Clinical trial results:
EMPOWER: EMesis in Pregnancy - Ondansetron With mEtoclopRamide.

Summary

EudraCT number	2017-001651-31
Trial protocol	GB
Global end of trial date	02 April 2020

Results information

Result version number	v1 (current)
This version publication date	24 October 2020
First version publication date	24 October 2020

Trial information

Trial identification

Sponsor protocol code	5.0

Additional study identifiers

ISRCTN number	ISRCTN16924692
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference : 17/NE/0325 , NUTH Sponsor Reference : 8367, NIHR HTA Funder Reference: 16/15/03

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Freeman Road, Newcastle upon Tyne , United Kingdom, NE7 7DN
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2020
Global end of trial reached?	Yes
Global end of trial date	02 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether, in addition to IV rehydration, ondansetron vs placebo ondansetron and metoclopramide vs placebo metoclopramide reduces the rate of treatment failure up to 10 days after initiation.

Protection of trial subjects:

A DMC was convened to undertake independent review. The purpose of this committee was to monitor safety. At the first meeting, the DMC agreed on its charter of operation and how many times the DMC would meet throughout the course of the study.

Background therapy:

Nausea and vomiting in pregnancy (NVP) affects up to 85% of women in the first half of pregnancy. Symptoms usually start at 6-8 weeks, peak by 9 weeks and for many women subside by 20 weeks gestation. Symptoms are often mild but 30% of sufferers experience more severe symptoms requiring medical intervention. The most severe form, hyperemesis gravidarum (HG), affects 0.3-3% of women and is characterised by intractable vomiting, dehydration, ketonuria and weight loss. HG can result in prolonged hospitalisation, multiple treatments and, where interventions fail, termination of pregnancy. NVP is associated with emotional and psychological distress and has a profound impact on quality of life. Women often feel unsupported, suffer higher rates of depression, anxiety and stress and often feel dissatisfied with care. Women with HG are also more likely to deliver preterm and to have small for gestational age infants although there is no association with congenital anomalies or perinatal death.

The aetiology remains unclear and there is no cure for NVP - treatment focuses on relieving symptoms and preventing morbidity. Most women with moderate or severe disease require clinician-initiated interventions in the form of intravenous fluids and antiemetic drugs, primarily antihistamines, dopamine antagonists and 5-HT3 antagonists.

Participants were randomised to one of the following regimes:

- Metoclopramide (10 mg three times daily [IV + PO]) + placebo [IV + PO]
- Ondansetron (4 mg three times daily [IV + PO]) + placebo [IV + PO]
- Metoclopramide (10 mg three times daily [IV + PO]) + ondansetron (4 mg three times daily [IV + PO])
- Double placebo three times daily [IV + PO]

Evidence for comparator: -	
Actual start date of recruitment	01 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 33

Worldwide total number of subjects	33
EEA total number of subjects	33

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	33
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Clinical staff on duty in the department where pregnant women present for assessment and treatment informed the research team if any women attended suffering from NVP or HG. The clinical team made the first approach to the potential participant. The research team then approached the patient. Participants were recruited between 29/5/18 and 7/8/19.

Pre-assignment

Screening details:

All women attending secondary care with NVP were assessed for eligibility by the research team and confirmed by a medically qualified doctor trained in GCP. A detailed medical and obstetric history was taken.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally by NCTU secure web-based system. Patients were randomised on a 1:1:1:1 basis using a block stratified method (stratified by site) to receive either (1) ondansetron + placebo, (2) metoclopramide + placebo, (3) metoclopramide + ondansetron or (4) double placebo. Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ondansetron plus placebo

Arm description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron PO 4mg tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm title	Metoclopramide plus placebo

Arm description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Metoclopramide plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm title	Ondansetron plus Metoclopramide

Arm description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus Metoclopramide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm title	Double placebo

Arm description:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Arm type	Placebo
Investigational medicinal product name	Double Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Number of subjects in period 1	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Started	8	8	9
Completed	8	8	9

Number of subjects in period 1	Double placebo
Started	8
Completed	8

Period 2

Period 2 title	Time Point 1 - 48 hours
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally by NCTU secure web-based system. Patients were randomised on a 1:1:1:1 basis using a block stratified method (stratified by site) to receive either (1) ondansetron + placebo, (2) metoclopramide + placebo, (3) metoclopramide + ondansetron or (4) double placebo. Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ondansetron plus placebo

