CLINICAL TRIAL REPORT

RCSI DEVELOPING HEALTHCARE LEADERS WHO MAKE A DIFFERENCE WORLDWIDE

Trial Title	**The IRELAnD Pilot Study - Investigating the Role of Early Low-dose Aspirin iN pre-existing Diabetes**
EudraCT Number	**2014-001332-11**
Study Ref. No.	**IRELAND _PILOT_V1**
Sponsor	**Royal College of Surgeons Ireland (RCSI)**
CT Ref. No.	**900/551/1-Nu-Seal**
Case No.	**2145429**
Date of Report	**06-Dec-2017**

CONFIDENTIAL

Signature pages for clinical trial report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: _____ Date: ___/___/_____

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1 TITLE PAGE

Study title:	Aspirin for Optimising Pregnancy Outcome in Pregestational Diabetes: Pilot for The IRELAnD Study (Investigating the Role of Early Low-dose Aspirin in preexisting Diabetes) – Pilot Study
Name of Test Drug:	Aspirin 75 mg (Nu-Seals®PA 943/6/1)
Indication studied:	Pregestational Diabetes
Study description:	A phase IV, multi-centre, randomised, open label trial investigating the use of aspirin for optimising pregnancy outcome in pregestational diabetes. Aspirin (Nu-Seals®PA 943/6/1) administered once daily by oral ingestion from first trimester (initiated between 8+0 and 11+6 weeks) to 36 weeks gestation for women with pregestational diabetes mellitus (type I or II). Participants randomised to the active treatment of aspirin 75mg or no aspirin (control). The patient population included women with a singleton pregnancy < 12 weeks of gestation, with type I or type II diabetes of at least six months duration prior to conception. The objective of the study was to investigate the proportion of eligible women with pregestational diabetes who participated in the pilot phase of a randomized trial of low-dose aspirin therapy in pregnancy, compliance with the study protocol, as judged by platelet function monitoring and analysis of all adverse events occurring after randomisation.
Sponsors:	Royal College of Surgeons Ireland (RCSI)
Protocol:	IRELAnD Pilot Clinical Trial Protocol version 4 18.07.2016
Clinical Phase:	Phase IV
Study dates:	First patient first visit: 26th May 2015 Last patient delivery: 6th December 2016
Investigators:	Chief Investigator Professor Fionnuala Breathnach, Consultant Obstetrician (MD FRCOG FRCPI DCH DipGUMed) Rotunda Hospital, Parnell Square, Dublin 1. Principle Investigator Professor Sean Daly Consultant Obstetrician (MA, MD, FRCOG, FRCPI) Coombe Hospital, Cork Street, Dublin 8.

Medical Monitor:	Professor Fionnuala Breathnach, Consultant Obstetrician (MD FRCOG FRCPI DCH DipGUMed) Rotunda Hospital, Parnell Square, Dublin 1.
Sponsor signatory:	Professor Raymond Stallings, Director of Research & Innovation, RCSI
GCP Statement:	This study was performed in compliance with ICH Good Clinical Practise (GCP) including the archiving of essential documents
Date of report:	6th December 2017.

2 SYNOPSIS

NAME OF SPONSOR:	Royal College of Surgeons Ireland (RCSI)
NAME OF FINISHED PRODUCT:	Aspirin (Nu-Seals®PA 943/6/1)
NAME OF ACTIVE INGREDIENT(S)	Acetylsalicylic acid

Title of Study	Aspirin for Optimising Pregnancy Outcome in Pregestational Diabetes: Pilot for The IRELAnD Study (Investigating the Role of Early Low-dose Aspirin in preexisting Diabetes) – Pilot Study
Phase:	Phase IV
Investigator(s)	Chief Investigator Professor Fionnuala Breathnach, Consultant Obstetrician (MD FRCOG FRCPI DCH DipGUMed) Principle Investigator Professor Sean Daly Consultant Obstetrician (MA, MD, FRCOG, FRCPI)
Study centre(s)	Rotunda Hospital, Parnell Square, Dublin 1. Coombe Hospital, Cork Street, Dublin 8.
Publication	N/A
Study period	First patient first visit: 26-May-2015 Last patient last visit: 06-Dec-2016
Objectives	**Primary Objective** To evaluate: 1. The 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 time points. **Secondary (Exploratory) Objective** Examination, through Light Transmission Aggregometry (LTA) of antiplatelet effects among women with pregestational diabetes, when compared with platelet function in diabetic women not taking antiplatelet therapy.
Methodology	• A phase IV, multi-centre, randomised, open label trial investigating the use of aspirin for optimising pregnancy outcome in pregestational diabetes. • Aspirin (Nu-Seals®PA 943/6/1) administered once daily by oral

	ingestion from first trimester (initiated between 8+0 and 11+6 weeks) to 36 weeks gestation for women with pregestational diabetes mellitus (type I or II). • Participants randomised to treatment of aspirin 75mg or no aspirin (control). The patient population included women with a singleton pregnancy < 12 weeks of gestation, with type I or type II diabetes of at least six months duration prior to conception. • The objective of the study was to investigate the proportion of eligible women with pregestational diabetes who participated in the pilot phase of a randomized trial of low-dose aspirin therapy in pregnancy, compliance with the study protocol, as judged by platelet function monitoring and analysis of all adverse events occurring after randomisation. • Four populations will be described and utilized in the statistical analyses: a) All Randomized b) Intention-to-treat (ITT): All randomized having a composite outcome measure c) Safety Population: All randomized who received at least one dose of study medication d) Per-protocol (PP): ITT population excluding major protocol violations and non-compliance with study treatment • Clinical outcomes (primary and secondary) will be described in the ITT and PP populations. • The primary study outcome variable of placental dysfunction will be analysed using logistic regression with treatment group as a factor. The 5% level of significance and 95% Confidence Interval will be used to determine the statistical significance of risk (odds-ratio).
Number of patients	Planned: 24 patients. Analysed: 23 patients. (1 patient withdrew consent prior to randomisation, therefore no data was collected)
Main criteria for inclusion	• Singleton pregnancy • Pre-pregnancy diagnosis of type I or type II diabetes of at least 6 months' duration
Test product, dose and mode of administration	Aspirin 75mg (Nu-Seals®PA 943/6/1) administered once daily by oral ingestion.
Duration of treatment	Aspirin 75mg (Nu-Seals®PA 943/6/1) initiated between 8+0 and 11+6 weeks (first trimester) up to 36 weeks gestation.
Criteria for evaluation	Primary: • Number of women screened; number meeting inclusion criteria; number willing to be randomised. • Compliance measured by a review of pill-packs (pill counting), examination of patient's log of aspirin taken, measurement of thromboxane A2 levels in study group, and controls. • The proportion of women completing the study measured by

	ascertaining the proportion of participants on whom completed data was obtained (demographic, laboratory, and outcome data). Secondary: • Antiplatelet effect, compared between study (aspirin) and control (no aspirin) groups measured using a platelet aggregometry. • Examination of the placenta for evidence of placental related changes due to pre-eclampsia.
Statistical methods	• Four populations will be described and utilized in the statistical analyses: a) All Randomized b) Intention-to-treat (ITT): All randomized having a composite outcome measure c) Safety Population: All randomized who received at least one dose of study medication d) Per-protocol (PP): ITT population excluding major protocol violations and non-compliance with study treatment • Clinical outcomes (primary and secondary) will be described in the ITT and PP populations. • The primary study outcome variable of placental dysfunction will be analysed using logistic regression with treatment group as a factor. The 5% level of significance and 95% Confidence Interval will be used to determine the statistical significance of risk (odds-ratio).

SUMMARY CONCLUSIONS	
Efficacy Results	The small sample size and design of this pilot study did not allow for the efficacy of Aspirin 75mg to be assessed.
Safety Results:	IRELAND study: 31 SAEs were reported in this study. Only one of these SAEs was considered to be related to the use of the Investigational Medicinal Product. The Serious Adverse Reaction (SAR) involved a female of 37 gestational weeks pregnancy. The participant took Aspirin up until 37 weeks gestation which met the serious criteria of important medical event. The MedDRA coding for the event was Intentional Product Misuse
Conclusion	The data obtained from the pilot study regarding eligible patient population, recruitment timelines, patient compliance and adherence will inform the large scale randomised, double-blind controlled trial
Date of the Report	06-Dec-2017