CLINICAL STUDY REPORT: PIPIN

Pravastatin for the Prevention of Preterm Birth in Women: A Phase II Feasibility Study

Study Report for ISRCTN

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Funder	Chief Scientist Office (Scotland)
Funding Reference Number	TCS/18/30
Chief Investigator	Professor Jane Norman
EudraCT Number	2017-005021-21
CTA Number	01384/0256/001-0001
REC Number	18/ES/0007
ISRCTN Number	82984919
Version Number and Date	Version 1 30/11/2020

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FINAL REPORT DATE: 19th January 2020

STUDY START DATE: 03/08/2018

STUDY END DATE: 29/11/2019

IMP: Pravastatin 40mg

Outcomes

Primary outcome data

1. Trial uptake: eligible participants as compared with recruitment.

Secondary Outcome Data

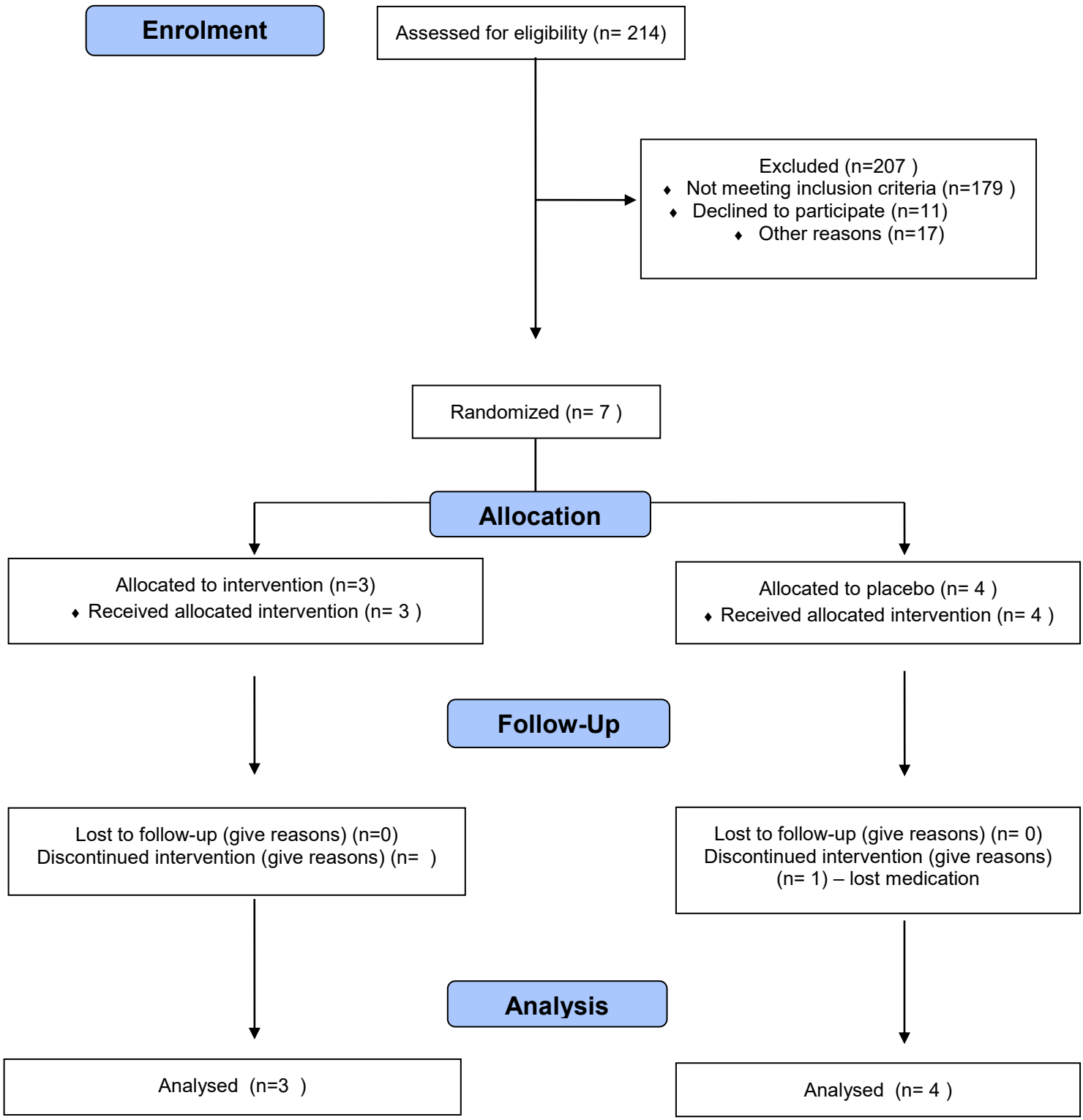
1. Routine participant demographics including past medical history and drug history
2. Any additional treatments received during inpatient stay (including magnesium sulphate, antibiotics, syntocinon / other methods of induction/augmentation and steroids)
3. Retention, adherence and ability to collect clinical outcomes from participants
4. Time from presentation with threatened preterm labour to delivery of first dose of IMP.
5. Time from presentation to acute care and assessment services with suspected preterm delivery to delivery itself, as well as gestation at delivery
6. Contraction frequency during treatment course, from presentation to delivery or cessation of regular uterine activity.
7. Bloods: Liver function tests, creatinine kinase levels (side effects), maternal and cord inflammatory profile (see 2.2.2 for details of measures within the inflammatory profile).
8. Compliance with treatment
9. Adverse events
10. Acceptability of the trial following completion of the protocol
11. Other clinical outcomes
    a. Maternal outcomes:
        i. Proven maternal infection
        ii. Safety of intervention to mother (self-reported AEs and biochemical monitoring of liver function tests and creatinine kinase).
        iii. Pre-labour ROM
        iv. Duration, location and level of care of hospital stay following presentation with suspected preterm labour AND following delivery.
    b. Neonatal morbidity and mortality, safety of intervention, gestational age at delivery, birthweight, duration, location and level of care required following delivery. If in utero transfer occur, cause of method of transport used.
12. Pharmacokinetics of pravastatin