Arm description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm title	Metoclopramide plus placebo

Arm description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Metoclopramide plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm title	Ondansetron plus Metoclopramide

Arm description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus Metoclopramide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm title	Double placebo

Arm description:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Arm type	Placebo
Investigational medicinal product name	Double Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Number of subjects in period 2	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Started	8	8	9
Completed	8	7	9
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

Number of subjects in period 2	Double placebo
Started	8
Completed	8
Not completed	0
Consent withdrawn by subject	-

Period 3

Period 3 title	Time Point 2 - 5 days
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally by NCTU secure web-based system. Patients were randomised on a 1:1:1:1 basis using a block stratified method (stratified by site) to receive either (1) ondansetron + placebo, (2) metoclopramide + placebo, (3) metoclopramide + ondansetron or (4) double placebo. Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ondansetron plus placebo

Arm description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron PO 4mg tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm title	Metoclopramide plus placebo

Arm description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Metoclopramide plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm title	Ondansetron plus Metoclopramide

Arm description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus Metoclopramide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm title	Double placebo

Arm description:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Arm type	Placebo

Investigational medicinal product name	Double Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Number of subjects in period 3	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Started	8	7	9
Completed	8	7	9

Number of subjects in period 3	Double placebo
Started	8
Completed	8

Period 4

Period 4 title	Time Point 3 - 10 days
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally by NCTU secure web-based system. Patients were randomised on a 1:1:1:1 basis using a block stratified method (stratified by site) to receive either (1) ondansetron + placebo, (2) metoclopramide + placebo, (3) metoclopramide + ondansetron or (4) double placebo. Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ondansetron plus placebo

Arm description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron PO 4mg tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm title	Metoclopramide plus placebo

Arm description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Metoclopramide plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Film-coated tablet, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm title	Ondansetron plus Metoclopramide

Arm description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus Metoclopramide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm title	Double placebo

Arm description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Double placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Solution for injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Oral ondansetron - 4mg given three times daily + placebo
Intravenous ondansetron - 4mg given three times daily + placebo

Number of subjects in period 4	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Started	8	7	9
Completed	8	7	9

Number of subjects in period 4	Double placebo
Started	8
Completed	8

Period 5

Period 5 title	Follow up after delivery
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally by NCTU secure web-based system. Patients were randomised on a 1:1:1:1 basis using a block stratified method (stratified by site) to receive either (1) ondansetron + placebo, (2) metoclopramide + placebo, (3) metoclopramide + ondansetron or (4) double placebo. Assignment to either arm was blinded to both participants and site staff including the PI. IMPs were manufactured and packaged to ensure participants and study staff were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ondansetron plus placebo

Arm description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron PO 4mg tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Arm title	Metoclopramide plus placebo

Arm description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm type	Experimental

Investigational medicinal product name	Metoclopramide plus placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Tablet, Film-coated tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Arm title	Ondansetron plus Metoclopramide

Arm description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm type	Experimental
Investigational medicinal product name	Ondansetron plus Metoclopramide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Arm title	Double placebo

Arm description:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Arm type	Experimental
Investigational medicinal product name	Double Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Tablet, Film-coated tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Number of subjects in period 5	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Started	8	7	9
Completed	8	6	9
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

Number of subjects in period 5	Double placebo
Started	8
Completed	8
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups	
Reporting group title	Ondansetron plus placebo
Reporting group description:	
ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day	
Reporting group title	Metoclopramide plus placebo
Reporting group description:	
metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day	
Reporting group title	Ondansetron plus Metoclopramide
Reporting group description:	
ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day	
Reporting group title	Double placebo
Reporting group description:	
placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets	

Reporting group values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Number of subjects	8	8	9
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	9
Age continuous			
age at time of recruitment			
Units: years			
median	34	27	27
full range (min-max)	21 to 38	18 to 34	21 to 38
Gender categorical Units: Subjects			
Male	0	0	0
Female	8	8	9
Ethnicity Units: Subjects			
White British	6	6	8
White Irish	0	1	0
Mixed white and black carribean	0	0	0
Pakistani	1	0	0
Any other Asian background	0	0	1
Indian	1	0	0
Mixed White and Asian	0	1	0
Multiple Birth in current pregnancy Units: Subjects			
Yes	1	1	1
No	7	7	8
Previous use of prochlorperazine for			

