.3 Assessments of AEs and SAEs

Assessment:

When assessing AEs and SAEs the investigator will refer to the product resumes 4.8.

Severity:

The severity of an AE/SAE is a clinical observation assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

Potential AEs/SAEs will be treated according to standard practice and if relevant follow-ups will be scheduled with relevant specialist.

Causality / Causal Relationship to IMP:

The following terms and definitions are used when assessing the relationship between an AE/SAE and the relevant trial product (IMP):

- Probable: good reason for sufficient documentation to assume a causal relationship
- Possible: a causal relationship is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to aetiology other than the trial product

Final outcome:

The outcome of an AE/SAE is assessed by the sponsor using the following definitions:

- Recovered/resolved: Fully recovered or has returned to baseline
- Recovered with sequelae: As a result of the AE the subject suffered persistent and significant disability/incapacity
- Not recovered: The condition has not returned to baseline, however symptoms may have improved
- Fatal: Event that results in death – An AE with fatal outcome must be reported as an SAE
- Unknown: The outcome is unknown. This term should only be used when no other definition is possible e.g. the subject is lost to follow-up

11.4 Reporting

SAE reporting will be performed in the e-CRF and reviewed by the sponsor. In case of IT breakdown, printed versions of the SAE form will be available at all study sites.
Both the sponsor and the primary investigator must be notified via e-mail or phone within 24 hours:

Sponsor:	Ellen Christine Leth Løkkegaard
Email address:	Eloe0002@regionh.dk
Primary investigator:	Anne Ostenfeld
Email address:	Anne.ostenfeld.02@regionh.dk
Emergency phone:	Not yet available

Serious Adverse Events:

SAEs must be reported to the above-mentioned persons immediately (within 24 hours of awareness). Any follow-up data must be detailed in a subsequent SAE form in due time.

The initial SAE report must contain as much information as possible including relevant information from the e-CRF (e.g. medical history, concomitant medication) and must be provided via the e-CRF system. If the reporter does not have access to the e-CRF, e-mail may be used.

The SAE report will remain open as long as new relevant data on the event may emerge. The report will be finalised when all relevant information is collected.

Suspected unexpected serious adverse reaction (SUSAR):

An unexpected serious adverse reaction where source or severity is not consistent with information in the current Summary of Product Characteristics (SmPC).

It is the responsibility of the Sponsor to determine whether a reported SAE is a SAR and whether a SAR is a SUSAR. A SUSAR resulting in death or life threatening must be reported within 7 days after the Sponsor becomes aware of the reaction. Within 8 days after reporting, the sponsor must notify the Danish Health and Medicines Authority and the Committee System on Biomedical Research Ethics of all relevant information concerning follow-up of the reaction. Any other SUSAR must be reported to the above-mentioned agencies within 15 days after the Sponsor becomes aware the reaction. SUSARs must also be reported to all local investigators on all study sites.

11.5 Annual reporting

The Sponsor is responsible for annually reporting SARs and SUSARs to the Danish Health and Medicines Authority and the Committee System on Biomedical Research Ethics and all local investigators on the involved study sites.

12. Data handling / Data Management

Data will be handled according to the law on handling personal data(persondataforordningen).
The trial has been reported to 'Datatilsynet' in Region Hovedstaden and approval has been granted (VD-2018-144, I-suite: 6385). The trial will be reported to all involved regions ahead of initiating the trial in each region.
Data will be stored for 10 years, after which they will be transferred to "Dansk Data Arkiv" or deleted or anonymised.

12.1 CRF

An electronic CRF (REDCap) is provided and all data related to the trial will be recorded here and provide the basis for a central database.

Data on ultrasound scan and birth outcome may be collected from the subject's medical journal and registered in the e-CRF. The new-born's medical journal will be assessed and possible data on congenital malformations and hospitalization during the first month will be registered in the e-CRF.

The e-CRF is to be completed by the investigator or a delegate at the time of the subject's visit to the clinic so that it always reflects the latest observations on the subject.
At the subject's final visit, the e-CRF should be verified and signed off by the responsible investigator or delegate at the site.