Changes to outcomes

Initially it was planned to Contraction frequency as monitored at presentation and from randomisation to delivery or cessation of regular uterine activity. However this proved to be unfeasible and therefore was discontinued.
Pharmacokinetics were not possible due to the small number of recruited participants. However, pravastatin levels in participant samples were reported in lieu of formal pharmacokinetics.

Results

Participant Flow (consort) diagram



Baseline Data

	Placebo			Pravastatin		
	Mean	Standard Deviation	Number	Mean	Standard Deviation	Number
Age	23.75	4.86	4	27	1.73	3
Gestational Age (days)	212.5 ($30+^{3}$)	29.49	4	224 ($32+^{0}$)	20.52	3
Cervical Dilation (cm)	0	0	4	2	2	3
Weight (kg)	51.5	8.66	4	77	10.44	3
Height (m)	1.64	0.06	4	1.62	0.05	3
BMI	19.1	1.98	4	29.55	5.8	3
Systolic Blood Pressure (mmHg)	101.75	8.5	4	109.33	1.15	3
Diastolic Blood Pressure (mmHg)	61.25	2.5	4	67	10.44	3
Caucasian	4			3		
Smoker	75%			66.7 %		
Parity	Primiparous		25%	Prim		0%
	Multiparous		75%	Mulitp		100%

Table 1: Baseline Characteristics of Participants in the PIPIN Trial

Primary outcome data – Recruitment

Patients Screened	Patients Eligible	Participants Recruited
214	35	7
	16% (95% CI: 11.7 – 22.0)	20% (95% CI 8.4 – 36.9)

Table 2: Primary Outcome from the PIPIN Trial

Patient eligibility was assessed by research staff, following identification of patients by clinical staff. Of the 214 patients screened, 35 (16%; 95% CI 11.7-22.0) were found to be eligible..

Recruitment of 7 of a possible 35 eligible participants represents a 20% (95% CI 8.4-36.9) recruitment rate. However, only 18 of a possible 35 eligible participants were approached by trial staff to discuss inclusion in the PIPIN trial.

Secondary Outcome Data

- Retention, adherence and ability to collect clinical outcomes from participants.

Outcome	Result
Collection of Clinical Outcomes	All except contraction frequency
Adherence to treatment protocol	6 of 7 participants (85.7%)
Sample Collection	31 of 43 collected (72.1%)
Completion of Study Feedback Form	1 of 7 (14.3%)

Table 3: Secondary Outcomes: Retention, adherence and ability to collect data

- Any additional treatments received during inpatient stay

	Placebo	Pravastatin
Antenatal Therapies		
Magnesium Sulphate	1 (25%)	1 (33%)
Antenatal Corticosteroids	3 (75%)	2 (66%)
Antenatal Antibiotics	2 (50%)	0
Other Therapies	Buscopan (1 – 25%) Dalteparin (1 – 25%)	0
Intrapartum Therapies		
Intrapartum antibiotics	2 (50%)	2 (66%)
Epidural Anaesthesia	0	1 (25%)
Spinal Anaesthesia	1 (25%)	0
General Anaesthesia	1 (25%)	0

Table 4: Antenatal and Intrapartum Therapy

- Time from presentation with threatened preterm labour to delivery of first dose of IMP. Time from presentation to acute care and assessment services with suspected preterm delivery to delivery itself (Latency to Delivery), and gestation at delivery.

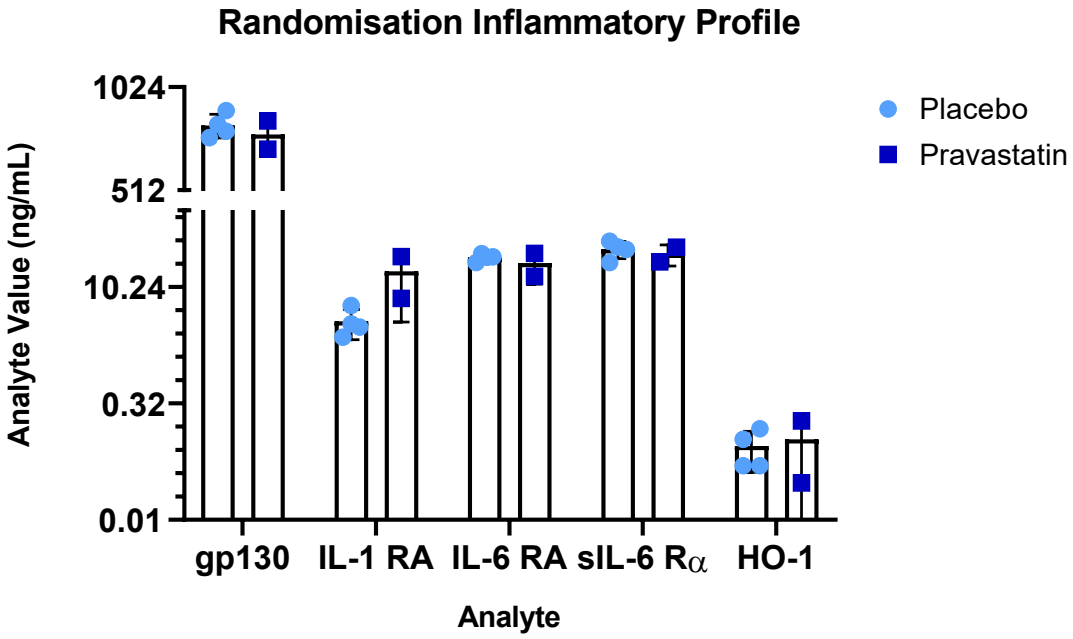
	Placebo	**Pravastatin**
Latency from Presentation to IMP Dispensing (hrs)	36 +/- 18	3.5 +/- 0.4
Latency to Delivery (hrs)	645 +/- 572	357 +/- 604
Gestational Age at Delivery (days)	238 +/- 6.2	239 +/- 33

Table 5: Latency to receive IMP, delivery and gestational age at delivery. Data presented as mean +/- standard deviation.

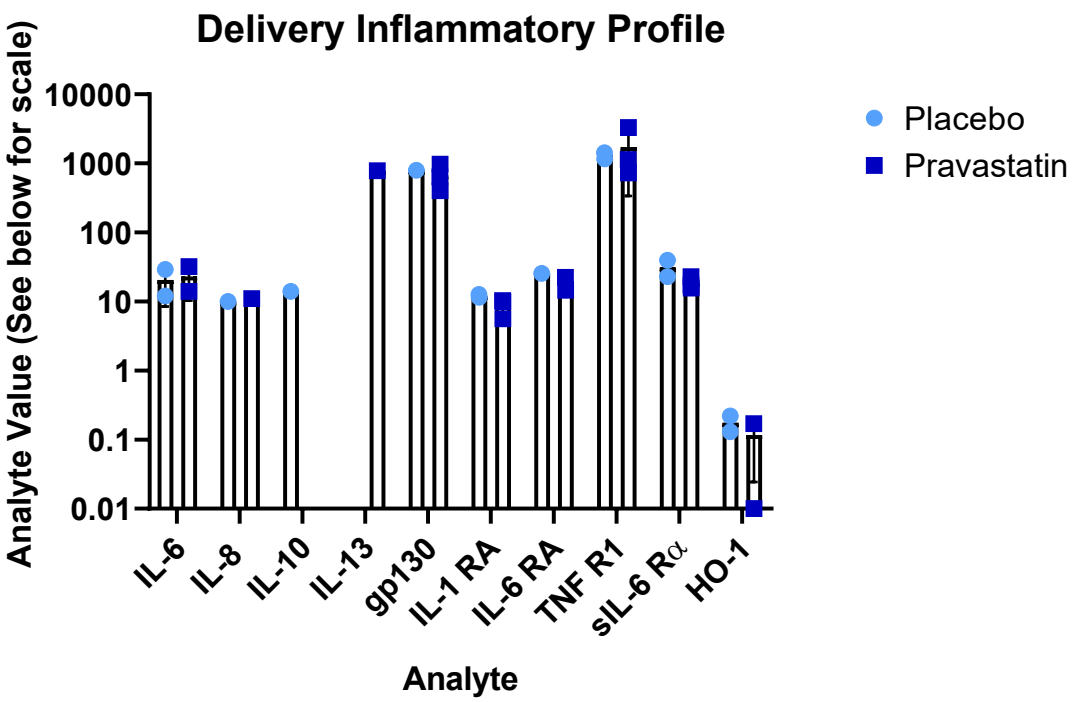
- Bloods: Liver function tests, creatinine kinase levels (side effects), maternal and cord inflammatory profile.

The number of samples obtained at each time point preclude analysis at some points. Direct comparisons between pravastatin and placebo at randomisation and delivery (both maternal and cord) are represented below:

A


Randomisation Inflammatory Profile
Analyte Value (ng/mL)
1024
512
10.24
0.32
0.01
gp130
IL-1 RA
IL-6 RA
sIL-6 Rα
HO-1
Analyte
Placebo
Pravastatin

B


Delivery Inflammatory Profile
Analyte Value (See below for scale)
10000
1000
100
10
1
0.1
0.01
IL-6
IL-8
IL-10
IL-13
gp130
IL-1 RA
IL-6 RA
TNF R1
sIL-6 Rα
HO-1
Analyte
Placebo
Pravastatin

