Clinical trial results:
Aspirin for Optimising Pregnancy Outcome in Pregestational Diabetes: Pilot for The IRELAND Study (Investigating the Role of Early Low-dose Aspirin iN preexisting Diabetes)

Summary

EudraCT number	2014-001332-11
Trial protocol	IE
Global end of trial date	06 December 2016

Results information

Result version number	v1 (current)
This version publication date	04 April 2020
First version publication date	04 April 2020
Summary attachment (see zip file)	EudraCT 2014-001332-11 Clinical Trial Report Summary (Ireland Clinical Trial Report Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	IRELANDPILOTV1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Royal College of Surgeons Ireland
Sponsor organisation address	111 St Stephens Green, Dublin, Ireland, Dublin 2
Public contact	Mandy Jackson, Royal College of Surgeons, 00353 18093863, mandyjackson@rcsi.ie
Scientific contact	Mandy Jackson, Royal College of Surgeons, 00353 18093863, mandyjackson@rcsi.ie

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	06 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2016
Global end of trial reached?	Yes
Global end of trial date	06 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The definitive IRELAND Study aims to investigate whether low-dose aspirin prescribed routinely to woman with pre-existing diabetes, initiated at 8+0 – 12 weeks' gestation and continued until 36 weeks gestation may modify the risk of adverse perinatal outcomes related to placental dysfunction. The purpose of the pilot phase of this study is to determine rates of patient participation and compliance with aspirin therapy throughout pregnancy in this high-risk population.
Primary objectives:

1. Proportion of eligible women who agree to participate in the pilot study.
2. Compliance with the study protocol, as judged by platelet function monitoring
3. Proportion of study participants who complete the study, with complete ascertainment of laboratory markers of glycaemic control, renal function and platelet function at all scheduled timepoints

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

The comparator group was a non treated (no aspirin) control group. The rationale for this control group is based on the lack of evidenced based recommendations (see NICE, RCOG, ACOG, HSE) for the use of aspirin in pregnant women with diabetes.

Actual start date of recruitment	26 May 2015
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	Ireland: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

24 subjects signed consent with one subject withdrawing consent prior to randomisation so 23 subjects were enrolled.
Subjects were recruited from two maternity hospitals in Ireland.
The first subject was recruited on 26-May-2015.

Pre-assignment

Screening details:

40 subjects were screened. 16 of these patients screen failed due to reasons including; miscarriage before 12 weeks gestation, difficultly communicating in English, taking Aspirin in the first trimester before the recruitment phase, twin pregnancies, screening after 12 weeks gestation and diagnoses of diabetes < 6 months prior to recruitment.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial was open label. No blinding of either the research participant or of the investigator occurred. Both the research participant and the investigator were aware of the investigational medicinal product that the research participant was allocated to receive.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aspirin arm

Arm description:

Aspirin therapy 75mg daily commencing after a satisfactory 1st trimester assessment, to include sonographic confirmation of fetal cardiac activity followed by 4-weekly blood draws for platelet function (dynamic platelet assay), serum fructosamine and renal profile, with quantification of microalbuminuria in each trimester(aspirin arm). Prenatal care will be delivered through the Combined Obstetric Endocrine service. Aspirin was provided free of charge to the patient.

Arm type	Experimental
Investigational medicinal product name	Aspirin (Acetylsalicylic acid) 75mg
Investigational medicinal product code	ATC code: B01A C06
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Arm 1: Aspirin Therapy: Aspirin 75mg daily commenced after satisfactory routine first trimester assessments, to include sonographic confirmation of foetal cardiac activity. Monthly blood was drawn during pregnancy up to week 36 for platelet function, serum fructosamine, and renal profile, with quantification of microalbuminuria in first and third trimester. Prenatal care was delivered as standard through the Combined Obstetric Endocrine service. Aspirin was provided free of charge to the participants through the local pharmacy in the hospital

Arm title	Control arm

Arm description:

Arm 2: Control Group: No aspirin therapy. Monthly blood was drawn during pregnancy up to week 36 for platelet function, serum fructosamine, and renal profile, with quantification of microalbuminuria in first and third trimester. Prenatal care was delivered as standard through the Combined Obstetric Endocrine service.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Aspirin arm	Control arm
Started	13	10
Data Safety Monitoring Board Meeting	13	10
Completed	13	10

Baseline characteristics

Reporting groups	
Reporting group title	Aspirin arm
Reporting group description:	
Aspirin therapy 75mg daily commencing after a satisfactory 1st trimester assessment, to include sonographic confirmation of fetal cardiac activity followed by 4-weekly blood draws for platelet function (dynamic platelet assay), serum fructosamine and renal profile, with quantification of microalbuminuria in each trimester(aspirin arm). Prenatal care will be delivered through the Combined Obstetric Endocrine service. Aspirin was provided free of charge to the patient.	
Reporting group title	Control arm
Reporting group description:	
Arm 2: Control Group: No aspirin therapy. Monthly blood was drawn during pregnancy up to week 36 for platelet function, serum fructosamine, and renal profile, with quantification of microalbuminuria in first and third trimester. Prenatal care was delivered as standard through the Combined Obstetric Endocrine service.	

Reporting group values	Aspirin arm	Control arm	Total
Number of subjects	13	10	23
Age categorical Units: Subjects			
Age continuous			
Age was equally distributed between both groups. Mean age was 32 years with minimum of 18 and maximum of 42 years.			
Units: years			
arithmetic mean	32	32	
full range (min-max)	18 to 42	18 to 42	-
Gender categorical Units: Subjects			
Female	13	10	23
Male	0	0	0
Ethnicity			
The total enrolled subjects (n=23) can be divided into 3 ethnicities; Asian, African and Caucasian			
Units: Subjects			
Asian	3	2	5
African	2	0	2
Caucasian	8	8	16
Diabetes Type Units: Subjects			
Type 1	6	5	11
Type 2	7	5	12

End points

End points reporting groups

Reporting group title	Aspirin arm

Reporting group description:

Aspirin therapy 75mg daily commencing after a satisfactory 1st trimester assessment, to include sonographic confirmation of fetal cardiac activity followed by 4-weekly blood draws for platelet function (dynamic platelet assay), serum fructosamine and renal profile, with quantification of microalbuminuria in each trimester(aspirin arm). Prenatal care will be delivered through the Combined Obstetric Endocrine service. Aspirin was provided free of charge to the patient.

Reporting group title	Control arm

Reporting group description:

Arm 2: Control Group: No aspirin therapy. Monthly blood was drawn during pregnancy up to week 36 for platelet function, serum fructosamine, and renal profile, with quantification of microalbuminuria in first and third trimester. Prenatal care was delivered as standard through the Combined Obstetric Endocrine service.

Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Overall number of women who agreed to participate in the trial.

Primary: proportion of women who agree to participate in the study

End point title	proportion of women who agree to participate in the study[1]

End point description:

This endpoint was assessed by counting the number of women who were approached to take part in the study, the number who agreed to take part and the number who dropped out or were subsequently included on an intention to treat basis only.

End point type	Primary

End point timeframe:

4 month period

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: This is a pilot study and so no statistical analysis (e.g. hypothesis tests) were performed.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: number of women				
No. of women approached for participation	47			
No. of women who agreed to participate	23			
No. of women who dropped out or included in ITT	2			

Attachments (see zip file)	Endpoint 1 supporting extract from final report/Endpoint 1

Statistical analyses

No statistical analyses for this end point

Primary: compliance with study protocol

End point title	compliance with study protocol[2]

End point description:

Compliance with the study protocol – assessing the number of patients who underwent all designated assessments as outlined within the designated time period for set assessments as specified in the study protocol

End point type	Primary

End point timeframe:

6-8 months

Notes:

[2] - 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: This is a pilot study and so no statistical analysis (e.g. hypothesis tests) were performed.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Subjects	23			

Attachments (see zip file)	Endpoint 2 supporting extract from final report/Endpoint 2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All Adverse Events occurring during the study observed by the investigator or reported by the subject were captured from Visit 1 until the post delivery visit.

Adverse event reporting additional description:

All Adverse Events occurring during the study observed by the investigator or reported by the subject, whether or not attributed to the study medication were recorded on the Case Report Form and all Serious Adverse Events were reported to the Sponsor within 24 hours of the site's knowledge of the event except for the non-reportable events

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Aspirin Group

Reporting group description:

Subjects exposed to Aspirin

Reporting group title	Non-aspirin group

Reporting group description:

Control group who were not exposed to aspirin

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events were not reported by the investigator in the final study report. A summary of the Serious Adverse Events that occurred during the trial have been provided.

Serious adverse events	Aspirin Group	Non-aspirin group	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	6 / 10 (60.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Intentional Product Misuse	Additional description: Patient attended for visit 7 at 37+4 and was still taking aspirin. Patient discontinued at week 37+4 and delivered at week 38+2		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension	Additional description: Admitted for 24 urine collection and BP monitoring and PET bloods. PET bloods normal 24 hour urine collection normal.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Foetal Death	Additional description: Intrauterine death/late miscarriage		
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal hypokinesia	Additional description: Patient previously lost 11stone and has gastric band in place. Reports reduced fetal movement Admitted for CTG which showed normal fetal activity		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum haemorrhage	Additional description: 1000cc blood loss secondary to atonic uterus. No blood transfusion needed		
subjects affected / exposed	4 / 13 (30.77%)	2 / 10 (20.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia	Additional description: But 24 hours urinary protein collection was within normal range. Final diagnosis was Pregnancy Induced Hypertension		
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal growth restriction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug Hypersensitivity	Additional description: Allergic reaction to Novorapid		
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vulvovaginal pain	Additional description: Admitted with vaginal pain candidias diagnosed. Pt prescribed antifungal and discharged.		

subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage	Additional description: Admitted for observation following history of PV bleed		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea	Additional description: Admitted with 24hr history of nausea, no diarrhoea. Subject was given IV stemetil and ranitidine FBC and U&E normal		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Admitted with 24hr history of vomiting no diarrhoea. Subject was given IV stemetil and ranitidine FBC and U&E normal		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	Additional description: Admitted from emergency room with sore throat and started on antibiotics		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis of pregnancy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Left leg pain from calf radiating to the groin for 1 day. Subject described pain as sharp pain rated 8/10. Subject was given Innohep as a precaution and sent for scan at a nearby hospital. No DVT was observed.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Influenza			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Aspirin Group	Non-aspirin group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2016	The protocol Version 3, dated 29-Jan-2015 was substantially amended to Version 4, dated 18-Jul-2016 to include a list of non-reportable adverse events. The protocol safety reporting section 12.1 was amended to list events anticipated in pregnancy as non-reportable events unless deemed by clinicians and/or investigators to occur to a disproportionate degree. These events are considered to be 'normal and expected' occurrences for the patient population and in particular were not influenced by the administration of aspirin. Treatment of these symptoms was as per clinical guidelines. The following events were listed in the protocol as not requiring reporting: Nausea/ vomiting prior to 14 weeks' gestational age Hospitalisation for labour and delivery Poor glycaemic control Hospitalisation for poor glycaemic control Pelvic girdle dysfunction Indigestion Fatigue Constipation Shortness of breath Urinary frequency/ nocturia Migraine and tension headache Nosebleeds and bleeding gums Varicose veins Haemorrhoids Back pain Palpitations Carpal tunnel syndrome Fetal normal variants on ultrasound: Pyelectasis, choroid plexus cysts, echogenic intracardiac focus

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported