CLINICAL STUDY REPORT

GUARD

Randomised controlled trial of Gestational treatment with Ursodeoxycholic Acid compared to metformin to Reduce effects of Diabetes mellitus

Sponsor Protocol Code:	GUARD
EudraCT Number:	2019-002880-82
ClinicalTrials.gov Identifier:	NCT04407650
ISRCTN number:	NA
REC Number:	20/LO/0504
Investigational Drugs (IMPs):	Ursodeoxycholic acid 500mg film-coated tablets (Ursofalk® Dr Falk), metformin 500mg tablets (Medley)
Indication:	Gestational diabetes mellitus
Development Phase:	Pilot Phase IV
Study Begin (FPFV):	18/06/2021
Study End (LPLV):	03/10/2024
Report Version & Issue Date:	1.0 24/07/2026
Co-sponsor Name and Address:	Ann Marie Murtagh King's Health Partners Clinical Trial Office, 16th Floor, Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT Rachel Fay, Guy's and St Thomas' NHS Foundation Trust R&D Department, 16th Floor Tower Wing, Great Maze Pond, London SE1 9RT
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Chief Investigator:	Dr Caroline Ovadia

SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice and all applicable laws and regulations.

This was a non-commercial academic trial, the results of this study are not intended to be used for a licensing application.

Chief Investigator:

Printed name	**Signature**	**Date**
Caroline Ovadia		

CONTENTS

Contents

APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service (London – Westminster Research Ethics Committee).

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent

Participants were selected from the antenatal service at participating hospitals with specialist obstetric/diabetes multidisciplinary teams, expert in the management of gestational diabetes mellitus. Participants were asked to provide written informed consent, following which they were recruited to the study.

2. Data Monitoring

Trial oversight was performed by a Trial Steering Committee, including the Trial Manager, Chief Investigator, an independent chair, statistician and 6 independent members, including 4 expert and 2 lay representatives. The TSC met in full from 14/01/2020 on four occasions, until the decision to halt recruitment to the IMP trial on 12/12/2022, with only the nested observational substudy (GUARD-MEC) continuing. At this point the Trial Management Group (including Trial Manager, CI, selected co-investigators, statistician, research midwife, Clinical Research Associate, and representatives from King's Health Partners Clinical Trials Office, Pharmacy and Trial Sponsors, who attended relevant meetings) continued with full responsibility for the study. The TMG met approximately 6 weekly from April 2020 until May 2025, throughout the full duration of the study.

An Independent Data Monitoring Committee (IDMC) was separately appointed and included the trial statistician. It met once, and then planned to review outcomes once 40 participants had given birth, however as the IMP-trial aspect of the study was halted before this number of participants were recruited, formal IDMC review was not required. The IDMC was informed of the decision to change the protocol to halt recruitment for IMP use in December 2022.

3. Sponsors, Investigators and Trial Sites

Co-Sponsors	
King's College London	**Guy's and St Thomas' NHS Foundation Trust**
Chief Investigator ***Caroline Ovadia***	King's College London and Guy's and St Thomas' NHS Foundation Trust
Former Chief Investigator (to 14/12/2023) ***Catherine Williamson***	King's College London and Guy's and St Thomas' NHS Foundation Trust Now Imperial College London
Trial sites: Guy's and St Thomas' NHS Foundation Trust Imperial College Healthcare NHS Trust King's College Hospital NHS Foundation Trust	

4. Co-Investigator(s), Statistician, Laboratories, Database Management

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5. Study Synopsis

Title of clinical trial	Randomised controlled trial of Gestational treatment with Ursodeoxycholic Acid compared to metformin to Reduce effects of Diabetes mellitus
Protocol Short Title/Acronym	GUARD
Study Phase	Pilot Phase 4 RCT
Sponsor name	King's College London and Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Dr Caroline Ovadia
Eudract number	2019-002880-82
REC number	20/LO/0504
IRAS project ID:	1003208
Medical condition or disease under investigation	Gestational diabetes Mellitus (GDM)
Purpose of clinical trial	To compare the impact of treatment with ursodeoxycholic acid vs metformin on glycaemic control in women with GDM
Primary objective	To assess the efficacy of UDCA compared to metformin to improve glycaemic control in GDM
Secondary objective (s)	To evaluate the impact of the treatments on maternal and neonatal lipid metabolism To assess the acceptability of UDCA compared to metformin to women with GDM. - To establish whether continuous glucose monitoring gives more informative overall assessment of maternal glycaemic control in pregnant women. - To compare maternal and

	fetal outcomes that could relate to treatment with UDCA or metformin. Exploratory objective: To assess whether metformin differentially alters the gut microbiome and whether this is associated with a change in endocrine signalling, serum glucose levels and lipid consumption in women consenting to the mechanistic study
Trial Design	Two-armed, randomised, controlled, open label, multicentre study with optional observational mechanistic study in a subgroup from each arm
Endpoints	Primary: Maternal fasting glucose concentration at 36 weeks' gestation measured with a blood sample Secondary: Quality of life assessment at baseline and 36 weeks', and treatment satisfaction scores at 36 weeks' gestation. Biomedical and clinical maternal outcomes Biomedical and clinical neonatal outcomes at birth Exploratory (GUARD-MEC Sub-study): 16S sequencing to analyse gut microbiome (optional samples) Targeted metabolite profiles to measure individual bile acid composition in faeces and serum (UPLC-MS/MS) (optional samples) Hormone assays to measure GLP1, FGF19, C4 Glucose-related hormones to measure: insulin, C-peptide, glucagon Serum measurements (done at participating sites): glucose, lipid profile, free fatty acids
Planned number of subjects	Main study (GUARD): 158 (79 per group) in the randomized controlled trial Mechanistic sub-study (GUARD MEC): 60 participants enrolled into one of three arms: - 20 women on metformin under routine clinical care - 20 women with GDM not requiring pharmacotherapy - 20 pregnant women without GDM
Summary of eligibility criteria	Main study (GUARD): 1. Women between 16 and 50 years of age with GDM diagnosed at 24+0 to 30+6 weeks' gestation in accordance with NICE guidelines (one or more glucose concentration of ≥ 5.6 mmol/L fasting or ≥ 7.8 mmol/L 2 hours after a standard 75g oral glucose tolerance

	test, and requiring pharmacological treatment). 2. Booking body mass index ≥18.5 kg/m2 3. Planned antenatal, intrapartum and postpartum care at the participating centre (i.e. not planning to move before delivery). Mechanistic sub-study (GUARD MEC): 1. Participants in GUARD CTIMP **OR** 2. Individuals with GDM receiving only lifestyle management or metformin for management (not insulin), and control individuals with no GDM in their pregnancy 3. Birth not planned before 36 weeks' 4. Other criteria as per main study
IMP, dosage and route of administration	Ursodeoxycholic acid oral 500mg bd
Active comparator product(s)	Metformin oral as per standard of care
Maximum duration of treatment of a subject	17 weeks plus 3 months' follow up Mechanistic sub-study (GUARD MEC) Not applicable
Version and date of protocol amendments	V1.0 dated 11/03/2020 V2.0 dated 29/07/2020 V3.0 dated 16/03/2021 V4.0 dated 21/10/2021 V5.0 dated 22/03/2022 V5.1 dated 11/10/2023 V6.0 dated 14/08/2024 V6.1 dated 13/12/2024

6. Glossary of terms

AE Adverse Event
AR Adverse Reaction
BD Twice a Day
BMI Body Mass Index
CGM Continuous Glucose Monitoring
CI Chief Investigator
CRP C Reactive Protein
CTIMP Clinical Trial of an Investigational Medicinal Product
eCRF / CRF (Electronic) Case Report Form
FU Follow Up
GDM Gestational Diabetes Mellitus
GSTFT Guy's and St Thomas' NHS Foundation Trust
HbA1C Glycated hemoglobin
HDL High Density Lipoprotein
HDPE High-density polyethylene

ICF	Informed Consent Form
ICP	Intrahepatic Cholestasis of Pregnancy
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ITT	Intention To Treat
LGA	Large for Gestational Age
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
OGTT	Oral Glucose Tolerance Test
PIS	Patient Information Sheet
PMU	Pharmacy Manufacturing Unit
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea & Electrolytes
UDCA	Ursodeoxycholic Acid

7. Publication (reference)

Holly Lovell, Alice Mitchell, Caroline Ovadia, Noelia Pitrelli, Annette Briley, Claire Singh, Hanns-Ulrich Marschall, Kennedy Cruickshank, Helen Murphy, Paul Seed, Catherine Williamson. A multi-centered trial investigating gestational treatment with ursodeoxycholic acid compared to metformin to reduce effects of diabetes mellitus (GUARD): a randomized controlled trial protocol. Trials 2022; 23(1):571. doi: 10.1186/s13063-022-06462-y.