C

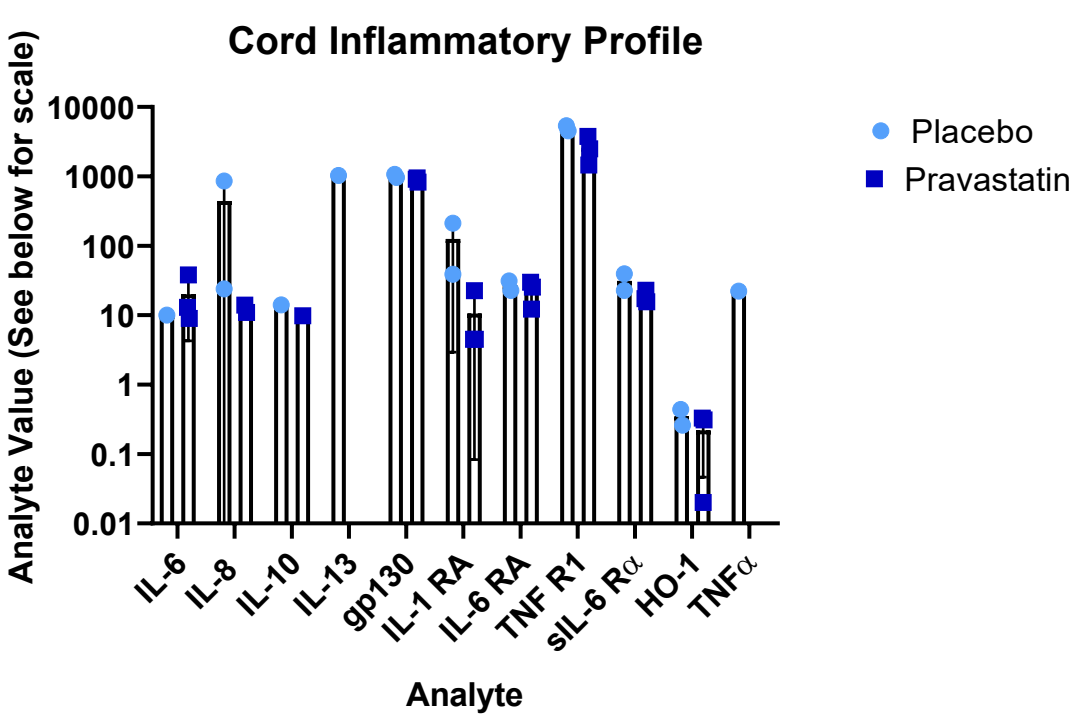


Figure 1: Inflammatory Profile Results at Randomisation (A) and Delivery (both maternal (B) and cord (C)). Data points represent values from individual samples, with n numbers as described above. Analyte scale: IL-6, IL-8, IL-10, IL-13, TNF R1 and TNFα all pg/mL; remaining analytes ng/mL.

- Adverse events

There were no adverse events in the pravastatin treatment group. The following adverse events all occurred in the placebo group.

Adverse Event	Number
Dysuria	1
Nausea	1
pPROM	2*
Retained placenta	1
Neonatal Death	1

Table 6: Adverse Events Occurring in Participants in the PIPIN trial. All events occurred in participants in the placebo allocation. *initially classified as a SAE, but after discussion with Data Monitoring Committee, reclassified as an AE.

- Other clinical outcomes
  a. Maternal outcomes:
     i. Proven maternal infection

2 participants were diagnosed with infection: 1 with Chlamydia on admission and 1 with

chorioamnionitis. Both participants were in the control group. The participant with chlamydia was treated on admission and discharged home pregnant; the participant with chorioamnionitis underwent emergency caesarean section for maternal sepsis.

ii. Safety of intervention to mother (self-reported AEs and biochemical monitoring of liver function tests and creatinine kinase).

The safety of the intervention was monitored through participant-reported adverse events (see table 5), and blood tests to check for the two most serious complications of statin therapy, liver dysfunction and rhabdomyolysis at baseline and day 7 of treatment. There were no incidences of statin treatment causing a rise in liver transaminases or creatinine kinase between randomisation and day 7 (figure 2).

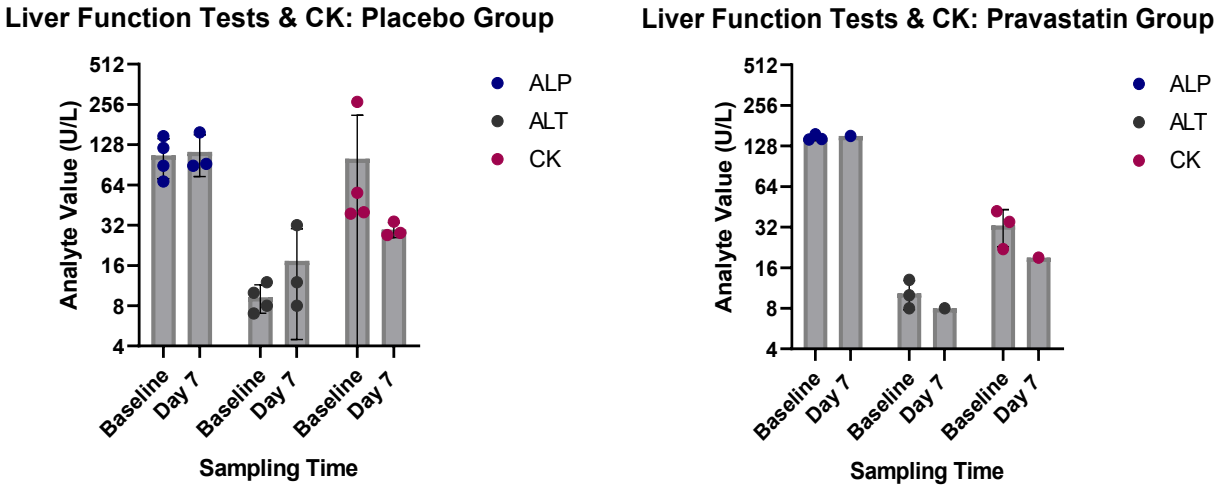


Figure 2: Liver Transaminase and Creatinine Kinases levels at Baseline and Day 7 in participants. Each data point represents an individual participant sample. ALP: alkaline phosphatase; ALT: alanine transferase; CK: Creatinine Kinase

iii. Pre-labour ROM

Two participants had a pPROM (premature prelabour rupture of membranes). Both of the affected participants were in the treatment group who received placebo.

iv. Duration, location and level of care of hospital stay following presentation with suspected preterm labour AND following delivery.

	Placebo (n=4)	Outcomes	Pravastatin (n=3)	Outcomes
Admission with Preterm Labour				
Duration of Stay (hrs)	74 +/- 35	75% discharged home pregnant	71	33% (1 patient) discharged home pregnant
Level of Care	Standard Antenatal		Standard antenatal	
Admission Leading to delivery				
Duration of Stay	182 +/- 169		101 +/- 43	

(hrs)			
Level of Care	Standard postnatal	66% Standard postnatal; 33% 6 hours HDU followed by standard postnatal	

Table 7: Maternal Duration and Level of care both during admission for threatened preterm labour, and admission leading to delivery (if these two were different). Data represented as mean +/- standard deviation

b. Neonatal morbidity and mortality, safety of intervention, gestational age at delivery, birthweight, duration, location and level of care required following delivery. If in utero transfer occur, cause of method of transport used.

Neonatal Outcomes are presented below:

	Placebo	Pravastatin
Mode of Delivery		
Spontaneous Vaginal	2	3
Assisted Delivery	1	
Caesarean Delivery	1	
Delivery Observations		
Baby Weight (g)	2400 +/- 1343	2503.3 +/- 1134
Apgar 1	9 +/- 0	7.67 +/- 0.58
Apgar 5	9 +/- 0	7.67 +/- 2.31
Venous pH	7.28 +/- 0.02	7.18 +/- 0.17
Arterial pH	7.27+/-0	7.1+/- 0.08
Neonatal Place and Duration of Care (Days)		
NICU	3.5±7.0	2±3.7
NHDU	6.5±13.0	17.3±30.0
SCBU	2.33±4.0	7±12.1
Standard	1.67±2.1	3±1.7
Total	**14**	**29**
Neonatal Complications		
Respiratory morbidity	1 (25%)	1 (33%)
GI morbidity	1 (25%)	
Early developmental morbidity	1 (25%)	
Jaundice	1 (25%)	2 (67%)
Neonatal Death	1 (25%)	

Table 8: Neonatal Outcomes from the PIPIN Trial (n=7). Data are presented as absolute numbers, mean +/- standard deviation or percentages where appropriate.

2. Pharmacokinetics of pravastatin

All blood samples were analysed by liquid-chromatography mass spectroscopy (LCMS) for both pravastatin and the most abundant metabolite, 3α-iso-pravastatin. Pravastatin was detected in 4 of 10 samples taken from participants receiving pravastatin during the treatment phase,

all of which were maternal. The shortest interval between dosing and sampling was 99 minutes. In this participant (marked black), pravastatin levels were 38.9 ng/ml. The remaining three samples were taken from a second participant in the treatment group, marked red, between 14 and 23 hours after dosing, and levels were 0.5 – 0.8 ng/mL. There was no pravastatin or metabolite detected in any cord samples.

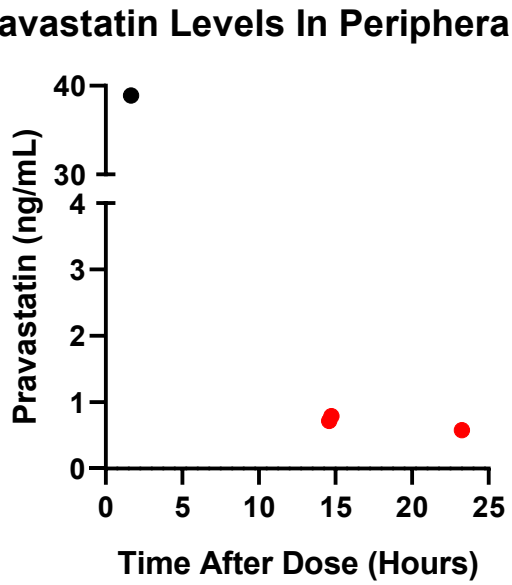


Figure 3: Pravastatin levels detected in peripheral blood from maternal samples taken during the treatment phase (n=4). Each data point represents a different sample. Pravastatin detected using liquid chromatography with tandem mass spectroscopy.