Clinical trial results:
STRIDER: A randomised controlled trial of sildenafil therapy in dismal prognosis early-onset intrauterine growth restriction.

Summary

EudraCT number	2013-005398-32
Trial protocol	GB
Global end of trial date	13 February 2017

Results information

Result version number	v1 (current)
This version publication date	01 March 2019
First version publication date	01 March 2019
Summary attachment (see zip file)	2013-005398-32 - End of Study Clinical Trial Report (SSSTR_R004.1 - STRIDER End of Study Clinical Trial Report.pdf) STRIDER UK Manuscript_17TLCHILD0261_Alfirevic_Published 06-12-2017 (STRIDER UK Manuscript_17TLCHILD0261_Alfirevic_Published 06-12-2017.pdf)

Trial information

Trial identification

Sponsor protocol code	UoL000984

Additional study identifiers

ISRCTN number	ISRCTN39133303
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	MHRA CTA reference: 04196/0032/001-0001, REC reference: 14/NE/0011, NIHR Portfolio reference: 16986, NIHR / EME Funding reference: 12/62/109

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	Block D Waterhouse Building, 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
Public contact	Dr Jane Harrold, Liverpool Clinical Trials Unit, 0151 7959565, jlh7@liverpool.ac.uk
Scientific contact	Professor Zarko Alfirevic , Women's and Children's Health, 0151 7959550, zarko@liverpool.ac.uk
Sponsor organisation name	Liverpool Women's NHS Foundation Trust
Sponsor organisation address	Liverpool Women's Hospital, Crown Street, Liverpool, United Kingdom, L8 7SS
Public contact	Louise Hardman, Research and Development, 0151 7024241, louise.hardman@lwh.nhs.uk
Scientific contact	Dr Andrew Sharp, Fetal Medicine Unit, 0151 7959560, asharp@liverpool.ac.uk

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	27 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2017
Global end of trial reached?	Yes
Global end of trial date	13 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Severe early-onset intrauterine growth restriction (IUGR) can lead to a range of adverse outcomes including fetal and neonatal death, neurodisability and lifelong risks to the health of the affected child. Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates the actions of nitric oxide, which leads to vasodilatation of the uterine vessels and might improve fetal growth in utero.

The overarching aim is to determine whether maternal treatment of oral sildenafil citrate improves perinatal outcomes in pregnancies complicated by severe early-onset IUGR without increasing risks to the mother. This study has a specific objective to evaluate the clinical efficacy of sildenafil i.e. its ability to lead to a delay of a clinical indication for delivery on fetal grounds by at least one week. The other specific objective is to add to the understanding of the mechanism of action of sildenafil by monitoring changes in the maternal, utero-placental and fetal circulation.

Protection of trial subjects:

Central and on-site monitoring was conducted to ensure the safety of participants and that study procedures, IMP administration, and laboratory and data collection processes were of high quality and met Sponsor and, where appropriate, regulatory requirements. A risk-based approach was adopted in order to determine the frequency and level of monitoring required, and a subsequent trial specific monitoring plan was developed. Throughout the course of the study regular Central Monitoring Reports were produced and reviewed by the Trial Management Team. In addition, on-site monitoring visits were performed for each research site following the hospital discharge of the first participant and surviving child. Safety was monitored via Liverpool Clinical Trials Unit (LCTU) pharmacovigilance procedures and oversight was provided by an ISDMC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	33 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 135
Worldwide total number of subjects	135
EEA total number of subjects	135

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)	1
Adults (18-64 years)	134
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The STRIDER trial recruited participants from within the UK only; 19 fetal medicine centres across England and Scotland opened for the study. A total of 135 women aged 16 years or older with a singleton pregnancy between 22+0 and 29+6 weeks gestation and a confirmed diagnosis of IUGR were recruited between 21st November 2014 and 6th July 2016.

Pre-assignment

Screening details:

In total 149 women were screened for trial eligibility. A physical examination, full history and first trimester ultrasound were used to determine if the study requirements were met. In each case, the diagnosis of severe early-onset IUGR was confirmed by a fetal medicine expert having excluded fetal anatomical abnormalities.

Period 1

Period 1 title	Study Intervention Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Blinding in terms of data and IMP were managed separately to the main study by the Clinical Trials Unit, British Columbia Women's Hospital and Sharp Clinical Services respectively.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Experimental arm

Arm type	Experimental
Investigational medicinal product name	Sildenafil
Investigational medicinal product code	EU/1/09/595
Other name	Viagra
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Sildenafil was manufactured by Actavis and supplied to each fetal medicine centre by Sharp Clinical Services. The encapsulated sildenafil tablets were prescribed at a dose of 25mg three times per day (orally) from baseline to 32+0 weeks gestation or delivery, whichever came first. Medication was issued weekly as 10-day (30 tablets) treatment packs to participants for self-administration if managed as an out-patient, or dispensed directly from pharmacy for those requiring in-patient care. In all cases, the initial study dose was administered in clinic, with participants being monitored 2 hours post treatment by research staff.

Arm title	Arm B

Arm description:

Standard arm

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo was supplied to each fetal medicine centre by Sharp Clinical Services. Placebo tablets were prescribed as per treatment arm A, three times per day (orally) from baseline to 32+0 weeks gestation or delivery, whichever came first. Medication was issued weekly as 10-day (30 tablets) treatment packs to participants for self-administration if managed as an out-patient, or dispensed directly from pharmacy for those requiring in-patient care. In all cases, the initial study dose was administered in clinic, with participants being monitored 2 hours post treatment by research staff.

Number of subjects in period 1	Arm A	Arm B
Started	70	65
Completed	70	65

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: Experimental arm	
Reporting group title	Arm B
Reporting group description: Standard arm	

Reporting group values	Arm A	Arm B	Total
Number of subjects	70	65	135
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	1	1
Adults (18-64 years)	70	64	134
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	29	33	
inter-quartile range (Q1-Q3)	26 to 34	28 to 36	-
Gender categorical Units: Subjects			
Female	70	65	135
Male	0	0	0
Ethnicity Units: Subjects			
White	48	43	91
Asian	6	8	14
African	6	7	13
Other	10	7	17
Smoking Units: Subjects			
Current smoker	12	2	14
Non-smoker	58	63	121
Parity Units: Subjects			
Nulliparous	35	25	60
Multiparous	35	40	75
Pre-eclampsia Units: Subjects			

Present	13	11	24
Absent	57	54	111
Gestational hypertension Units: Subjects			
Present	12	23	35
Absent	58	42	100
Current antihypertensive treatment Units: Subjects			
Yes	25	27	52
No	45	38	83
Gestational diabetes Units: Subjects			
Present	2	3	5
Absent	68	62	130
Antepartum haemorrhage Units: Subjects			
Present	1	0	1
Absent	69	65	134
Preterm prelabour rupture of membranes Units: Subjects			
Present	0	1	1
Absent	70	64	134
Gestation <26+0 weeks Units: Subjects			
<26+0 weeks	40	35	75
≥26+0 weeks	30	30	60
Umbilical Artery Doppler Units: Subjects			
End-diastolic flow absent	46	45	91
End-diastolic flow reversed	24	20	44
Ductus Venosus a-wave Units: Subjects			
Present	66	61	127
Absent	4	4	8
Uterine Artery Doppler Units: Subjects			
Normal	24	18	42
Abnormal (PI >1.45 or bilateral notching)	46	45	91
Missing	0	2	2
Estimated fetal weight <500g Units: Subjects			
<500g	33	36	69
≥500g	37	29	66
Height Units: centimetres (cm)			
median	164	163	
inter-quartile range (Q1-Q3)	158 to 167	158 to 166	-
Weight Units: kilogram(s) (kg)			
median	68	70	

inter-quartile range (Q1-Q3)	59 to 82	60 to 82	-
Body-mass index Units: kilogram(s)/square meter (kg/m²)			
median	25	26	
inter-quartile range (Q1-Q3)	23 to 32	23 to 31	-
Estimated fetal weight Units: gram(s) (g)			
median	451	436	
inter-quartile range (Q1-Q3)	352 to 613	326 to 594	-
Gestation Units: weeks			
median	25.1	25.6	
inter-quartile range (Q1-Q3)	24.0 to 27.5	24.1 to 27.4	-
Systolic blood pressure Units: millimetre of mercury (mm Hg)			
median	135.5	134.0	
inter-quartile range (Q1-Q3)	125.5 to 147.5	120.5 to 144.5	-
Diastolic blood pressure Units: millimetre of mercury (mm Hg)			
median	88.5	86.5	
inter-quartile range (Q1-Q3)	80.5 to 95.5	78.0 to 94.5	-
Mean arterial pressure Units: millimetre of mercury (mm Hg)			
arithmetic mean	103	109	
standard deviation	± 12	± 38	-
Creatinine Units: mole(s)/litre (mol/L)			
arithmetic mean	57.4	62.4	
standard deviation	± 1.9	± 2.7	-
Urea Units: millimole(s)/litre (mmol/L)			
arithmetic mean	4.0	4.4	
standard deviation	± 0.2	± 0.5	-
Uric acid Units: millimole(s)/litre (mmol/L)			
arithmetic mean	300.6	288.6	
standard deviation	± 13.4	± 14.7	-
Aspartate transaminase Units: units per litre (U/L)			
arithmetic mean	26.0	32.4	
standard deviation	± 3.3	± 5.7	-
Albumin Units: gram(s)/litre (g/L)			
arithmetic mean	31.8	32.4	
standard deviation	± 0.7	± 0.7	-

End points

End points reporting groups	
Reporting group title	Arm A
Reporting group description: Experimental arm	
Reporting group title	Arm B
Reporting group description: Standard arm	
Subject analysis set title	Full analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The final analysis dataset following the Intention to treat principle	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: 29 Patients removed due to major protocol deviation	

Primary: Randomisation to birth interval	
End point title	Randomisation to birth interval
End point description: Primary outcome was randomisation to birth interval. One week difference in the mean randomisation to birth interval was considered to be clinically important.	
End point type	Primary
End point timeframe: From randomisation to birth	

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	70	65	135	
Units: Days				
median (inter-quartile range (Q1-Q3))	17 (7 to 24)	18 (8 to 28)	18 (7.5 to 27)	

Attachments (see zip file)	Primary outcome according to treatment/Primary outcome Primary outcome - Kaplan-Meier plot /Primary outcome

Statistical analyses	
Statistical analysis title	Analysis of Randomisation to Birth Interval
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.282
Method	Wilcoxon (Mann-Whitney)

Secondary: Neonatal Outcome - Birthweight

End point title	Neonatal Outcome - Birthweight

End point description:

End point type	Secondary

End point timeframe:

At delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	65		
Units: Weight (g)				
arithmetic mean (inter-quartile range (Q1-Q3))	604 (496 to 766)	590 (430 to 842)		

Statistical analyses

Statistical analysis title	Secondary Outcome: Neonatal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.815
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - Intention To Treat (ITT)

Secondary: Neonatal Outcome - NICU Admission Duration

End point title	Neonatal Outcome - NICU Admission Duration

End point description:

End point type	Secondary

End point timeframe:
From delivery to neonatal discharge / death

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	43		
Units: Days				
arithmetic mean (inter-quartile range (Q1-Q3))	25 (10 to 50)	16 (8 to 55)		

Statistical analyses

Statistical analysis title	Secondary Outcome: Neonatal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.684
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Notes:
[2] - Intention To Treat (ITT)

Secondary: Neonatal Outcome - Intracranial Haemorrhage

End point title	Neonatal Outcome - Intracranial Haemorrhage

End point description:

End point type	Secondary

End point timeframe:
From delivery to discharge

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	33		
Units: Yes / No (BInary)	13	8		

Statistical analyses

Statistical analysis title	Secondary Outcome: Neonatal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.75
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.91

Notes:

[3] - Intention To Treat (ITT)

Secondary: Neonatal Outcome - Retinopathy of Prematurity

End point title	Neonatal Outcome - Retinopathy of Prematurity

End point description:

End point type	Secondary

End point timeframe:

From delivery to discharge / death

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	43		
Units: Yes / No (Binary)	6	10		

Statistical analyses

Statistical analysis title	Secondary Outcome: Neonatal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.27
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.36

Notes:

[4] - Intention To Treat (ITT)

Secondary: Neonatal Outcome - Necrotising Enterocolitis

End point title	Neonatal Outcome - Necrotising Enterocolitis

End point description:

End point type	Secondary

End point timeframe:

From delivery to discharge / death

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	43		
Units: Yes / No (Binary)	8	12		

Statistical analyses

Statistical analysis title	Secondary Outcome: Neonatal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.393
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.3

Notes:

[5] - Intention To Treat (ITT)

Secondary: Neonatal Outcome - Ventilator Days

End point title	Neonatal Outcome - Ventilator Days

End point description:

End point type	Secondary

End point timeframe:
From delivery to discharge / death

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	43		
Units: Days				
arithmetic mean (inter-quartile range (Q1-Q3))	7 (2 to 21)	10 (3 to 27)		

Statistical analyses

Statistical analysis title	Secondary Outcome: Neonatal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.576
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	7

Notes:
[6] - Intention To Treat (ITT)

Secondary: Maternal Outcome - Pre-eclampsia

End point title	Maternal Outcome - Pre-eclampsia

End point description:

End point type	Secondary

End point timeframe:
From randomisation to delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	65		
Units: Yes / No (Binary)	15	12		

Statistical analyses

Statistical analysis title	Secondary Outcome: Maternal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.83
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.29

Notes:

[7] - Intention To Treat (ITT)

Secondary: Maternal Outcome - Antenatal Corticosteroids

End point title	Maternal Outcome - Antenatal Corticosteroids

End point description:

End point type	Secondary

End point timeframe:

From randomisation to delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	65		
Units: Yes / No (Binary)	41	37		

Statistical analyses

Statistical analysis title	Secondary Outcome: Maternal
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.862
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.37

Notes:

[8] - Intention To Treat (ITT)

Secondary: Maternal Outcome - Magnesium Sulphate

End point title	Maternal Outcome - Magnesium Sulphate

End point description:

End point type	Secondary

End point timeframe:

At delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	65		
Units: Yes / No (Binary)	40	25		

Statistical analyses

Statistical analysis title	Secondary Outcome: Maternal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.04
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.14

Notes:
[9] - Intention To Treat (ITT)

Secondary: Maternal Outcome - Caesarean Section

End point title	Maternal Outcome - Caesarean Section

End point description:

End point type	Secondary

End point timeframe:
At delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	65		
Units: Yes / No (Binary)	47	43		

Statistical analyses

Statistical analysis title	Secondary Outcome: Maternal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.247
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.29

Notes:
[10] - Intention To Treat (ITT)

Secondary: Fetal Outcome - Umbilical Artery Doppler

End point title	Fetal Outcome - Umbilical Artery Doppler

End point description:

End point type	Secondary

End point timeframe:
From randomisation to delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	47		
Units: Yes / No (Categorical, 3 levels)				
Improvement	5	5		
No change	25	25		
Deterioration	21	17		

Statistical analyses

Statistical analysis title	Secondary Outcome: Fetal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.915
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.88

Notes:

[11] - Intention To Treat (ITT)

Secondary: Fetal Outcome - Ductus Venosus a-wave

End point title	Fetal Outcome - Ductus Venosus a-wave

End point description:

End point type	Secondary

End point timeframe:

From randomisation to delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	42		
Units: Yes / No (Categorical, 3 levels)				
Improvement	0	0		
No change	36	38		

Deterioration	15	4		

Statistical analyses

Statistical analysis title	Secondary Outcome: Fetal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.021
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	3.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	8.6

Notes:

[12] - Intention To Treat (ITT)

Secondary: Fetal Outcome - Middle Cerebral Artery	
End point title	Fetal Outcome - Middle Cerebral Artery
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to delivery	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	40		
Units: Yes / No (Categorical, 3 levels)				
Improvement	4	2		
No change	33	24		
Deterioration	13	14		

Statistical analyses

Statistical analysis title	Secondary Outcome: Fetal
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.65
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.39

Notes:

[13] - Intention To Treat (ITT)

Secondary: Fetal Outcome - Uterine Artery Doppler

End point title	Fetal Outcome - Uterine Artery Doppler

End point description:

End point type	Secondary

End point timeframe:

From randomisation to delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	42		
Units: Yes / No (Categorical, 3 levels)				
Improvement	41	36		
No change	1	3		
Deterioration	3	3		

Statistical analyses

Statistical analysis title	Secondary Outcome: Fetal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.608
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	4.38

Notes:

[14] - Intention To Treat (ITT)

Secondary: Fetal Outcome - Abdominal Circumference Change

End point title	Fetal Outcome - Abdominal Circumference Change

End point description:

End point type	Secondary

End point timeframe:

From randomisation to delivery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	41		
Units: millimetres (mm)				
median (inter-quartile range (Q1-Q3))	14 (6 to 20)	18 (8 to 25)		

Statistical analyses

Statistical analysis title	Secondary Outcome: Fetal
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.449
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	4.5

Notes:

[15] - Intention To Treat (ITT)

Secondary: NEONATAL - Gestation Time

End point title	NEONATAL - Gestation Time

End point description:

Outcome Measures as the estimated time of gestation until delivery.

End point type	Secondary

End point timeframe:

Analysis conducted at the end of the study.

End point values	Arm A	Arm B	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	70	65	135	
Units: Weeks				
median (inter-quartile range (Q1-Q3))	28.1 (26.7 to 29.7)	28.4 (27.3 to 30.1)	28.3 (26.9 to 29.7)	

Statistical analyses

Statistical analysis title	Analysis of Gestation Time
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were recorded by clinicians on an eCRF platform at weekly clinic visits from recruitment to discharge. Participants were encouraged to record any side-effects or AEs that would then be reviewed and documented during each clinical visit

Adverse event reporting additional description:

All Serious Adverse Events (SAE) were reported in accordance with the study specific Pharmacovigilance plan from recruitment to the end of the follow up period. A Development Safety Update Report (DSUR) was submitted annually in line with the Development International Birth Date (DIBD) to the regulatory authorities.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Arm A

Reporting group description:

Experimental arm

Reporting group title	Arm B

Reporting group description:

Standard arm

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 70 (47.14%)	35 / 65 (53.85%)	
number of deaths (all causes)	31	29	
number of deaths resulting from adverse events	2	0	
Pregnancy, puerperium and perinatal conditions			
Congenital, familial & genetic disorder - other			
subjects affected / exposed	1 / 70 (1.43%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac abnormality			
subjects affected / exposed	1 / 70 (1.43%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			

subjects affected / exposed	0 / 70 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage - other (fetal - IVH)			
subjects affected / exposed	1 / 70 (1.43%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture (fetal fracture / osteopenia)			
subjects affected / exposed	0 / 70 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage - other (maternal - antepartum)			
subjects affected / exposed	0 / 70 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal death	Additional description: Please note: all fetal and neonatal deaths were reported as SAEs as per Sponsor requirements, despite being expected within this study population.		
subjects affected / exposed	21 / 70 (30.00%)	22 / 65 (33.85%)	
occurrences causally related to treatment / all	0 / 21	0 / 22	
deaths causally related to treatment / all	0 / 21	0 / 22	
Death neonatal	Additional description: Please note: all fetal and neonatal deaths were reported as SAEs as per Sponsor requirements, despite being expected within this study population.		
subjects affected / exposed	10 / 70 (14.29%)	7 / 65 (10.77%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 10	0 / 7	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 70 (34.29%)	18 / 65 (27.69%)	
Pregnancy, puerperium and perinatal conditions			

Flushing			
subjects affected / exposed	16 / 70 (22.86%)	10 / 65 (15.38%)	
occurrences (all)	29	16	
Other	Additional description: Including nasal congestion, dry mouth and headache.		
subjects affected / exposed	19 / 70 (27.14%)	10 / 65 (15.38%)	
occurrences (all)	31	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2014	STRIDER Protocol Version 3.0 (18/AUG/2014) Main changes from version 2.0: Date: 20/FEB/2014 1. Clarification on reporting of SAE's - section 9.3 2. A list of individual study drug discontinuation criteria included - section 7.3 3. Inclusion of prohibited medications to the exclusion criteria - section 4.2 4. Guidance about concomitant medication has been added with reference to the SmPC - section 7.7 5. Justification as to why only one dose range has been proposed in section 7.1 - rationale for why a dose of 25mg 3 times per day is deemed appropriate has been included 6. Clarification on infant outcomes in fetal, infant and maternal outcomes table - section 6.3.2 7. Additional information added to the Placental sampling studies - section 8.2
07 March 2016	STRIDER Protocol Version 4.0 (03/FEB/2016) Main changes from version 3.0: Date: 18/AUG/2014 1. Change of R&D Lead at LWH - page 3 2. Trial design – patient recruitment figure – 135 - page 8 3. Number of patients - page 9 4. System Failure number for Canada - section 5.3 5. Visit Schedule - section 6.1 6. Vascular profiling, amended wording and clarification for the Angiogenic bloods, placenta biobanking and the cardiovascular assessments - section 8 7. PV – removal of MACRO PV database for sites - section 9.3.1 8. PV – neonatal SAE's clarification on prolonged admission to be recorded on the eCRF as an AE - section 9.3.1 9. PV – removal of LCTU PV system details - section 9.6.1 10. Steps for reporting – addition of date of offset and gestation age etc. - section 9.6.1 11. General Typos/corrections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29282009