12.2 Laboratory Data

Values from blood and urine samples and ECG will obtained from the medical journal and be entered manually into the e-CRF.

13. Statistical evaluation

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 changes in PUQE-24 score 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.

Before the randomisation code will be added to the cleaned dataset, a prespecified statistical analysis plan (SAP) will be elaborated and accepted by the statistician and investigators.

All data will be described including data-incompleteness as well as reasons for data-incompleteness. Data will be analysed blinded by the statistician. Any changes to the statistical analysis plan will be described in any future publications.

For further information on the final analysis refer to the SAP.

14. End of trial

Within 90 days after the trial completion the sponsor must inform the Danish Health Authorities and Ethics Committee about the completion. The result of the trial must be submitted within 12 months.

14.1 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.

14.2 Subject Discontinuation

The subject will be advised in the informed consent form that he/she has the right to withdraw from the trial at any time without prejudice. Where discontinuation from the trial is initiated by the subject, the investigator is to ascertain the primary reason for discontinuation from the list below:

- An AE for which the investigator did not consider discontinuation from the trial necessary
- Co-existing disease
- Withdrawal of consent
- Other reasons including treatment failure

The subject may at any time be discontinued from the trial at the discretion of the investigator.

Subjects must be discontinued from the trial under the following circumstances:

- If a criterion equivalent to an exclusion criterion occurs
- If, in the investigator's opinion, continuation in the trial would be detrimental to the subject's well-being
- Occurrence of intolerable AE(s) as determined by the investigator and/or subject
- Subject lost to follow-up
- If the randomisation code is broken
- If informed consent is withdrawn

In all cases, the primary reason for discontinuation must be recorded in the e-CRF and in the subject's medical records. Follow-up on the subject is necessary to establish whether the reason was an AE. If so, this must be reported in accordance with the appropriate procedures.

As far as possible, all examinations scheduled for the final visit must be performed on subjects who receive the IMP but do not complete the trial according to the protocol.
Data obtained until discontinuation will be entered in the clinical database and used for statistical analyses.

15. Administrative procedures

15.1 Source data and subject data protection

Source data will be registered in patient records or on source data sheets or directly in the e-CRF.

Prior to start of data recording from subjects, the investigator will prepare a Source Data Location Agreement to document where the first recording of data is done.

As a minimum requirement, the following data must be source data-verifiable in source documentation other than the e-CRF:

- Subjects informed consent
- Date of informed consent
- List of randomised subjects

A common e-CRF will be constructed and provide the basis for a central database. Data will in the central database be stored in coded form according to the rules of the Danish Data Protection Agency (Datatilsynet) with whom the trial is registered.

In accordance with the Danish Data Protection Agency data processing will be completed by 01.06.2028. Afterwards data in paper form will be destroyed and electronic data will be transferred and stored at the Danish Data Archives (Statens Arkiver).
Anne Ostenfeld will be responsible for data collection and processing.
In addition, Ellen Løkkegaard, Tonny Studsgaard Petersen, Lars Henning Pedersen, Hanne Brix Westergaard, Jon Thor Trærup Andersen and Andreas Emil Kryger Jensen will be involved in data processing.

The investigator will have direct access to source data and documents in case of monitoring, auditing or inspection from health authorities (Lægemiddelstyrelsen, Videnskabsetisk komité, GCP-enhederne).

15.2 Quality control and assurance

The trial will be carried out according to the protocol, ICH-GCP and current law and it will follow the Declaration of Helsinki.
Quality control and assurance will be carried out in accordance with ICH-GCP and standard procedures will be followed including monitoring, auditing or inspection from health authorities (Lægemiddelstyrelsen, Videnskabsetisk komité, GCP-enhederne).

15.3 Monitoring

Regular monitoring visits will be performed according to ICH-GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The monitor will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.
The regional GCP units will conduct the monitoring of sites, regulatory compliance, and review of e-CRFs to source documents. The monitoring will be coordinated from the GCP-unit at Bispebjerg University Hospital, Copenhagen, Denmark. It is the responsibility of the Sponsor that the trial is monitored.

15.4 Research Biobank

During the trial blood samples will be stored at -80^{0}C in a research biobank at Nordsjællands Hospital in pseudo anonymized form. After end of trial and unblinding plasma-mirtazapine and plasma-ondansetron will be analyzed in the respective groups and any left-over material in this research biobank will be kept in a biobank for future research if the subjects have concented to this, or be destroyed in case the subjects have not consented to participate in the biobank.

15.5 Biobank

A biobank for possible future research will be established at Nordsjællands Hospital.
The biobank will store blood in pseudo anonymized form at -80 ^{0}C for possible later analysis of biomarkers.
Samples in the biobank will be stored for 10 years provided subjects acceptance; hereafter the material will be destroyed.
Additional analysis will only be performed after approval by the Committee System on Biomedical Research Ethics. All project related data and samples that can be referred directly to an individual subject will be destroyed immediately or by the closure of the trial.

15.6 Financing

The initiative for this trial was taken by the sponsor, investigator and advisors, none of whom have any financial interest in the trial.
Financial support for the conduct of this study has so far been given to sponsor's research account at Nordsjællands Hospital from Regionernes Medicinpulje who supported the trial with 1,685,096 DKK. This will cover the majority of the trial expenses; salaries (VIP and TAP), laboratory costs, transportation costs for trial subjects and investigator, trial medication, IT-equipment and open access publication. Sponsor, investigator and advisors have no financial links to Regionernes Medicinpulje.
Furthermore, The Research Foundation at Nordsjællands Hospital has supported the trial with 75,000 DKK to cover part of VIP salary.
We are currently applying to other funds for further financing.

15.7 Financial compensation to subjects

The trials subjects will be financially compensated for any documented costs caused by their participation in the trial.

15.8 Insurance

Patients will be covered according to current regulations. Trials in the Danish regions are covered by the patient-insurance (Patienterstatningen).

15.9 Ethical Considerations

Irrespective of the outcome of the trial it will provide useful information on treatment of HG.
The result of the trial will thereby provide physicians and patients with new relevant information guiding their choice of treatment. Currently the treatment offered for severe NVP is not profoundly evidence based and it is often not sufficiently effective, thus 27% of this patient population consider ending the pregnancy and 75% do not wish to become pregnant again.
Based on the number of women exposed to mirtazapine and ondansetron in pregnancy we consider both treatments safe to use in early pregnancy.
All three groups will be allowed to use metoclopramide as rescue medication so no subjects are completely excluded from effective treatment.

16. Publication

The trial is investigator-initiated and data are owned by Region Hovedstaden. Both positive, negative and in-conclusive study results will be published via www.clinicaltrials.gov and in an international peer-reviewed scientific journal by the investigators of the study group. Anne Ostenfeld will draft the first manuscript.

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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 (3)

Appendix 2

Schematic overview of case-reports where NVP/HG has been treated with mirtazapine

Case and refer-ence	**Symptoms**	**Treatment prior to mirtazapine**	**Mirtazapine dosage**	**Effect**	**Gestation-al age at initiation of mirta-zapine treatment**	**Pregnancy outcome**
Case 1(23)	Severe NVP and panic attacks. Wanted pregnancy termination.	Not specified.	15 mg daily until 17 weeks, then 7,5 mg daily until delivery. When trying dosage reduction symptoms reoccurred immediately.	Significant reduction in NVP. The abortion was cancelled.	Between week 5 and 17. Not specified.	Healthy infant delivered at 36 weeks by c-section. Normal development.

Case 2(23)	Severe NVP.	Not specified.	7,5 mg daily. Slowly tapered off at 11weeks.	Symptoms subsided completely within a few days.	Not specified.	Abortion at 16 weeks due to trisomy 18.
Case 3(23)	Severe NVP and severe depression.	Not specified.	7,5 mg daily. When trying dosage reduction symptoms reoccurred immediately. Continued mirtazapine until late 2nd trimester.	NVP subsided within a few days.	Week 15.	Healthy infant delivered at 38 weeks. Normal development.
Case 4(23)	Moderate NVP.	Not specified.	3,75 mg daily. Discontinued after less than one week.	NVP subsided almost immediately. NVP did not reoccur after discontinuation.	Week 9.	Healthy infant delivered at term. Normal development.
Case 5(23)	Severe NVP, 5 kg weight loss.	Oral doxylamine, i.v. chlorpromazine, ondansetron and clorazepate.	15 mg daily without effect, however she had been vomiting the mirtazapine. Then administered only when not vomiting. Dosage increased to 30 mg daily at 11 weeks. At 14 weeks decreased to 15 mg daily until delivery.	When administered only when not vomiting NVP subsided slowly and had subsided completely after 8 days. No further NVP.	Between week 8 and 11. Not specified.	Healthy infant delivered at term. Normal development.
Case 6(47)	Treatment resistant HG with 30 vomiting episodes daily. 12 kg weight loss. Need of parenteral nutrition. Considered pregnancy termination.	I.v. dimenhydrinate, ranitidine, metoclopramide and trifluprom azine, all without effect. Lorazepam orodisolvable tablet.	6 mg i.v. daily for 3 days, then 15 mg oral tablet daily for 4 weeks. Then dosage decrease to 15 mg every other day for 2 weeks and then discontinued.	Stagnation of symptoms after 1 day. Symptoms completely subsided after 3 days.	Week 16.	Healthy infant delivered at week 37.
Case 7(48)	HG, severe weight loss, dehydration and hypokalemia. Wanted pregnancy termination.	Metoclopramide and promethazine, insufficient effect.	30 mg daily for 6 days.	Responded in 24 hours and could resume diet after 3 days.	Week 12.	Healthy infant delivered at 35 weeks by c-section because of preterm premature rupture of membranes. Normal development at 1 year of age.

Case 8(48)	HG, 5 kg weight loss, dehydration. Wanted pregnancy termination.	I.v. metoclopramide.	30 mg daily for 10 days.	Responded promptly and could resume diet after 4 days. Occasional vomiting in 2nd and 3rd trimester.	Week 10.	Healthy infant delivered at 39 weeks. Normal development at 1 year of age.
Case 9(48)	HG, 2.5 kg weight loss. Wanted termination of pregnancy.	Metoclopra-mide and promethazine without effect.	30 mg daily for 7 days	Responded promptly and could resume diet after 4 days.	Week 5.	Healthy infant delivered at 40 weeks. Normal development at 1 year of age.
Case 10 (49)	Severe NVP and stomach cramps, 13 kg weight loss. Wanted termination of pregnancy.	Dimenhydrinate, metoclopramide, triflupromazine and pyridoxine with minimal effect.	6 mg i.v. daily for 3 days, then 30 mg oral tablet daily for 2 weeks. Slowly tapered and finally discontinued after 4 weeks. Treatment reinstalled in week 27 due to gastroenteritis. Discontinued in week 33.	Symptoms resolved within hours.	Week 15.	Healthy twins delivered at 36 weeks by c-section. Normal development at 6 months of age.
Case 11 (50)	HG, anxiety and depressive symptoms. Need of parenteral nutrition.	Ondansetron, droperidol.	15 mg daily. Dosage increased to 30 mg daily at week 19 because of anxiety. Discontinuation tried in week 15, which lead to reoccurrence of symptoms.	Symptoms resolved within days.	Week 13.	Healthy infant delivered at 40 weeks by c-section because of frustran induction.
Case 12 (50)	HG, history of depression.	Ondansetron without effect. From week 19 ondansetron pump with effect.	15 mg daily, increased to 45 mg daily at week 23 because of anxiety and depressive symptoms.	No effect of 15 mg daily, but symptoms resolved after the dosage increase in week 23.	Week 10.	Healthy infant delivered at 39 weeks.
Case 13 (50)	NVP, dehydration, depression.	Promethazine without effect, metoclopramide.	15 mg daily for 2 weeks, then discontinued because of the price.	Symptom relief. Recurrence of symptoms after discontinuation.	Week 17.	Healthy infant delivered at term.
Case 14 (50)	HG, dehydration. Need of parenteral nutrition.	Metoclopramide and ondansetron tried, but discontinued due to side effects. Trimetho-benzamide with some effect.	15 mg daily throughout pregnancy.	At week 13 only some nausea persisted.	Week 11.	Healthy infant delivered at term.