current NVP Units: Subjects			
Prochlorperazine	3	2	4
not used	5	6	5
Gravida Units: Subjects			
Gravida 1	1	3	3
Gravida 2	3	1	4
Gravida 3	0	2	1
Gravida 4	1	2	0
Gravida 5+	3	0	1
Parity Units: Subjects			
Parity 0	1	4	4
Parity 1	4	2	4
Parity 2	0	2	0
Parity 3	3	0	1
Previous use of cyclizine for current NVP Units: Subjects			
Cyclizine	7	7	7
not used	1	1	2
Previous use of promethazine for current NVP Units: Subjects			
Promethazine	1	0	3
not used	7	8	6
Gestation (in weeks) at randomisation Units: weeks			
median	8.9	7.9	7.9
full range (min-max)	7.9 to 16.3	6.7 to 13.4	5 to 12.7
PUQE score			
Participant reported symptom severity scores at baseline via the PUQE questionnaire (Pregnancy Unique Quantification of Emesis)			
Units: total score			
median	14	11	13
full range (min-max)	10 to 15	8 to 15	10 to 15
NVPQOL score			
Participant reported symptom severity scores at baseline via the NVPQOL questionnaire (Nausea and vomiting in pregnancy, quality of life questionnaire)			
Units: total score			
median	186	178	186
full range (min-max)	168 to 203	165 to 189	136 to 205
EPDS score			
Participant reported symptoms of depression and anxiety at baseline via the EPDS questionnaire (Edinburgh Post-natal Depression Scale)			
Units: total score			
median	17	14	14
full range (min-max)	4 to 26	4 to 21	3 to 20
STAI Score			
Participant reported symptoms of depression and anxiety at baseline via the STAI questionnaire (Spielberger State-Trait Anxiety Inventory - short questionnaire)			
Units: total score			
median	15	17	14

full range (min-max)	12 to 23	9 to 20	6 to 24
MSSS Score			
Participant reported maternal social support at baseline via completion of the MSSS questionnaire (maternal social support scale)			
Units: total score			
median	29	29	30
full range (min-max)	27 to 30	25 to 30	27 to 30

Reporting group values	Double placebo	Total	
Number of subjects	8	33	
Age categorical Units: Subjects			
Adults (18-64 years)	8	33	
Age continuous			
age at time of recruitment			
Units: years			
median	24		
full range (min-max)	18 to 32	-	
Gender categorical Units: Subjects			
Male	0	0	
Female	8	33	
Ethnicity Units: Subjects			
White British	6	26	
White Irish	0	1	
Mixed white and black carribean	1	1	
Pakistani	1	2	
Any other Asian background	0	1	
Indian	0	1	
Mixed White and Asian	0	1	
Multiple Birth in current pregnancy Units: Subjects			
Yes	0	3	
No	8	30	
Previous use of prochlorperazine for current NVP Units: Subjects			
Prochlorperazine	4	13	
not used	4	20	
Gravida Units: Subjects			
Gravida 1	5	12	
Gravida 2	0	8	
Gravida 3	0	3	
Gravida 4	2	5	
Gravida 5+	1	5	
Parity Units: Subjects			
Parity 0	6	15	
Parity 1	1	11	
Parity 2	1	3	

Parity 3	0	4	
Previous use of cyclizine for current NVP Units: Subjects			
Cyclizine	5	26	
not used	3	7	
Previous use of promethazine for current NVP Units: Subjects			
Promethazine	1	5	
not used	7	28	
Gestation (in weeks) at randomisation Units: weeks			
median	9.6		
full range (min-max)	6.7 to 15.7	-	
PUQE score			
Participant reported symptom severity scores at baseline via the PUQE questionnaire (Pregnancy Unique Quantification of Emesis)			
Units: total score			
median	14		
full range (min-max)	7 to 15	-	
NVPQOL score			
Participant reported symptom severity scores at baseline via the NVPQOL questionnaire (Nausea and vomiting in pregnancy, quality of life questionnaire)			
Units: total score			
median	182		
full range (min-max)	132 to 206	-	
EPDS score			
Participant reported symptoms of depression and anxiety at baseline via the EPDS questionnaire (Edinburgh Post-natal Depression Scale)			
Units: total score			
median	10		
full range (min-max)	5 to 17	-	
STAI Score			
Participant reported symptoms of depression and anxiety at baseline via the STAI questionnaire (Spielberger State-Trait Anxiety Inventory - short questionnaire)			
Units: total score			
median	13		
full range (min-max)	8 to 19	-	
MSSS Score			
Participant reported maternal social support at baseline via completion of the MSSS questionnaire (maternal social support scale)			
Units: total score			
median	29		
full range (min-max)	25 to 30	-	

End points

End points reporting groups

Reporting group title	Ondansetron plus placebo
Reporting group description:	
ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day	
Reporting group title	Metoclopramide plus placebo
Reporting group description:	
metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day	
Reporting group title	Ondansetron plus Metoclopramide
Reporting group description:	
ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day	
Reporting group title	Double placebo
Reporting group description:	
placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets	
Reporting group title	Ondansetron plus placebo
Reporting group description:	
ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day	
Reporting group title	Metoclopramide plus placebo
Reporting group description:	
metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day	
Reporting group title	Ondansetron plus Metoclopramide
Reporting group description:	
ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day	
Reporting group title	Double placebo
Reporting group description:	
placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets	
Reporting group title	Ondansetron plus placebo
Reporting group description:	
ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day	
Reporting group title	Metoclopramide plus placebo
Reporting group description:	
metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day	
Reporting group title	Ondansetron plus Metoclopramide
Reporting group description:	
ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day	
Reporting group title	Double placebo
Reporting group description:	
placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match	

ondansetron PO tablets and placebo to match metoclopramide PO tablets

Reporting group title	Ondansetron plus placebo

Reporting group description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Reporting group title	Metoclopramide plus placebo

Reporting group description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Reporting group title	Ondansetron plus Metoclopramide

Reporting group description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Reporting group title	Double placebo

Reporting group description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Reporting group title	Ondansetron plus placebo

Reporting group description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Reporting group title	Metoclopramide plus placebo

Reporting group description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Reporting group title	Ondansetron plus Metoclopramide

Reporting group description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Reporting group title	Double placebo

Reporting group description:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Primary: number of participants experiencing a treatment failure

End point title	number of participants experiencing a treatment failure[1]

End point description:

The primary endpoint was the number of participants experiencing a treatment failure. Treatment failure was defined as the need for further treatment as a participant's symptoms had worsened between 12 hours and 10 days post treatment. Where further treatment was required a participant was placed on third line antiemetic treatment (i.e. high dose ondansetron or corticosteroids) unless the clinician considered further second line treatment more appropriate.

End point type	Primary

End point timeframe:

between 12 hours and 10 days post study treatment commencing

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the trial did not progress past the internal pilot due to low numbers recruited, no formal statistical analyses were performed and descriptive analysis only was used.

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	7	9	8
Units: number				
Yes	2	4	4	5
No	6	3	4	2
Not assessable	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Participant reported symptom severity

End point title	Participant reported symptom severity

End point description:

The PUQE score was used to assess severity of symptoms. The scale quantifies the amount of nausea, vomiting and retching experienced over the previous 24 hours. The PUQE score was collected as part of the study at 48 hours, 5 days and 10 days post treatment commencing. Data from these timepoints is reported in this section.

End point type	Secondary

End point timeframe:

collected between baseline and 10 days post treatment commencing

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	5
Units: Total score				
median (full range (min-max))	5 (3 to 13)	9 (3 to 13)	7 (3 to 11)	8 (3 to 12)

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	7	4
Units: Total score				
median (full range (min-max))	7 (3 to 13)	7 (5 to 8)	7 (3 to 11)	8 (4 to 15)

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	5	2
Units: Total score				
median (full range (min-max))	8 (3 to 14)	7 (6 to 9)	5 (3 to 9)	6 (3 to 9)

Statistical analyses

No statistical analyses for this end point

Secondary: Participant reported severity of nausea

End point title	Participant reported severity of nausea

End point description:

A visual analogue score (VAS) for nausea was used alongside the PUQE symptoms severity score to examine more subtle changes in nausea. The VAS asked participants to rate, on a scale of 0-10 where 10 was the worst possible nausea you could feel, how bad their nausea was now. The VAS score was collected as part of the study at 48 hours, 5 days and 10 days post treatment commencing. Data from these timepoints is reported in this section.

End point type	Secondary

End point timeframe:

collected 10 days post treatment commencing

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	7	5
Units: total score				
median (full range (min-max))	0 (0 to 8)	6 (0 to 9)	3 (0 to 8)	5 (0 to 6)

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	7	4
Units: total score				
median (full range (min-max))	5 (0 to 9)	5 (1 to 5)	6 (0 to 10)	4 (2 to 7)

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus	Double placebo

			Metoclopramide	
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	5	2
Units: total score				
median (full range (min-max))	5 (0 to 7)	4 (3 to 8)	1 (0 to 9)	2 (0 to 3)

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life

End point description:

The Health-Related Quality of Life for Nausea and Vomiting during Pregnancy (NVPQOL) provided a total score and 4 domain scores (physical symptoms and aggravating factors; fatigue; emotions; limitations). The NVPQOL was collected 10 days post treatment commencing. Data from this timepoint is reported in this section.

Of primary interest was the total NVPQOL score which is reported here.

End point type	Secondary

End point timeframe:

collected at baseline and again at day 10

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	5	2
Units: total score				
median (full range (min-max))	160 (88 to 196)	148 (88 to 175)	155 (40 to 170)	105 (81 to 128)

Statistical analyses

No statistical analyses for this end point

Secondary: Anxiety

End point title	Anxiety

End point description:

This parameter was measured using the following scale validated for use in pregnancy:
- State Trait Anxiety Inventory [STAI]

STAI score data was collected at 10 days. Data from this timepoint is reported in this section.

End point type	Secondary

End point timeframe:
collected at baseline and day 10

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	6	2
Units: total score				
median (full range (min-max))	16 (6 to 24)	15 (13 to 21)	14.5 (6 to 22)	9 (6 to 12)

Statistical analyses

No statistical analyses for this end point

Secondary: Depression

End point title	Depression

End point description:

This parameter was measured using the following scale validated for use in pregnancy:
- Edinburgh Post-natal Depression Scale (EPDS) [19].

Data was collected as the total EPDS score (depression) at 10 days. Data from this timepoint is reported in this section.

End point type	Secondary

End point timeframe:
collected at baseline and day 10

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	5	2
Units: total score				
median (full range (min-max))	14 (3 to 18)	12 (11 to 22)	13 (10 to 22)	8 (5 to 11)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical indicators of anti-emetic effectiveness - relapse at Day 5

End point title	Clinical indicators of anti-emetic effectiveness - relapse at Day

	5

End point description:

Defined as a PUQE score ≤ 6 at 48 hours followed by an increase to > 12 at 5 days.

End point type	Secondary

End point timeframe:

collected 5 days post starting trial medication

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	7	4
Units: number				
Yes	0	0	0	0
No	6	5	7	4

Statistical analyses

No statistical analyses for this end point

Secondary: Pregnancy outcome

End point title	Pregnancy outcome

End point description:

pregnancy outcome

End point type	Secondary

End point timeframe:

collected via final follow up (via chart review by site team) after delivery of baby

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	9	8
Units: number				
Liveborn	7	6	8	7
Termination for fetal abnormality	1	0	0	0
Termination for other reasons	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical indicators of anti-emetic effectiveness - Relapse at Day 10

End point title	Clinical indicators of anti-emetic effectiveness - Relapse at Day 10

End point description:

Defined as a PUQE score ≤ 6 at 48 hours followed by an increase to > 12 at 10 days.

End point type	Secondary

End point timeframe:

collected 10 days post starting trial medication

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	5	2
Units: number				
Yes	0	0	0	0
No	5	3	5	2

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical indicators of anti-emetic effectiveness - Remission at Day 10

End point title	Clinical indicators of anti-emetic effectiveness - Remission at Day 10

End point description:

Defined as a PUQE score ≤ 6 at 48 hours with return to persistent symptoms [PUQE score ≥7] at 10 days.

For clarification the definition of remission in this instance is the number of patients whose symptoms had improved by 48h (PUQE≤6) but they then returned to having moderate or severe symptoms (PUQE≥7) by Day 10.

End point type	Secondary

End point timeframe:

assessed 10 days post starting trial medication

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	5	2
Units: number				
Yes	1	0	1	0

No	4	3	4	2

Statistical analyses

No statistical analyses for this end point

Secondary: Neonatal Outcomes

End point title	Neonatal Outcomes

End point description:

Information on congenital anomalies detected prior to discharge were collected by the research teams at site via review of participant medical records. In the case of multiple births, this information was collected for each infant.