8. Study period (years)

Total years from approval to end of study – 5 years.
End of trial was defined as database lock and submitted to the MHRA on 29/05/2025
FPFV: 18/06/2021
LPLV: 03/10/2024
Participant recruitment completed: 29/08/2024
The study was approved in May 2020, but was unable to start until 18th November 2020 due to a pause on commencing new studies at the sponsor site during the COVID-19 pandemic. Recruitment was then paused at the lead site between 23/12/2020 and 05/03/2021 due to the COVID-19 pandemic; recruitment was also paused between 13/10/2023 and 14/12/2023 at all sites due to regulatory requirements around the change of the study chief investigator.
The main trial was terminated prematurely on 12/12/2022 by email to halt recruitment due to inability to recruit participants at a sufficient rate, with continuance only of the mechanistic sub-study (GUARD-MEC). The decision to halt recruitment for IMP-receiving participants was also informed by results of a parallel study, performed in Spain, which compared the impacts of UDCA versus placebo in gestational diabetes. This demonstrated that the primary trial objective (fasting blood glucose concentration at 36 weeks' gestation) did not differ between treatment groups (https://doi.org/10.1016/j.ajogmf.2025.101732).
The last participant in the main study (receiving IMP) was recruited on 3/11/2022, and their last visit was 30/11/2022.

9. Phase of development

This was a Phase IV pilot study

10. Objectives

Primary objective:

- to assess the efficacy of UDCA compared to metformin to improve glycaemic control in gestational diabetes mellitus

Secondary objectives:

- to evaluate the impact of the treatments on maternal and neonatal lipid metabolism
- to assess the acceptability of UDCA compared to metformin to women with gestational diabetes mellitus.
- To establish whether continuous glucose monitoring gives more informative overall assessment of maternal glycaemic control in pregnant women.
- to compare maternal and fetal outcomes that could relate to treatment with UDCA or metformin

Exploratory objectives of the GUARD-MEC sub study:

11. to assess whether metformin differentially alters the gut microbiome and whether this is associated with a change in endocrine signalling, serum glucose levels and lipid composition, in women consenting to the mechanistic sub-study.

12. Background and Context

Each year in the UK, approximately 35,000 women develop diabetes during pregnancy, a condition called gestational diabetes mellitus (GDM), which increases the risk of adverse outcomes for both mother and child[1]. Complications for the mother include increased risk of hypertensive diseases of pregnancy, including preeclampsia[2], and higher rates of cardiovascular disease and type 2 diabetes mellitus (T2DM) in later life[3–5]. Aside from hyperglycaemia, GDM is further complicated by maternal dyslipidaemia. Specifically, triglyceride and free fatty acid concentrations are increased in maternal blood, whilst high density lipoprotein (HDL)-cholesterol is reduced[6,7]. Modern metabolomic studies show disturbances of lipid metabolism, particularly intermediary metabolites (e.g. acyl-carnitines, phospholipids)[7,8]. Early decline in plasma adiponectin, an indicator of poorer mitochondrial oxidation in overweight and obese women, is an almost universal finding in GDM pregnancy[9]. Thus, GDM is a potentially vasculotoxic condition, associated with abnormal lipid and glucose metabolism[10].

GDM is also associated with accelerated fetal growth and increased risk of being large for gestational age (LGA), defined as birth weight above the 90th percentile for sex and gestational age[1,11]. GDM is also complicated by higher rates of preterm birth, caesarean section and birth injuries, including shoulder dystocia, which is particularly increased with LGA[1,2,12]. Due to the complications of preterm delivery and LGA, GDM offspring are more likely to require admission to neonatal intensive care units for treatment of hypoglycaemia, jaundice and respiratory distress[11]. GDM causes fetal dyslipidaemia, with increased free fatty acids and triglycerides in the umbilical cord blood; this is also associated with increased risk of LGA[13–15]. The children of women with GDM have increased rates of obesity, childhood cardiovascular disease and T2DM in later life, likely related to exposure both to maternal hyperglycaemia and maternal hyperlipidaemia in utero[16,17].

11.1 Effectiveness of current treatments

In the UK, women with risk factors for GDM have a 75g oral glucose tolerance test (OGTT) at 24-28 weeks' gestation. Those that test positive (fasting glucose concentration ≥5.6 and/or 2-hr ≥7.8mmol/L) start self-monitoring of blood glucose and are given dietary and lifestyle advice. If unable to achieve the National Institute for Health and Care Excellence (NICE) recommended glucose control targets (fasting glucose <5.3, 1hr <7.8mmol/L and/or 2hr <6.7mmol/L), they are prescribed either pharmacological oral glucose lowering medications, e.g. metformin/glibenclamide, or subcutaneous insulin injections. Metformin is the most commonly used first line pharmacological treatment. However, there is increasing concern about its widespread use during pregnancy, both because of its limited efficacy and because of potential safety concerns. Metformin crosses the placenta, has growth inhibitory properties and suppresses mitochondrial respiration which could theoretically adversely affect the developing fetus[18,19]. The Metformin in Gestational Diabetes (MiG) trial demonstrated that mothers randomised to metformin, compared to insulin, had reduced maternal weight gain and gestational hypertension[20]. However, the rate of LGA was not affected and the offspring had more subcutaneous fat at 2 years of age[21]. A study of maternal metformin treatment for women with polycystic ovary syndrome also did not show an impact on LGA, and the offspring were heavier at 1 year of age[22]. Thus, the current data have raised concerns that metformin, currently used by many women with GDM, does not adequately prevent adverse outcomes such as LGA, and may have negative long-term effects on the

metabolic health of the children[23,24]. This may be, at least in part, because metformin has less effect on serum triglyceride concentrations than insulin[20]. It is noteworthy that in the MiG trial, metformin alone was inadequate for achieving glycaemic targets in approximately 50% of women, necessitating supplementary treatment with insulin[20]. Indeed, even insulin treatment (the "gold standard" pharmacological approach) was not shown to be of definitive benefit for GDM offspring in the most recent Cochrane review, and was thought to possibly increase the risk of raised blood pressure compared to oral treatments[25]. Glibenclamide is the other oral hypoglycaemic agent used to treat GDM. It has not been shown to be superior to insulin treatment used in randomised trials[26], or as an add-on therapy to metformin[27]. Therefore, there is an urgent unmet need for additional therapies that improve maternal-fetal glucose and lipid metabolism, and the longer-term health outcomes of GDM exposed offspring.

Ursodeoxycholic acid (UDCA) is currently not an established/licensed treatment for GDM. However, a meta-analysis that included data from 7 trials that reported the impact of UDCA on glycaemic markers showed that it improved fasting glucose, insulin and HbA1c concentrations[28]. Furthermore, our pilot data from studies of UDCA treatment of women with intrahepatic cholestasis of pregnancy have demonstrated improved insulin resistance, indicating that it has the potential to be an effective treatment to improve glycaemic control GDM. UDCA is commonly used in pregnancy for the treatment of ICP, and a recent randomised, placebo-controlled trial did not show any increase in adverse events, including gastrointestinal symptoms, in women treated with UDCA compared to placebo[29]. Our pilot data also show that UDCA improves fetal serum lipid parameters (https://doi.org/10.1038/s41598-020-67301-1), so it may be more effective than metformin at reduction of the frequency of large for gestational age infants in GDM.

A recent study of UDCA treatment of 20 people with T2DM and hepatic impairment showed reduced weight and HbA1c (glycosylated haemoglobin) after treatment for 12 weeks (a similar duration to that proposed for this study)[30]. Furthermore, a recently published meta-analysis in people with non-alcoholic fatty liver disease (a disorder that is commonly associated with T2DM, previous GDM)[28,31] reported that UDCA treatment was associated with significant reduction in fasting glucose, HbA1c and plasma insulin concentration. UDCA is therefore a biologically plausible treatment but has not yet been evaluated in GDM. **We believe it is important and timely to evaluate the impact of UDCA on maternal and fetal outcomes in GDM.**

Continuous Glucose Monitoring (CGM) was used in this trial alongside conventional capillary glucose monitoring to compare the impact of UDCA and metformin on maternal glycaemic control. CGM measures interstitial glucose concentration every five minutes through a sensor that is placed subcutaneously. With 288 glucose measurements/day, CGM provides detailed glucose information about overnight and post-prandial glucoses, providing direct insight into fetal exposure to maternal glycaemia[32]. A recent large international consensus paper highlighted CGM as a robust research tool and emphasised the accuracy of contemporary sensors, the detailed information they provide and non-invasive nature compared to frequent capillary glucose monitoring.[33]

We proposed that UDCA is a new potential treatment for GDM. UDCA alters gut metabolites (via microbial modification of the drug). We hypothesised that this will result in increased release of gut hormones (GLP-1 and FGF19) that improve maternal/fetal blood concentrations of lipids, e.g. triglycerides, glycaemic control and reduce rates of obstetric and neonatal complications. We have

pilot data to support this hypothesis from studies of women with intrahepatic cholestasis of pregnancy (ICP) treated with UDCA.

11.2 Rationale

The GUARD trial intended to compare the impact of treatment with ursodeoxycholic acid (UDCA) -a drug with pilot data to support its effectiveness to treat GDM- to metformin on glycaemic control (primary outcome) in women with GDM. It was decided to early terminate the main trial (in which participants received IMP) due to two reasons. Firstly, the poor recruitment of GUARD participants not able to reach the number of participants needed. Secondly, the results of a study in Spain comparing Ursodeoxycholic acid (UDCA) for glycaemic control in women with gestational diabetes versus placebo which found that changes to lifestyle had considerable impact on disease control in those with gestational diabetes (https://doi.org/10.1016/j.ajogmf.2025.101732), and this did not enable further impact of UDCA to be demonstrated in the small number of women that needed further treatment. This was agreed with the TSC and IDMC committees and following sponsor agreement, it was decided that trial will continue with the observational Mechanistic sub-study alone recruiting to the non-UDCA arms (GUARD-MEC).

The observational Mechanistic study is an important study to continue as it will give information on the impact of metformin on the bile acid and short chain fatty acid (SCFA) composition of the faeces and the way this affects release of gut hormones that have a direct impact on diabetes severity. It will enable us to evaluate the impact of metformin on the hormone GLP-1 that influences insulin secretion.

13. Methodology

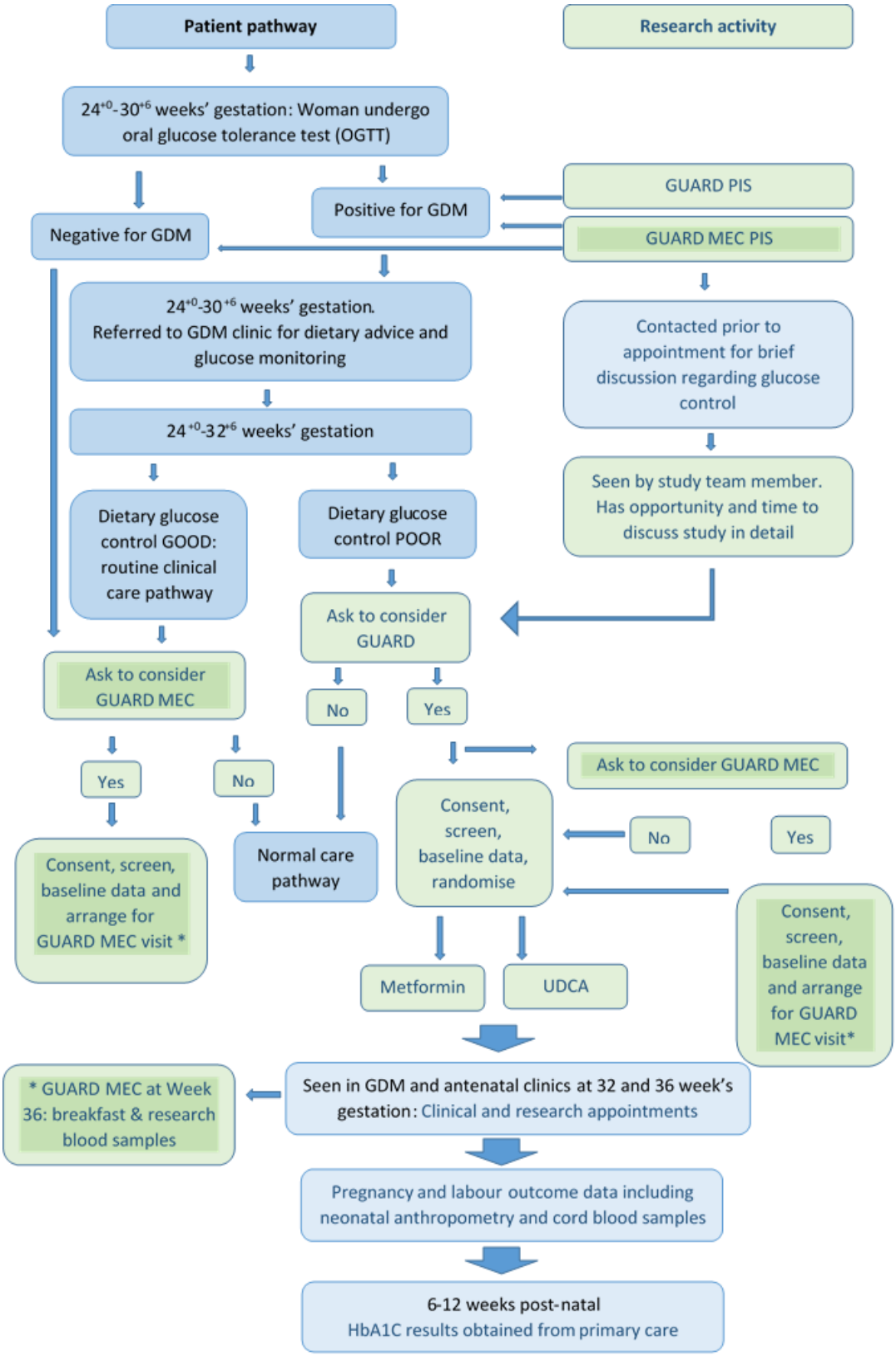
13.1 GUARD

GUARD was a pilot phase IV two-armed, open label, multi-centre randomised, controlled trial, designed to discover possible new uses for UDCA, a drug commonly used in pregnancy for other conditions. We aimed to recruit 158 women with a clinical diagnosis of GDM that requires management with pharmacological intervention, and randomised to one of two trial interventions: UDCA or metformin (standard of care).

12.2 GUARD MEC

In parallel, and continuing following the decisions to stop recruitment to receive IMP as the main trial, individuals with GDM receiving dietary management only, metformin treatment or without GDM were recruited to the GUARD-MEC substudy. Individuals randomised to UDCA in the main trial were eligible for participation in GUARD-MEC before the decision to stop giving IMP in the main part of the study (as per the original consent process prior to approval of Protocol 6.1) . Thus, the original 4 arms of the GUARD-MEC study recruiting 20 per arm (80 in total) was reduced to 3 arms recruiting 60 participants.

Initial study flow diagram for both the GUARD main trial and the GUARD MEC substudy :



Participants were initially approached during their antenatal care, and following diagnosis of gestational diabetes from 24 gestational weeks'. If recruited and randomised within the main study(receiving IMP), trial duration continued until birth, at which point trial medication was stopped;

final samples were obtained following birth (neonatal samples), and final data collection was up to 12 weeks postnatal, where postpartum measurement results from Hba1c testing performed during routine clinical care were collected. Thus, proposed total trial duration was up to 30 weeks.

Schedule of events:
Original schedule of events is below, reflecting the events for participants both in the main study (receiving IMP) and in the GUARD MEC sub study. The schedule of events specific to GUARD MEC is below.

Visit name & approximate pregnancy week	Participant identification	Baseline	Follow up 1	Follow up 2	Birth	Post-birth
	26^{+0}-30^{+6}	27^{+0}-31^{+6} [a]	$32^{+0} \pm 1$ [b]	$36^{+0} \pm 1$ [b]		3 month post birth[c]
Patient information *	X [h]					
Informed consent *		X				
Inclusion / exclusion criteria*		X				
Demographics *		X				
Medical and obstetric personal and family history *		X				
Adverse events*		X	X	X	X [n]	
Concomitant medication *		X	X	X	X [o]	
Weight *		X	X	X		
Blood pressure and pulse [d]		X	X	X		
Fasted glucose	X [u]			X		
HbA1c	X [i]	X [j]		X		X [t]
Liver function tests, bile acids and high sensitivity C-reactive protein, U&E		X		X		
Fasting lipid profile				X		
1,5-Anhydroglucitol and non-fasting metabolic hormones[e]		X	X			
1,5-Anhydroglucitol and fasting free fatty acids & metabolic hormones [e]				X		
Optional faecal sample [e] *				X [k]		
Optional GUARD MEC Blood samples after a breakfast [e] *				X [l]		
Cord blood samples [e]					X	
Meconium collection [e]					X	
Randomisation		X				
IMP dispensing		X	X	X		
IMP administration		X (continuously)				
Dispense diary card		X				
Drug diary review			X	X	X	
Continuous Glucose Monitoring [f] *		X	X	X		
Download CGM data *			X	X	X	
Optional vascular studies [g] *		X	X	X		
Quality of life questionnaires (EQ-5D-5L)		X		X		
Treatment satisfaction questionnaires (DTSQs)				X		
4-day food diary *			[m]	X [m]		
Labour and birth data *					X [p]	
Neonatal anthropometry *					X [q r]	
Neonatal data *					X [r s]	

* - assessments applicable to patients in GUARD MEC, to be done during the GUARD MEC study visit.
a - If participants are recruited earlier or later than expected, follow up visits will be adjusted according to clinical pathways and to ensure the participant has been receiving IMP for at least 2 weeks.
b - Women must fast for at least 3 hours

c - To occur at local GP practice approximately 3 months post-delivery (as per standard of care).
d - Blood pressure in triplicate and pulse only for woman who don't consent to the vascular studies. Use non-dominant arm
e - Research samples, for storage.
f - CGM will be in place for 10 days after each study visit. Women to be trained to remove the device themselves.
g - Vascular studies: blood pressure pulse wave velocity, central arterial pressure, augmentation index.
h - PIS to be given after OGTT appointment.
i - Pre-enrolment HbA1c and glucose: samples analysed within 3 weeks before baseline can be used. If no results are available, an HbA1c sample must be collected at baseline.
j - Only collect if no previous results within 3 weeks are available
k - Faecal samples are optional and should be produced at approximately 36 weeks. If the woman is unable to give a faecal sample on the day, a stool sample collection kit may be provided and the sample collected by courier from the participant's home.
l – Optional GUARD MEC: a hospital standardised breakfast will be provided. Four blood samples will be taken at the following timepoints: before breakfast, 15 minutes, 1 hour and 2 hours postprandially.
m - Food diaries should be given to patients at FU 1 to be completed the 4 days prior to FU 2. This should occur prior to providing a faecal sample (if applicable).
n - Adverse event data will be collected at each visit from baseline to discharge from hospital of mother and infant.
o - Standard of care concomitant medication given at labour do not need to be recorded.
p - Labour and birth data: onset of labour, genital tract trauma, post-partum haemorrhage, mode of birth, gestational age at delivery, NICU admission, morbidity, feeding at discharge.
q - Neonatal anthropometry: birth weight and the following measurements in triplicate:
- With blank tapes (then checked measured these with a steel rule): head circumference, chest circumference, abdominal circumference, midarm circumference
- Skinfold thicknesses in triplicate: subscapular and triceps
- Crown rump length, crown foot length
r - Neonatal assessments will be performed on the day of delivery, or as soon as feasible.
s - Apgar scores: 5 min post-birth
t - HbA1c samples will be drawn at the local GP and samples requested where clinically available
u – Fasted and 2 hours post prandial glucose taken from the OGTT appointment

A summary of the visits and trial follow up is below:

Identification (24 – 30^{+6} weeks' gestation)

Patients diagnosed with gestational diabetes at their routine screening oral glucose tolerance test (between 24-30+6 weeks' gestation) were provided with the main study and sub-study PIS/ICF by a member of the clinical or research team, alongside an explanation of the trial.

Informed consent (24 – 32^{+6} weeks' gestation)

Patients were clinically reviewed as per standard of care, and those formally diagnosed with GDM who required pharmacological treatment were offered the opportunity to participate in the main study and the optional sub-study, either in person or by telephone conversations.

Patients without GDM, or those who did not require pharmacological treatment for the management of their GDM, were not eligible to participate in the main study; these patients were identified during routine antenatal care, and invited to participate in the sub-study GUARD MEC. Once the decision to cease recruitment to the main CTIMP occurred, individuals receiving metformin for GDM but not otherwise participating in the CTIMP were also invited to participate in GUARD-MEC.

Following detailed explanation by trained and delegated clinical or other research staff, patients agreeing to participate signed the ICF and the investigator at that visit. Remote consent via telephone or video could occur if the participant was not due for a hospital appointment.

GUARD visits for individuals receiving IMP in the main study

Baseline visit

The baseline visit was scheduled at 24^{+0}-32^{+6} weeks' gestation. Following informed consent, screening procedures confirmed patient's eligibility. Further assessments included recording of demographics, concomitant medications, inclusion/exclusion criteria, weight, baseline clinical blood tests and research blood tests. Education on the use of continuous glucose monitoring, measurement of blood pressure and pulse, administration of the EQ-5D-5L quality of life questionnaire occurred. Participants were randomised by the eCRF, IMP and a diary card were dispensed.

Follow up 1

Follow-up 1 was scheduled to coincide with antenatal clinics or ultrasound scans at approximately 32^{+0} weeks' gestation (±2 weeks). If the baseline visit took place after 31^{+6} weeks of pregnancy, the follow-up 1 visit was not required. The following assessments took place: a concomitant medications check, recording of adverse events, optional weight measurement, non-fasting research blood samples obtained, download of CGM data and provision of new equipment, measurement of blood pressure and pulse, confirmation of IMP dosing and compliance, diary card checks and dispensation of IMP. A 4-day food diary was provided and training given for completion in advance of follow up 2.

Follow up 2

Follow-up visit 2 was scheduled to coincide with antenatal clinics or ultrasound scans at approximately 36^{+0} weeks' gestation (±1 week). The research team contacted the participant prior to the appointment to remind them of the requirement to be fasted at least 3 hours before the appointment. The following assessments took place: a check on concomitant medications, recording of adverse events, measurement of weight, collection of blood samples for in-hospital analysis and storage for research assessment, download of CGM data and new equipment supply, measurement of blood pressure and pulse, dose confirmation of IMP dose and compliance, dispensation of IMP, diary card checks, administration of quality of life questionnaires (EQ-5D-5L) and treatment satisfaction questionnaires (DTSQs), collection of 4-day food diary and optional faecal sample.

Birth and immediate postpartum period

Participants were expected to take the last dose of IMP on the day they gave birth, where possible. At that visit and during the subsequent days, recording was performed of adverse events, concomitant medications check, CGM data were downloaded and devices collected, remaining IMP was collected and diary card checked, current dose of IMP before birth confirmed. Where possible, umbilical cord blood samples and blood spots from the umbilical cord or newborn heel prick were collected, along with meconium from the nappy. Clinical data were recorded on labour, birth and neonatal outcomes.

Post birth

As per standard care patients will have an HbA1c measurement at their local GP approximately 3 months post-delivery. These data to be obtained by the study team.

GUARD-MEC visits

The schedule of events for GUARD-MEC was as follows:

Visit name & approximate pregnancy week	Consent	GUARD MEC visit	Labour
	26^{+0}-36^{+6}	$36^{+0} \pm 1$ [b]	
Patient information	X		
Informed consent	X	X [k]	
Inclusion / exclusion criteria	X	X	
Demographics		X	
Medical and obstetric personal and family history		X	
Adverse events		X [e]	
Concomitant medication		X	
Weight		X	
Blood pressure and pulse [a]		X	
Optional faecal sample [b]		X [f]	
Fasted glucose, HbA1c, lipids, liver function tests, bile acids and C-reactive protein, U&E		X	
GUARD MEC Blood samples after a breakfast b		X [g]	
Continuous Glucose Monitoring [c]		X	
Download CGM data & collect device			X
4-day food diary [d]		X [d]	
Labour and birth data			X [h]
Neonatal birth weight			X [j]
Neonatal data			X [j]

a - Blood pressure in triplicate and pulse. Use non-dominant arm.
b - Research samples, for storage.
c - CGM will be in place for 10 days after each study visit. Women to be trained to remove the device themselves and return it at their next visit or at labour.
d - Food diaries should be given to patients at baseline to be completed the 4 days prior to Follow up 2. This should occur prior to providing a faecal sample (if applicable).
e –Only study procedure-related adverse events will be collected from the day of the visit until the CGM is disconnected, i.e. 10 days after.
f -Faecal samples are optional and should be produced at approximately 36 weeks. If the woman is unable to give a faecal sample on the day, a stool sample collection kit may be provided and the sample collected by courier from the participant's home.
g - A hospital standardised breakfast will be provided. Four blood samples will be taken at the following timepoints: before breakfast, 15 minutes, 1 hour and 2 hours postprandially.
h - Labour and birth data: onset of labour, genital tract trauma, post-partum haemorrhage, mode of birth, gestational age at delivery, NICU admission, morbidity, feeding at discharge.
i - Neonatal assessments will be performed on the day of delivery, or as soon as feasible.
j - Apgar scores: 5 min post-birth
k – Informed consent can be taken during a routine clinic visit or at the GUARD MEC visit.

After signing informed consent (which was taken during a routine clinic visit or at the GUARD MEC visit), only one study visit was required for participation in GUARD MEC. Prior to this visit, participants were be given a food diary to record their food intake 4 days before their appointment. Participants attended the hospital at 36^{+0} weeks' gestation (+/-1 week), after an overnight fast (at least 8hs) and were given a standardised breakfast with pre-determined lipid and glucose content consisting of 50 g of fat, 75 g carbohydrates, ≥750 kcal. The research midwife or member of the research team contacted the participant the day before the appointment to remind them that they were required to fast overnight. Participants unable to ingest at least 80% of the breakfast will be withdrawn.

At the study visit, the following assessments were performed: confirmation of inclusion/exclusion criteria, collection of participant demographics, selected personal and family medical history, previous obstetric history, concomitant medication, measurement of weight, application of continuous glucose monitoring, measurement of blood pressure and pulse, collection equipment given for optional faecal

sample, collection of 4-day food diary, recording of any adverse events associated with study procedures, completion of eCRF.

During the study visit, blood samples were taken when fasting, 15 minutes, 1 hour and 2 hours after breakfast finish time. The samples were used to evaluate LFTs, lipid (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, free fatty acids) and glucose metabolism (glucose, C-peptide, insulin, HbA1c) by either standard laboratory analysis or ELISA (for gut hormone secretion, insulin, C-peptide and free fatty acids). Leftover serum and plasma samples were stored at -80°C for subsequent analysis of incretins and metabolic markers, for which they were shipped securely to Imperial College London.

Details of blood samples collected are below:

Time	FO	SST	EDTA
Fasting	4 mL	1 x 3.5 mL vacutainers (send to laboratory: 1 x liver function test, U&E, CRP and lipid profile, total bile acids) 1 x 5 mL vacutainer for storage	1 x 6 mL (1 x HbA1c, send to laboratory) 1 x 6 mL (storage)
0h15 postprandial	4 mL	1 x 3.5 mL vacutainer (lipid profile – send to laboratory) 1 x 5 mL vacutainer for storage	1 x 6 mL (storage)
1h00 postprandial	4 mL	1 x 3.5 mL vacutainer (lipid profile – send to laboratory) 1 x 5 mL vacutainer for storage	1 x 6 mL (storage)
2h00 postprandial	4 mL	1 x 3.5 mL vacutainer (lipid profile – send to laboratory) 1 x 5 mL vacutainer for storage	1 x 6 mL (storage)
Estimated total volume of blood collected:	**16 mL**	**34.0 mL**	**30 mL**

Following the study visit, collection of continuous glucose monitoring device and data download were timed to coincide with a hospital visit for the patient. Following birth, labour, birth and neonatal data were collected from the medical notes.

Trial Medication

The Pharmacy Manufacturing Unit, Guy's and St Thomas' NHS Foundation Trust (GSTFT PMU) Pharmaceuticals is licensed to support clinical trials under an MIA (IMP) license granted by the MHRA license. GSTFT PMU supplied, re-packaged, labelled and distributed both IMPs for this clinical trial. Analytical testing, Annex 13 compliant labelling, and temperature controlled and monitored storage and shipment were implemented.

Ursodeoxycholic acid 500mg film-coated tablets (Ursofalk®, Dr Falk) were packed into packs of 28 tablets (2 weeks' supply) in a high-density polyethylene (HDPE) container with child-resistant, tamper evident closure.

Metformin 500 mg tablets (Medley) were packed into packs of 56 tablets (2 weeks' supply) in an HDPE container with child-resistant, tamper-evident closure with integrated silica gel desiccant tablets.

Dosing Regimen

Starting treatment for UDCA was 500 mg twice a day (BD) orally with the morning and evening meals. Metformin was started following the local Trust's dose escalation scheme to minimise side effects.

Participants could be recruited and randomised to either treatment arm if Metformin had already been started as per standard of care, and they had been taking the Metformin for 14 days or less during pregnancy at the time of informed consent. If Metformin had already been started, participants

continued the Metformin dose escalation scheme as per their standard of care.

In both cohorts, participants took the first dose within 2 days of the baseline visit, and continued self-administration at home, while they undertook regular glucose control checks in line with current clinical practice. If a participant was already taking Metformin and was subsequently randomised to UDCA, it was acceptable to swap the treatment type on consecutive days.

14. Number of patients (planned and analysed)

14.1 Planned

GUARD main study – IMP recipients: 158 participants (79 per group)
A study size of 158 participants would provide sufficient statistical power to detect a 6% reduction of 0.304 mmol/L in maternal fasting glucose at 36 weeks whilst allowing for a 18% withdrawal rate (complete data on 130 women).

GUARD MEC substudy: 80 participants (to average 20 per group: with GDM - UDCA, metformin, lifestyle measures only, and without GDM)
Sample calculations were based upon GLP1 area under the curve, with 86.5% power for 17 participants per group to determine significant difference between groups, anticipating 15% withdrawal rate from original 20.

14.2 Analysed

GUARD IMP recipients (main study)

Arm	Active (UDCA)	Comparator (metformin)
# patients screened	76 individuals were screened prior to the decision to cease recruitment to the CTIMP part of the study	
# patients randomised per study arm	2	2
# patients completed per study arm	1	2
Reasons for non-completion if applicable	1 x withdrawal	-

Analysis of the GUARD IMP recipients (main study) was not attempted as any results would be underpowered. The challenges of participant recruitment to CTIMPs in pregnancy is recognised to be particularly challenging, and the associated paucity of data regarding evidence behind use of pharmaceutical agents in pregnancy is well documented (https://doi.org/10.1093/clinchem/hvaf149). Examples of recent pregnancy-specific CTIMPs that have required early termination due to failure to recruit include HOLDS (https://ncbi.nlm.nih.gov/books/NBK619420/) and OHANA (https://doi.org/10.1111/liv.70523), whilst Dutch population data reveal that 55% of randomised controlled trials in obstetrics and gynaecology failed to recruit to target (https://doi.org/10.1136/bmjopen-2024-087766). Thus, the inability to recruit sufficient participants is in line with other studies in this therapeutic area.

GUARD MEC substudy: *given that the main IMP part of the study stopped recruitment prematurely, participants could not be assessed from the active investigational treatment (UDCA) group, therefore the substudy was modified to include only individuals receiving standard care (sample size reduced from 80 to 60)*

Arm	GDM taking metformin	GDM managed with lifestyle only	No GDM (control)
# patients screened	134 individuals, including those screened for GUARD CTIMP part of the study participation		
# patients per study arm	10	22	19
# patients completed per study arm	8	21	16
Reasons for non-completion if applicable	Withdrew after fasting sample x2	Lost to follow up after study day	Withdrew before first sample x 2 Did not attend study day x1

NB: participants with incomplete data were censored in the analysis.

Table: The reasons for patient withdrawal from the study

Study Component	Study Arm	Reason	Number of Participants
GUARD	UDCA	Intolerance to study medication	1
GUARD MEC	GDM (Metformin)	Declined further blood sampling	1
GUARD MEC	GDM (Metformin)	Vasovagal episode following initial blood sampling	1
GUARD MEC	GDM (Lifestyle)	Gave birth abroad; did not return for follow-up	1
GUARD MEC	No GDM	Cannulation unsuccessful	2
GUARD MEC	No GDM	Did not attend study visit	1

15. Diagnosis and main criteria for inclusion

14.1 GUARD participants randomised for IMP (main study): gestational diabetes mellitus as per protocol 5.1, 11/10/2023

Inclusion criteria:
- individuals between 16 and 50 years of age with GDM diagnosed at 24+0 to 30+6 weeks' gestation, in accordance with the NICE guidelines (one or more glucose concentrations of ≥5.6 mmol/l fasting or ≥7.8 mmol/l 2 hours after a standard 75g oral glucose tolerance test, and requiring pharmacological treatment)
- booking body mass index ≥18.5 kg/m^2
- planned antenatal, intrapartum and postpartum care at the participating centre (i.e. not planning to move before delivery).

Exclusion criteria:
- unwilling/unable to give written informed consent and comply with the requirements of the study protocol
- multiple pregnancies (twins, triplets etc) in current pregnancy
- congenital anomaly on ultrasound requiring fetal medicine input
- previous diagnosis of diabetes outside pregnancy
- HbA1c at booking of current pregnancy of >48 mmol/mol or ≥6.5% (if available)
- significant pre-pregnancy comorbidities that increase risk in pregnancy, for example renal failure, severe liver disease, transplantation, cardiac failure, psychiatric conditions requiring in-patient admission (within previous year) in the opinion of the responsible clinician or the chief investigator
- significant co-morbidity in the current pregnancy, i.e. physical or psychological conditions likely to interfere with the conduct of the study and/or interpretation of the trial results in the opinion of the responsible clinician or the chief investigator
- not fluent in English and absence of interpreter or translation services (ie telephone translation services)
- participating in another intervention study where the results could influence GDM-related endpoints, in the opinion of the responsible clinician or the chief investigator, or participation in a CTIMP during current pregnancy
- known allergy/hypersensitivity/intolerance to the active substance or excipients, or patients taking any medications which are contraindicated as per IMP SmPC.

14.2 GUARD-MEC substudy Version 6.1, 11/12/2024, participants with gestational diabetes treated either with metformin or not requiring pharmacotherapy, or without diabetes in their pregnancy, were included, as follows:

Inclusion criteria – for all groups:
- individuals between 16 and 50 years of age
- booking body mass index ≥18.5 kg/m^2
- planned antenatal, birth and postpartum care at the participating centre (i.e. not planning to move before delivery).

Exclusion criteria – for all groups:
- unwilling/unable to give written informed consent and comply with the requirements of the study protocol
- multiple pregnancies (twins, triplets etc) in current pregnancy
- congenital anomaly on ultrasound requiring fetal medicine input
- previous diagnosis of diabetes outside pregnancy
- HbA1c at booking >48 mmol/mol or ≥6.5% during current pregnancy (if available)
- not fluent in English and absence of interpreter or translation services (ie telephone translation services)
- participating in another intervention study where the results could influence GDM-related endpoints, in the opinion of the responsible clinician or the CI, or participation in a CTIMP during current pregnancy
- known food allergy to nuts or any of the components of the GUARD MEC breakfast.

Additional inclusion criterion – for patients with GDM requiring metformin
- GDM diagnosed at 24+0 to 30+6 weeks' gestation in accordance with the NICE guidelines (one or more glucose concentrations of ≥5.6 mmol/l fasting or ≥7.8 mmol/l 2 hours after a standard 75g OGTT), and have commenced metformin as part of clinical care between 24+0-30+6 weeks' gestation

Additional inclusion criterion – for patients with GDM not requiring pharmacotherapy

- GDM diagnosed at 24+0 to 30+6 weeks' gestation in accordance with the NICE guidelines (one or more glucose concentrations of ≥5.6 mmol/l fasting or ≥7.8 mmol/l 2 hours after a standard 75g OGTT), and NOT requiring pharmacological treatment.

Additional inclusion criterion – for patients without GDM
- individuals who have not been diagnosed with GDM by the time of the study visit.

16. Test product, dose and mode of administration (GUARD only)

IMP **-** Ursodeoxycholic acid 500mg film-coated tablets (Ursofalk® Dr Falk), taken orally.

Two participants received this IMP, both received 500mg bd for the duration of their participation in the trial. Both completed their IMP prior to the decision to halt recruitment to the IMP-receiving part of the study; the last participant last visit was 30/11/2022 for this main part of the trial.

17. Duration of treatment

One participant received the medication for 73 days, the other participant received the medication for a maximum of 7 days.

18. Reference therapy, dose and mode of administration

Metformin 500mg tablets (Medley), taken orally. Two participants received this medication. Doses ranged from 500mg od to 1g bd. The total duration of medication was 53 days and 72 days for the two individuals. Both completed their IMP prior to the decision to halt recruitment to the IMP-receiving part of the study; the last participant last visit was 30/11/2022 for this main part of the trial.

19. Criteria for evaluation: Endpoints

18.1 GUARD main IMP=receiving study:

Primary endpoint
Maternal fasting glucose concentration at 36 weeks' gestation measured with a blood sample.

Secondary endpoints
- Quality of Life assessment (EQ-5D-5L) at baseline and 36 weeks, and treatment satisfaction scores at 36 weeks.
- Biomedical and clinical maternal outcomes:
1. Glucose metabolism at baseline, Follow up 1 and 2 assessed by:
a) Continuous glucose monitoring (CGM) to assess glycaemic control. This will determine the percentage time spent within target (glucose levels 3.5-7.8mmol/L), percentage time spent above target (>7.8mmol/l and ≥6.7mmol/l), time spent below target (≤3.5 and ≤3.0 mmol/l), measures of glucose variability including glucose standard variation (SD), co-efficient of variation (CV), frequency and duration of glycaemic excursions measured by the area under the curve (AUC) for the pre-specified glucose thresholds.

b) Serum concentrations of 1,5-anhydroglucitol; a novel marker of short-term glycaemia 4,43
c) HbA1c concentration; a conventional marker of medium-term glycaemia (except at Follow up 1)
2. Lipid metabolism at Follow up 2 assessed by blood triglyceride, total cholesterol, calculated LDL-cholesterol, HDL-cholesterol and free fatty acid concentrations
3. Biochemical analysis of maternal blood for liver function tests at Follow up 2 (ALT, bilirubin, ALP), bile acids, C reactive protein (including highly sensitive analyses)
4. Proportion of women requiring insulin treatment (time until treatment and total dose of insulin required)
5. Maternal gestational weight change at 36 weeks compared to weight at first trimester screening visit.
6. Estimated blood loss at time of delivery.
- Biomedical and clinical neonatal outcomes at birth:
1. Mode of birth (rates of caesarean section, (elective & emergency), assisted vaginal birth and spontaneous vaginal delivery)
2. Gestational age at birth
3. Apgar scores @ 5 minutes post birth
4. Occurrence of shoulder dystocia
5. Cord blood C-peptide, triglyceride, total cholesterol, calculated LDL-cholesterol, HDL-cholesterol, free fatty acid concentrations and lipid composition by mass spectrometry
6. Infant birth weight (customised birth weight percentile, proportion of babies born large for gestational age (LGA), proportion of babies born small for gestational age (SGA)
7. Neonatal morbidity (treatment for neonatal hypoglycaemia, neonatal jaundice, respiratory distress or birth trauma)
8. Neonatal intensive care and special care unit admission (duration of hospital stay)
9. Stillbirth and neonatal death

18.2 GUARD-MEC substudy

Exploratory endpoints
- Hormone assays to measure: GLP-1, FGF19, C4
- Glucose-related hormones to measure: Insulin, C-peptide, Glucagon
- Serum measurements (done at the participating sites): glucose, lipid profile, free fatty acids
From optional samples:
- 16S sequencing to analyse gut microbiome (optional samples)
- Targeted metabolite profiles to measure individual bile acid composition in faeces and serum (UPLC-MS/MS) (optional samples)

20. Statistical Methods

The analyses for the GUARD study were not undertaken in accordance with the Statistical Analysis Plan (SAP) as the analysis would be underpowered to draw robust conclusions; only analyses for the GUARD MEC substudy were performed. For reference, the SAP specified the following:

Appropriate summary statistics (means, medians, percentages and measures of dispersion such as the standard deviation and interquartile range) will be generated according to treatment assignment for important baseline covariates and for primary and secondary outcomes. At all follow-up visits, summary statistics for the observed values and for changes from baseline will be computed and tabulated for all primary, secondary and safety outcomes. In the event that a participant stops the intervention, they will be encouraged to continue to be part of the study. These participants will form part of the final analysis on an intention to treat basis.

Interim analysis will be conducted. The stopping rule will be based on the Peto principle[53], that the trial should continue except in the face of overwhelming evidence (P<0.0001), sufficient to make a recommendation affecting all future pregnant women.

The main analysis will follow the intention to treat (ITT) principle, using all available data on randomised women, according to the intended treatment option (The ITT database). Should there be a large number of women (over 20%) not following the randomised treatment, a per protocol (PP) dataset limited to women following the intended treatment will also be established and a secondary PP analysis will be conducted.

All comparisons by treatment group will be adjusted for all variables used in the randomisation. Data derived from the CGM will be analysed at 36 weeks. The differences caused by the randomised treatment, adjusting for the baseline randomisation measurements by multiple regression. This method (also known as ANCOVA) will increase the power and accuracy of these comparisons.
The primary focus of the trial is benefit for the mothers, but for the treatment to be clinically and ethical acceptable, there must also be no evidence of harm for the neonates, as shown by a non-inferiority analysis.

Analysis of the GUARD-MEC substudy was performed, with similar principles to describe summary statistics. Analyses determined whether significant differences between participant groups exist with regards to gut hormone signalling following a standardised diet, defined by p<0.05. Given the small number of participants and exploratory nature of analyses, participants were analysed according to received treatment up to the day of the study, and missing data assumed to be missing at random and not included within the analyses; imputation for missing data was therefore not be performed. Given that these are descriptive outcomes between disease and treatment groups, results will not be used to infer superiority or non-inferiority of any treatment.

Total numbers of participants (60) for the GUARD-MEC study were estimated based upon the area under the curve of GLP-1 concentration to determine a significant difference between compared groups (90% power, alpha 0.05). This estimated 17 participants per group, thus aiming to recruit 20 per group to enable 3 participants to drop out or abandon the study as per previous experience. Due to difficulties in recruiting participants taking metformin for treatment, power was improved by over-recruitment of participants in other groups to have a >1:1 ratio of participants. Hormone concentrations measured during the GUARD MEC study were presented with their geometric means and standard deviations, with ratios of means compared. Area under the curve during the study period was compared between groups for GLP1 concentrations – this is the primary outcome upon which the

sample size was determined; comparisons between hormone levels was performed using linear mixed models to account for missing datapoints. As faecal sample collection was optional within the protocol, sufficient samples were not obtained to justify further statistical analysis.

21. Changes in the Trial Plan

As described above, due to an inability to recruit participants at sufficient rate for a feasible study to be performed, the trial was terminated early (after recruitment of four participants of the planned 158 to receive IMP as the main study). Continuation of the exploratory mechanistic substudy continued, recruiting only individuals receiving standard care (i.e. metformin for clinical treatment not within the provision of the CTIMP, GDM not receiving pharmacotherapy and no GDM, therefore not eligible for the main CTIMP study).

Initial changes in the trial plan were performed with the intention of improving recruitment to both parts of the study. These included increasing the upper age limit of participants from 45 to 50 years (Protocol V3.0 16/03/2021), extending the window for diagnosis of GDM to start at 24+0 weeks' gestation from 26+0 week's gestation (Protocol V3.0 16/03/2021), reducing the minimal body mass index (BMI) of participants from 25 kg/m2 to 18.5 kg/m2 (Protocol V3.0 16/03/2021), recruiting individuals already taking metformin as standard of care (Protocol V5.0 22/03/2022), , and allowing for different metformin doses as the comparator medication to align with clinical practice at the individual recruiting sites at initiation (Protocol V5.0 22/03/2022). Due to the COVID-19 pandemic, substantial amendments included permitting virtual consent and research conversations and facilitating remote visits to react to the changing delivery of healthcare during this period (Protocol V2.0 29/07/2020). To reduce complexity of the study and participant burden, the optional detailed vascular assessments were replaced with simpler methods of assessment of maternal cardiovascular status, and further nested substudies (e.g. MRI imaging of participants) were not introduced (all permitted within the original Protocol V1.0 11/02/2020).

For the GUARD-MEC substudy, alterations in the inclusion criteria to be permissive of individuals having received antibiotics earlier in the pregnancy improved eligible participants to be included within the study. Also the sample size for the GUARD MEC sub-study was reduced to 60 to reflect the removal of ARM 2 (GUARD participants randomised to UDCA). The protocol was amended with observational study arms in GUARD MEC alone to continue until the end of study (GUARD MEC Arm 1: GDM Metformin (participants taking Metformin for their standard of care), GUARD MEC Arm 3: GDM no pharmacotherapy, GUARD MEC Arm 4 : Healthy pregnant control).

20.1 Protocol Deviations

There were no breaches in the study protocol judged to be of a serious nature; given the early termination of the study and decision not to analyse the main CTIMP results from the randomised part of the study, no protocol deviation affected this part of the analysis. Given the observational nature of the nested mechanistic substudy, there were some protocol deviations that affected the study analysis – as samples were pre-assessed to be missing at random, the decision was made not to include multiple imputation for missing data; linear mixed models were used in the analysis to enable statistical comparison in the absence of results from missing timepoints.
During the study period, the clinical laboratory at one of the recruiting sites experienced a cyber attack that resulted in pausing of sample analysis. For these clinical samples, analysis occurred following freezing of aliquots, rather than contemporaneously. Extensive literature reviews confirmed the approaches by which this could occur with appropriate validity; capillary blood glucose machines were used to measure glucose concentrations from venous blood for these two participants.

The following tables summarise protocol deviations and actions/impacts:

GUARD CTIMP randomised participants

Nature of protocol deviation	Number of participants	Action / impact
Unable to perform arteriography	1	Decision to stop arteriography as part of the study
Meconium not collected	1	Nil – not analysed
Meconium timing of collection not available	1	Nil – not analysed
Continuous glucose monitoring data not downloaded – software not working	1	Nil – not analysed
Retrospective documentation of IMP administration details	1	Nil – not analysed
Location of documentation (directly onto eCRF)	1	Nil – data entry assumed accurate

GUARD-MEC mechanistic substudy participants

Nature of protocol deviation	Number of participants	Action / impact
Unable to perform arteriography	1	Decision to stop arteriography as part of the study
Missing birthweight centile data	8	Calculated using recorded gestational age of birth and birthweight
Missing blood sample 15 minutes post meal	2	Use of linear mixed model statistical analysis
Missing blood sample 60 minutes post meal	2	Use of linear mixed model statistical analysis
Missing blood sample 120 minutes post meal	1	Use of linear mixed model statistical analysis
Implausible results from biological testing at 120 minute sample	1	Excluded from statistical analysis as biological outlier
Early completion of participant details in eCRF and allocation of participant ID prior to consent – consent not completed as ineligible on arrival on study day (not fasted)	1	Nil – not included in analysis as per protocol analysis used, no additional data collected
Data entry error for start date for concomitant medications – where date was unknown, standardised inaccurate date used (01/01/year of study) to enable eCRF saving	All participants where relevant	Duration of concomitant medication use not included in data analysis/
Non-standard food diary data collection performed	1	Participant food diary printed and filed in its original format
Maternal weight not collected at study visit	2	Weight included from most recent clinical visit to study date
Maternal blood test (LFT) not measured at study visit	2	Result included from most recent clinical visit to study date
Loss to follow up	1	No CGM or birth outcome data – these were not included in data analysis
Non-contemporaneous measurement of clinical samples due to inability of clinical laboratory to process samples	2	Sample freezing and storage, with later measurement from frozen samples
Use of point of care test for venous blood glucose measurement due to inability of clinical laboratory to process samples	1	Nil
Fasting research EDTA sample not taken (for GLP1 measurement) due to protease inhibitor not being added	1	Use of linear mixed model statistical analysis

22. Summary – Conclusions

21.1 Demographic data

The primary objective was not met (due to an early decision to halt recruitment to the IMP-receiving part of the trial upon which this was based).
The following tables summarise the demographics of the study population (of all participants for both parts of the study):

Number of Subjects			
Age (years)	**Male**	**Female**	**Total**
Pre-term new-born infants (<37 weeks)	0	0	0
New-borns (0-27 days)	1	2	3
Infants and toddlers (28 days – 23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	55	55
From 65-84 years	0	0	0
85 years and over	0	0	0
Total	**1**	**57**	**58**

All adult participants were female as this was a maternity population. Three neonates were included from the three completing participants of the GUARD IMP=receiving main part of the study, of these, two were female and one was male.

Of the four GUARD IMP-receiving maternity participants, the mean age was 32 years (range 21-38), ethnicities were 2x Black African and 2x White. Given the small numbers in this group, remaining figures and tables refer to participants of the GUARD MEC substudy.

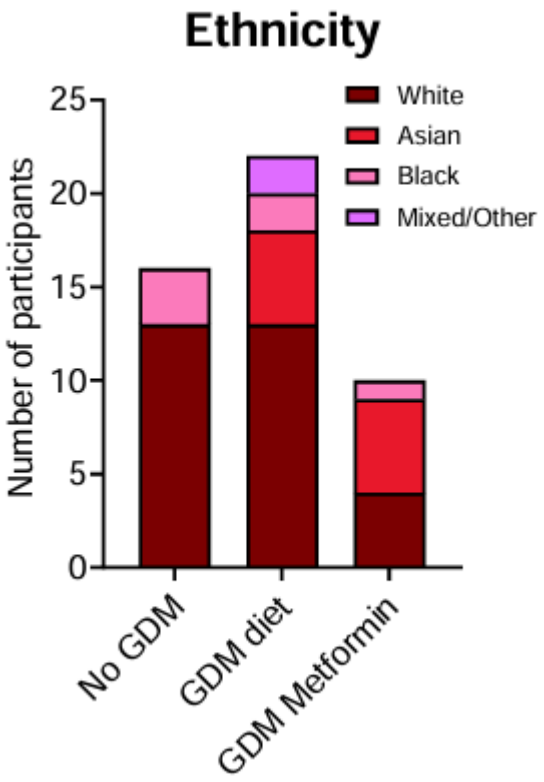
Table: Demographic data for GUARD MEC participants

Number of Subjects			
Characteristic	**GDM metformin (10)**	**GDM lifestyle management (22)**	**No GDM (16)**
Age (years, median, IQR)	37 (33 to 39)	33 (32 to 37)	35 (31 to 37)
Ethnicity (number, %)			
Asian	1	5	0
Black	5	2	3
White	4	13	13
Mixed/other	0	2	0
Nulliparous (number, %)	5 (30)	8 (36)	5 (31)
Previous pregnancies (median, range)	3.3 (1-6)	1.5 (1-3)	2.5 (1-10)
Previous GDM (number, %)	2/7 (29%)	3/14 (21%)	2/11 (18%)
Previous pre-eclampsia (number, %)	1/7 (14%)	2/14 (14%)	0/11
PCOS (number, %)	3 (30%)	3 (14%)	1 (6%)
IVF (number, %)	0	4 (18%)	1 (6%)
Smoker (number, %)	0	1 (5%)	1 (6%)

Table: Baseline characteristics of the per protocol population Frequency (%) is displayed unless otherwise specified.

Number of Subjects			
Characteristic	**GDM metformin (10)**	**GDM lifestyle management (22)**	**No GDM (16)**
Body mass index – pregnancy booking (median, IQR)	30.9 (27.4 – 33.6)	26.1 (24.6 – 30.4)	22.4 (20.4 – 25.7)
Gestational age – study visit, days (median, IQR)	252 (251 – 255)	253 (252 – 255)	252 (250 - 253)
Hba1c (mmol/mol) (median, IQR)	36.5 (33.0 – 43.3)	35.0 (29.0 – 36.0)	32.0 (30 – 33.3)

Figure: Ethnicity of the GUARD-MEC participants



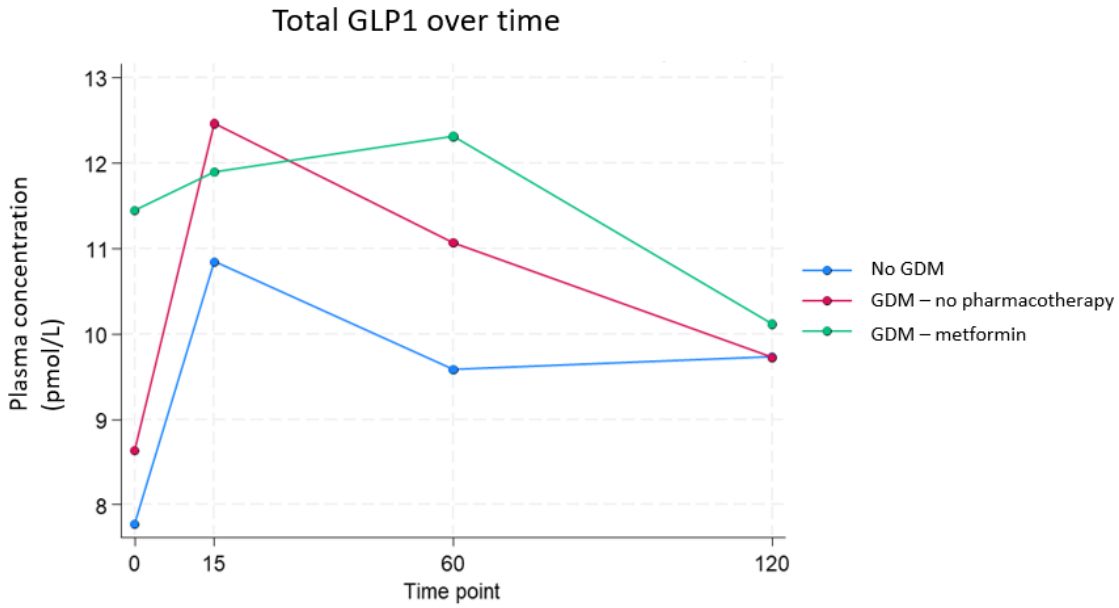
21.2 Primary outcome

As the GUARD IMP part of the study was ceased before sufficient participants were recruited for meaningful analysis, the decision was made not to analyse data from GUARD IMP-receiving participants from the main study. Therefore, no primary outcome data were compared. The mean maternal fasting glucose concentration at 36 gestational weeks was 4.7 mmol/L (SD 0) for the participant receiving UDCA, and 4.7 mmol/L (SD 0.7) for the participants receiving metformin.

The exploratory outcomes from the GUARD MEC substudy were analysed. Given that this substudy sample size was calculated based upon GLP1 area under curve, these results are presented.

Analysed using linear mixed models, there was no significant difference in GLP1 area under the curve comparing GDM (either treatment) and no GDM in pregnancy.

Figure: Total GLP-1 concentration over time for the GUARD-MEC participants



21.3 Safety results

Two individuals reported adverse events, one of who participated in the GUARD IMP-receiving main part of the study, and one who participated in the GUARD MEC substudy, giving a total of two adverse events. For the former, this was classified as a Serious Adverse Event, resulting in participant hospitalisation or prolongation of hospitalisation; its severity was classified as "Mild", and was thought unlikely related to the study intervention. For the second, this was classified as an Adverse Event, that was not classified as being serious, the severity was "Mild", and it was thought likely related to the study intervention.

There were no SARs / SUSARs, and no deaths associated with the study

Table: Listing of Adverse Events for all patients
(MedDRA dictionary 25.1)

Part of GUARD study	**GUARD IMP-receivers (main study)**		**GUARD-MEC substudy**		
	UDCA arm	**Metformin arm**	**GDM metformin arm**	**GDM no pharmacotherapy arm**	**No GDM arm**
Total Number of AEs per Study Arm	1	0	1	0	0
Subjects affected by non-serious adverse events:	0	0	1	0	0

Table: Listing of Serious Adverse Events for all patients

Part of GUARD study	GUARD IMP-receivers (main study)		GUARD-MEC substudy		
	UDCA arm	Metformin arm	GDM metformin arm	GDM no pharmacotherapy arm	No GDM arm
Total number of SAEs per study arm	1	0	0	0	0
Total number of all cause deaths per study arm	0	0	0	0	0
Total number of deaths resulting from adverse events per study arm	0	0	0	0	0

Within the per protocol population of the IMP-receiving part of the study, a total of 1 AEs, including 1 SAE, were identified as treatment-emergent and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

Overall, 2 patients from the whole study (4x IMP-receiving participants and 51x Mechanistic substudy participants, and 3 neonates included in the follow up of participants receiving IMP) (3.4%) patients experienced at least one AE. The proportion that experienced at least one SAE was 1.7% (n=1).

Incidence of adverse drug reactions (ADRs): 0 / 2 AEs (0%) were assessed as related to at least one study drug and 0 / 4 patients (0 %) experienced 0 ADR.

There were 0 Serious Adverse Reactions (SARs), 0 unexpected SARs and 0 SUSARs.

23. Conclusion

This CTIMP of UDCA compared with metformin was unable to recruit sufficient participants to determine the impact of UDCA on blood glucose control for individuals with gestational diabetes mellitus. Whilst the mechanistic substudy on gut hormone responses to a standardized diet, comparing individuals with GDM controlled using metformin or no pharmacotherapy with individuals without GDM, was able to recruit sufficient participants to assess clinical and hormonal outcomes, there was no significant difference identified between the three groups in the release of the gut hormone GLP1 following food.

24. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 24/07/2026

APPENDICES

i) Summary of treatment-emergent AEs in the per protocol population

For CTIMP participants (UDCA versus Metformin)

System Organ Class	Preferred Term	Number of Subjects Experiencing the AE in Active Arm (UDCA)	Total Number of Occurrences of the AE	Number of Subjects Experiencing the AE in Placebo Arm (metformin)	Total Number of Occurrences of the AE
Pregnancy, puerperium and perinatal conditions*	Pre-eclampsia	1 (50%)	1	0 (0%)	0

Recorded as "Vascular Disorders" in final data extract. Changes to coding were approved by the Chief Investigator.

For GUARD-MEC substudy participants (GDM metformin, GDM no pharmacotherapy, or no GDM)

System Organ Class	Preferred Term	Number of subjects experiencing the AE in GDM metformin arm	Total number of occurrences of the AE	Number of subjects experiencing the AE in GDM no pharmacotherapy arm	Total number of occurrences of the AE	Number of subjects experiencing the AE in no GDM arm	Total number of occurrences of the AE
Nervous system disorders**	Syncope***	1 (10%)	1	0 (0%)	0	0 (0%)	0

Recorded as "Cardiac Disorders" in final data extract. Changes to coding were approved by the Chief Investigator.

****Recorded as "Vasovagal" in final data extract. Changes to coding were approved by the Chief Investigator.***

ii) Summary of treatment-emergent ARs in the per protocol population

There were no treatment-emergent ARs in the per protocol population of the CTIMP part of the study. One participant in the GUARD-MEC substudy, receiving metformin treatment as standard of care and not randomized for the CTIMP, had a vasovagal syncopal episode following phlebotomy at the start of the study. Further blood samples were not taken, the severity of the AR was classified as mild, and the participant recovered fully within minutes.

iii) Summary of treatment-emergent SAEs in the study population

One participant randomized to receive UDCA for treatment of her GDM in the CTIMP later developed pre-eclampsia in her pregnancy. This was classed as an SAE, although of mild impact, from which the patient fully recovered. This was thought unlikely related to the study medication.

System organ classification	Sponsor Ref. No.	Lower-level term	Preferred Term	Serious Adverse Event details
Pregnancy, puerperium and perinatal conditions 10036585	3599_SAE1	Pre-eclampsia 10036485	Pre-eclampsia 10036485	In-patient hospitalisation with diagnosis of pre-eclampsia. Subject withdrew from IMP on 05/11/2022. SAE occurred on 10/11/2022

iv) Summary of treatment-emergent SARs in the study population

There were no treatment-emergent SARs in the study population.

Appendix 2: References

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Appendix 3: Lay Summary

Randomised controlled trial of Gestational treatment with Ursodeoxycholic Acid compared to metformin to Reduce effects of Diabetes mellitus

GUARD TRIAL LAY SUMMARY

Purpose

Gestational diabetes happens in pregnancy when a mother's blood glucose is higher than normal. The GUARD trial compared a new treatment with a medicine that we normally use.

High glucose in pregnancy can increase the baby's growth. So, we aim to keep mother's glucose below a target level. Firstly, mothers make changes to their diet and exercise to lower their blood glucose. If the glucose is still high, we give medicines to help. In the UK, we use the medicine metformin first. However, some people are worried that metformin may cause increased growth and size for children later in life.

UDCA is a safe medicine in pregnancy; its full name is ursodeoxycholic acid. We already use UDCA to treat a liver condition in pregnancy. We found that people taking UDCA have lower blood glucose. We wanted to compare metformin with UDCA in gestational diabetes, to see if UDCA is better at lowering blood glucose. We planned to treat 79 patients with each medicine.

What happened?

The study started during the COVID-19 pandemic. There were delays and difficulties with patient recruitment. So, we stopped the main GUARD study with only four participants. We did not compare their results due to the small numbers.

However, we did continue part of the study, called GUARD-MEC. This looked at how gestational diabetes and metformin affect gut hormones. Gut hormones are small messengers that the intestine produces. They send messages from the intestine to other organs, like the pancreas, liver, and fat. They help to control how the body stores and releases glucose and fats. One of the main gut hormones that lowers glucose is GLP1.

We took blood from pregnant people before and three times after food. We measured levels of a variety of gut hormones, including GLP1, in the blood. We compared what happens to people without gestational diabetes to those with gestational diabetes. We compared what happens when people used only diet changes and exercise to treat their diabetes with what happens when people also use metformin.

Results

51 people took part in GUARD-MEC. We found that GLP1 levels in the blood were similar between participants. However, our results suggested that people with gestational diabetes taking metformin may have higher levels of GLP1 than those without diabetes. We think that this means that patients with gestational diabetes taking metformin have stronger messages from the intestine to tell the pancreas to lower glucose. It may also mean that patients with gestational diabetes may respond less well to gut hormone signals. This could explain why some patients get gestational diabetes.

What this means for patients

People with gestational diabetes taking metformin had better glucose control than those only using diet and exercise. This may suggest that more patients would benefit from metformin than we are currently giving this to.

Kings College London and Guy's and St Thomas' NHS Trust managed this study. The Jon Moulton Charity kindly funded the research. You can ask for further information from covadia@ed.ac.uk.

We are incredibly grateful to the 55 participants (and their babies) for taking part. This will help us to understand diabetes better. It will also improve treatments for future patients with gestational diabetes.