Case 15 (50)	HG. Chronic depression and anxiety.	Promethazine ondansetron.	7.5 mg daily. Tapered off at 28 weeks.	Symptom relief.	Week 10.	7-pound infant with persistent fetal circulation and pulmonal hypertension, needing a ventilator. Discharged 3 days later.
Case 16 (50)	NVP, mild depression and anxiety. Need of parenteral nutrition. **(Same patient as case 11, but new pregnancy)**	Ondansetron 10 mg twice daily and diphenhydramine hydrochloride and famotidine with insufficient effect. Droperidol tried but discontinued due to side effects.	15 mg daily throughout pregnancy.	Prompt symptom relief. Other medications discontinued.	Week 12.	7-pound healthy infant delivered by elective c-section.
Case 17 (50)	Nausea and depression.	None.	7.5 mg daily increased to 15 mg daily after 2 weeks, remained on this dosage throughout pregnancy.	Patient felt better after starting mirtazapine, and symptoms subsided completely after dosage increase.	Week 10.	7-pound healthy infant delivered at 37 weeks by c-section because of shoulder dystocia.
Case 18 (51)	Treatment resistant HG since week 12, 9 kg weight loss. Type 1 diabetes.	Metoclopramide and dimenhydrinate with insufficient effect.	6 mg i.v. daily. Discontinuation lead to recurrence of symptoms within days. Then (week 29) started on 45 mg daily until delivery.	Symptoms resolved within days and subsided completely after 3 days.	Week 25.	Premature infant delivered at 34 weeks by c-section due to preeclampsia and intrauterine growth restriction. Developed withdrawal symptoms after 34 hrs that persisted for 36 hrs.
Case 19 (52)	Severe NVP, 3 kg weight loss, depressive symptoms.	Metoclopramide without effect.	7.5 mg daily, increased to 15 mg daily until week 28.	Moderate effect of 7.5 mg daily. Symptoms subsided completely after dosage increase.	Week 14	Healthy infant delivered at 40 weeks.
Case 20 (52)	Severe NVP, weight loss, depressive symptoms.	Antiemetics (not specified) with some effect.	15 mg daily until week 34, then 7.5 mg daily until delivery.	Significant effect in NVP within days and decrease in depressive symptoms within 2 weeks.	Week 18	Healthy infant delivered at 40 weeks.

Case 21 (53)	Severe nausea, 3 kg weight loss insomnia, panic attacks.	No antiemetics. Citalopram for anxiety symptoms from week 18.	7.5 mg daily until delivery. Discontinuation was tried but lead to recurrence of symptoms.	Dramatic decrease in symptoms.	Week 22	Healthy infant delivered at 38 weeks by elective c-section.
Case 22 (53)	Nausea, decreased appetite, insomnia, depressive symptoms.	Sertraline 50 mg daily started simultaneously with mirtazapine.	7.5 mg daily until delivery. Discontinuation was tried but lead to recurrence of symptoms.	Significant decrease in symptoms.	Week 24.	Healthy infant delivered at 40 weeks.
Case 23 (54)	HG, dehydration. Need of parenteral nutrition. Type 1 diabetes.	Dimenhydrinate, metoclopramide, ondansetron, haloperidol, dexamethasone without effect.	30 mg i.v. daily for 3 days, then 30 mg tablet daily until delivery.	Symptoms subsided completely within 48 hrs.	Week 21.	Delivery be c-section at 35 weeks.