End point type	Secondary

End point timeframe:

collected via final follow up after delivery of baby

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	9	8
Units: number				
Congenital Abnormality Recorded	0	0	0	1
No congenital abnormality recorded	8	6	9	7

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical indicators of anti-emetic effectiveness - number of participants experiencing a treatment failure at 48 hours

End point title	Clinical indicators of anti-emetic effectiveness - number of participants experiencing a treatment failure at 48 hours

End point description:

End point type	Secondary

End point timeframe:

between 12 hours and 48 hours post study treatment commencing

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	7	8	7
Units: number				
Yes	0	1	1	1
No	8	6	7	6

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical indicators of anti-emetic effectiveness - readmission rate

End point title	Clinical indicators of anti-emetic effectiveness - readmission rate

End point description:

End point type	Secondary

End point timeframe:

the number of participants readmitted with NVP within 10 days of recruitment

End point values	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide	Double placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	9	8
Units: number				
Yes - readmitted	2	2	4	1
No - not readmitted	6	4	5	7

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) and adverse reactions (ARs) occurring from start of administration of IMP through to 24 hours post last IMP dose were recorded. Symptoms which were present at baseline and did not worsen were not recorded in the eCRF.

Adverse event reporting additional description:

Adverse events were coded using the MedDRA dictionary and are presented by preferred term, grouped by system organ class.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Ondansetron plus placebo

Reporting group description:

ondansetron 4mg IV three times a day and placebo to match metoclopramide IV three times a day followed by ondansetron 4mg PO tablets three times a day and placebo to match metoclopramide PO tablets three times a day

Reporting group title	Metoclopramide plus placebo

Reporting group description:

metoclopramide 10mg IV three times a day and placebo to match ondansetron IV three times a day followed by metoclopramide PO 10mg tablets three times a day and placebo to match ondansetron PO tablets three times a day

Reporting group title	Ondansetron plus Metoclopramide

Reporting group description:

ondansetron 4mg IV three times a day and metoclopramide 10mg IV three times a day followed by ondansetron 4mg PO tablets three times a day and metoclopramide 10mg PO tablets three times a day

Reporting group title	Double Placebo

Reporting group description:

placebo to match ondansetron IV and placebo to match metoclopramide IV followed by placebo to match ondansetron PO tablets and placebo to match metoclopramide PO tablets

Serious adverse events	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Termination of Pregnancy due to abnormalities			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Right Calf Deep Vein Thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Incidental paronychia whilst recruiting for EMPOWER.			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Termination of Pregnancy due to abnormalities			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Right Calf Deep Vein Thrombosis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Incidental paronychia whilst recruiting for EMPOWER.			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ondansetron plus placebo	Metoclopramide plus placebo	Ondansetron plus Metoclopramide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	3 / 8 (37.50%)	3 / 9 (33.33%)
Vascular disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Headaches			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Swollen tongue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Psychiatric disorders			
anxiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nightmare			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Feeling funny in legs			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Double Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)		
Vascular disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headaches			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Oral candidiasis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Swollen tongue			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			

Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Psychiatric disorders anxiety subjects affected / exposed occurrences (all) Nightmare subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Musculoskeletal and connective tissue disorders Feeling funny in legs subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2017	Protocol updated based on advice from the TSC regarding further treatment options for those who fail EMPOWER treatment – clarification provided regarding eligibility criteria – administrative updates
26 February 2018	Protocol updated to clarify that the PUQE questionnaire could be collected after consent for sites where the PUQE is not routinely collected on admission
12 September 2018	Protocol updated to include staff participants in qualitative interviews
13 November 2018	- Protocol updated to reflect extension of the internal pilot phase - Update to the eligibility criteria to include women who had received suboptimal treatment with ondansetron or metoclopramide based on findings during the pilot phase at that point - Minor administrative changes/correction of typos
25 February 2019	Protocol updated regarding the following: - Update to exclusion criteria amended in last update to provide clarity following feedback from sites from. - Addition of foot note to above mention amendment criteria to be provide clarification regarding intramuscular formulation. - Option provided to collect PUQE, VAS and Health Utilisation Questionnaire via phone at day 10 (other questionnaires still be completed by patient in booklet and returned). - Update title of "Participant Resource Use Questionnaire" in the protocol to "Health Care Utilisation Questionnaire" and "Contingent valuation survey" in protocol to 'Willingness to Pay' to match Questionnaire booklet. - Clarification added that participants should have been off SSRIs for at least 2 weeks to be eligible to take part in EMPOWER

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none reported

Notes: