Clinical trial results:
A randomised controlled trial of a Synthetic Osmotic cervical dilator for induction of Labour in comparison to dinoprostone Vaginal insErt (SOLVE trial)

Summary

EudraCT number	2016-004726-42
Trial protocol	GB
Global end of trial date	06 February 2021

Results information

Result version number	v1 (current)
This version publication date	28 October 2021
First version publication date	28 October 2021

Trial information

Trial identification

Sponsor protocol code	17/BW/MAT/PO14

Additional study identifiers

ISRCTN number	ISRCTN20131893
ClinicalTrials.gov id (NCT number)	NCT03001661
WHO universal trial number (UTN)	U1111-1189-2757

Notes:

Sponsors

Sponsor organisation name	Birmingham Women's and Children's NHS Foundation Trust
Sponsor organisation address	Steelhouse Lane, Birmingham, United Kingdom, B4 6NH
Public contact	Amanda Cotterill, Birmingham Clinical Trials Unit, University of Birmingham, +44 7795303779, a.cotterill.2@bham.ac.uk
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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	01 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2021
Global end of trial reached?	Yes
Global end of trial date	06 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effectiveness of the synthetic osmotic cervical dilator in cervical ripening, for IoL, in comparison to dinoprostone vaginal insert to achieve vaginal delivery.

Protection of trial subjects:

Trial patients were treated as in normal clinical practice where the insertion of the Dilapan devices was done in a comfortable position, usually on labour ward and legs in lithotomy position. Entonox was given if required for relaxing the women. There was also the availability of analgesia if required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2017
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	United Kingdom: 674
Worldwide total number of subjects	674
EEA total number of subjects	0

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)	8
Adults (18-64 years)	666
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Open to recruitment on 19th December 2017
Suspended 18th March 2020
Re-opened on 17th September 2020: after COVID lockdown restrictions were lifted
Closed to recruitment on 27th January 2021: due to further COVID restrictions
Study ended 6th February 2021

Recruitment target 860
Actual recruitment figure 674
Shortfall of 186 recruit

Pre-assignment

Screening details:

Any adult female who has a singleton pregnancy greater than 37 weeks and is deemed suitable for both mechanical and pharmacological induction of labour will be eligible for inclusion.
8364 were screened for the SOLVE trial, of these 674 were randomised.

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Dilapan-S

Arm description:

DILAPAN-S® is a class IIa medical device. The device is CE marked and available on the market for use wherever cervical softening and dilation are desired.

Arm type	Experimental
Investigational medicinal product name	DILAPAN-S
Investigational medicinal product code	CO3_DSPlen-RevG_09_2019-03
Other name	Dilapan
Pharmaceutical forms	Endocervical gel
Routes of administration	Endocervical use

Dosage and administration details:

First series of Dilapan-S inserted at Baseline.
Removed and second series inserted up to a maximum of 24 hours after baseline.
Second series removed up to a maximum of 24 hours after insertion i.e. each series was up to 24 hours duration

Arm title	Dinoprostone

Arm description:

Slow release 10 mg vaginal drug delivery system (Prostaglandin E2)

Arm type	Active comparator
Investigational medicinal product name	DINOPROSTONE
Investigational medicinal product code	Product code 135 (taken from SmPc)?
Other name	Propess, Prostaglandin E2
Pharmaceutical forms	Pessary, Vaginal delivery system, Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

First series of DINOPROSTONE (10mg) inserted at baseline. Removed up to a maximum of 24 hours after baseline. Second series inserted (10mg) + further 24 hours. This will include any timeframe given in local policies between the 1st and 2nd series for DINOPROSTONE as these may vary

At least 30 minutes should elapse between removal of DINOPROSTONE vaginal insert and initiation of oxytocin therapy.

Number of subjects in period 1	Dilapan-S	Dinoprostone
Started	337	337
Have primary outcome data	337	335
Completed	337	335
Not completed	0	2
Not eligible - randomised in error	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Dilapan-S
Reporting group description:	
DILAPAN-S® is a class IIa medical device. The device is CE marked and available on the market for use wherever cervical softening and dilation are desired.	
Reporting group title	Dinoprostone
Reporting group description:	
Slow release 10 mg vaginal drug delivery system (Prostaglandin E2)	

Reporting group values	Dilapan-S	Dinoprostone	Total
Number of subjects	337	337	674
Age categorical Units: Subjects			
<20	19	19	38
20 to <30	148	150	298
30 to <40	149	147	296
40+	21	21	42
Age continuous			
Maternal age			
Units: years			
arithmetic mean	30.0	29.9	
standard deviation	± 6.1	± 6.2	-
Gender categorical Units: Subjects			
Female	337	337	674
Male	0	0	0
Maternal obesity at first antenatal visit Units: Subjects			
BMI <30	221	219	440
BMI >= 30	116	118	234
Parity Units: Subjects			
Nulliparous	269	272	541
Multiparous	68	65	133
Ethnicity Units: Subjects			
White (British/Irish/other)	223	228	451
Black/Black British (Caribbean/African/other)	33	19	52
Asian/Asian British (Indian/Pakistani/other)	60	63	123
Mixed (White/Black/Asian/other)	6	7	13
Other	14	16	30
Declined to give information	1	1	2
Missing	0	3	3
Post-term pregnancy Units: Subjects			
Yes	120	133	253

No	217	202	419
Missing	0	2	2
Intrauterine growth restriction/oligohydramnios Units: Subjects			
Yes	75	57	132
No	262	278	540
Missing	0	2	2
Reduced fetal movement Units: Subjects			
Yes	73	57	130
No	264	278	542
Missing	0	2	2
Diabetes mellitus/ gestational diabetes Units: Subjects			
Yes	52	45	97
No	285	290	575
Missing	0	2	2
Large for gestational age Units: Subjects			
Yes	42	44	86
No	295	291	586
Missing	0	2	2
Pre-eclampsia Units: Subjects			
Yes	13	18	31
No	324	317	641
Missing	0	2	2
Gestational hypertension Units: Subjects			
Yes	13	11	24
No	324	324	648
Missing	0	2	2
Small for gestational age Units: Subjects			
Yes	16	8	24
No	321	327	648
Missing	0	2	2
Maternal age Units: Subjects			
Yes	11	11	22
No	326	324	650
Missing	0	2	2
Low PAPP-A Units: Subjects			
Yes	10	7	17
No	327	328	655
Missing	0	2	2
Maternal hepatic disease Units: Subjects			
Yes	4	3	7

No	333	332	665
Missing	0	2	2
Elected by mother Units: Subjects			
Yes	3	4	7
No	334	331	665
Missing	0	2	2
Rhesus isoimmunisation /increasing antibody titre Units: Subjects			
Yes	4	1	5
No	333	334	667
Missing	0	2	2
Maternal renal disease Units: Subjects			
Yes	2	2	4
No	335	333	668
Missing	0	2	2
Previous miscarriages Units: Subjects			
None	248	254	502
≥ 1	89	81	170
Missing	0	2	2
Previous termination of pregnancies Units: Subjects			
None	292	300	592
≥ 1	45	35	80
Missing	0	2	2
Previous deliveries >24 weeks Units: Subjects			
No	268	270	538
Yes	69	65	134
Missing	0	2	2
Presence of risk factor for GBS Units: Subjects			
Yes	25	31	56
No	312	304	616
Missing	0	2	2
Bishop score on initiation of cervical ripening ≥ 6 Units: Subjects			
Yes	53	49	102
No	284	287	571
Missing	0	1	1
Randomising centre Units: Subjects			
Birmingham Women’s Hospital	234	236	470
City Hospital Birmingham	30	33	63
Heartlands	35	34	69
Princess Royal Hospital Telford	38	34	72

BMI			
BMI continous			
Units: kilogram(s)/square meter			
arithmetic mean	28.4	28.1	
standard deviation	± 6.6	± 6.6	-
Weight at booking antenatal visit			
Units: kilogram(s)			
arithmetic mean	76.4	75.2	
standard deviation	± 19.3	± 18.5	-
Height			
Units: centimeter			
arithmetic mean	164.0	163.6	
standard deviation	± 7.1	± 6.7	-

End points

End points reporting groups

Reporting group title	Dilapan-S
Reporting group description:	
DILAPAN-S® is a class IIa medical device. The device is CE marked and available on the market for use wherever cervical softening and dilation are desired.	
Reporting group title	Dinoprostone
Reporting group description:	
Slow release 10 mg vaginal drug delivery system (Prostaglandin E2)	

Primary: Primary: Failure to achieve vaginal delivery (caesarean section)

End point title	Primary: Failure to achieve vaginal delivery (caesarean section)
End point description:	
Where 'Yes' indicates a caesarean section or a vaginal delivery after the time frame specified	
End point type	Primary
End point timeframe:	
Baseline / birth	

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[1]		
Units: Binary (Yes/ No)				
Yes	126	115		
No	211	220		

Notes:

[1] - 2 women are missing primary outcome data

Statistical analyses

Statistical analysis title	Failure to achieve vaginal delivery
Statistical analysis description:	
Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects, where DINOPROSTONE is the reference category and a risk ratio value <1 favours DILAPAN-S.	

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.35

Secondary: Secondary: Change in bishop score from baseline to completion of cervical ripening

End point title	Secondary: Change in bishop score from baseline to completion of cervical ripening

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[2]	282[3]		
Units: Bishop score				
arithmetic mean (standard deviation)	3.2 (± 2.3)	3.6 (± 2.7)		

Notes:

[2] - 61 women were missing outcome data

[3] - 55 women do not have outcome data

Statistical analyses

Statistical analysis title	Change in bishop score from baseline to completion

Statistical analysis description:

Mean differences < 0 favour DILAPAN-S

Mean difference is estimated using a mixed effects linear regression adjusted for Bishop score in addition to minimisation variables (age, BMI and parity) and randomising centre as a random effect.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	558
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.18

Secondary: Secondary: Time between Bishop scores measured at baseline and completion of cervical ripening (hours)

End point title	Secondary: Time between Bishop scores measured at baseline and completion of cervical ripening (hours)

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287[4]	282[5]		
Units: hour				
arithmetic mean (standard deviation)	30.5 (± 28.7)	30.6 (± 23.5)		

Notes:

[4] - 50 missing outcome

[5] - 45 missing outcome

Statistical analyses

Statistical analysis title	Time between Bishop scores

Statistical analysis description:

The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum) and is used for summarising skewed data. Comparative analysis uses a ratio of the geometric means.

Geometric mean ratios <1 favour DILAPAN-S®.

The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimisation variables and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.987
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.15

Secondary: Secondary: Use of analgesia during cervical ripening

End point title	Secondary: Use of analgesia during cervical ripening

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[6]	332[7]		
Units: Binary (Yes/No)				
Yes	170	220		
No	162	112		

Notes:

[6] - 5 women are missing outcome data

[7] - 5 women are missing outcome data

Statistical analyses

Statistical analysis title	Use of analgesia during cervical ripening

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	664
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.87

Secondary: Secondary: Time between randomisation and start of analgesia use for cervical ripening

End point title	Secondary: Time between randomisation and start of analgesia use for cervical ripening

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[8]	219[9]		
Units: hour				
arithmetic mean (standard deviation)	15.0 (± 24.5)	15.3 (± 14.1)		

Notes:

[8] - 8 women are missing outcome data
162 women did not use analgesia

[9] - 6 women are missing outcome data
112 women did not use analgesia

Statistical analyses

Statistical analysis title	Time between randomisation and start of analgesia

Statistical analysis description:

The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum) and is used for summarising skewed data. Comparative analysis uses a ratio of the geometric means.

Geometric mean ratios <1 favour DILAPAN-S®.

The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimisation variables and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.62

Secondary: Secondary: Any complications during cervical ripening

End point title	Secondary: Any complications during cervical ripening

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	333[10]	327[11]		
Units: Binary (Yes/No)				
Yes	35	66		
No	298	261		

Notes:

[10] - 4 women are missing outcome data

[11] - 10 women are missing outcome data

Statistical analyses

Statistical analysis title	Any complications during cervical ripening

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.
Risk ratio is estimated using a mixed poisson model with a log link adjusting for age, BMI and parity as fixed effects, and randomising centre as a random effect.

Comparison groups	Dinoprostone v Dilapan-S
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.79

Secondary: Secondary: Time between removal of last series of intervention to amniotomy

End point title	Secondary: Time between removal of last series of intervention to amniotomy

End point description:

Amniotomy undertaken for induction of labour only.

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[12]	118[13]		
Units: hour				
arithmetic mean (standard deviation)	30.3 (± 28.6)	30.9 (± 35.7)		

Notes:

[12] - 34 women missing outcome data.
100 women did not have amniotomy for induction performed

[13] - 29 women are missing outcome data
190 women did not have amniotomy for induction performed

Statistical analyses

Statistical analysis title	Time between removal of last series to amniotomy

Statistical analysis description:

The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum) and is used for summarising skewed data. Comparative analysis uses a ratio of the geometric means.

Geometric mean ratios <1 favour DILAPAN-S®.

The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimisation variables and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.633
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.49

Secondary: Secondary: Time between first insertion of intervention to when labour started

End point title	Secondary: Time between first insertion of intervention to when labour started

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257[14]	258[15]		
Units: hour				
arithmetic mean (standard deviation)	54.8 (± 33.8)	48.1 (± 37.9)		

Notes:

[14] - 80 women missing outcome data

[15] - 79 women missing outcome data

Statistical analyses

Statistical analysis title	Time between insertion of intervention to labour

Statistical analysis description:

The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum) and is used for summarising skewed data. Comparative analysis uses a ratio of the geometric means.

Geometric mean ratios <1 favour DILAPAN-S®.

The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimisation variables and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.52

Secondary: Secondary: Amniotomy undertaken for induction of labour

End point title	Secondary: Amniotomy undertaken for induction of labour

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[16]	331[17]		
Units: Binary (Yes/No)				
Yes	235	141		
No	100	190		

Notes:

[16] - 2 women are missing outcome data

[17] - 6 women are missing outcome data

Statistical analyses

Statistical analysis title	Amniotomy undertaken for induction of labour

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	1.89

Secondary: Secondary: Amniotomy undertaken for augmentation of labour

End point title	Secondary: Amniotomy undertaken for augmentation of labour

End point description:

End point type	Secondary

End point timeframe:

Induction of labour process

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336[18]	331[19]		
Units: Binary (Yes/No)				
Yes	15	25		
No	321	306		

Notes:
[18] - 1 woman is missing outcome data
[19] - 6 women are missing outcome data

Statistical analyses

Statistical analysis title	Amniotomy undertaken for augmentation of labour

Statistical analysis description:
DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	667
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.08

Secondary: Secondary: Required oxytocin for induction of labour

End point title	Secondary: Required oxytocin for induction of labour

End point description:

End point type	Secondary

End point timeframe:
Induction of labour process

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[20]	331[21]		
Units: Binary (Yes/No)				
Yes	210	130		
No	125	201		

Notes:
[20] - 2 women are missing outcome data
[21] - 6 women are missing outcome data

Statistical analyses

Statistical analysis title	Required oxytocin for induction of labour

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	1.99

Secondary: Secondary: Required oxytocin for augmentation of labour

End point title	Secondary: Required oxytocin for augmentation of labour

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336[22]	331[23]		
Units: Binary (Yes/No)				
Yes	25	43		
No	311	288		

Notes:

[22] - 1 women is missing outcome data

[23] - 6 women are missing outcome data

Statistical analyses

Statistical analysis title	Required oxytocin for augmentation of labour

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	667
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.91

Secondary: Secondary: Use of analgesia/anaesthesia during labour

End point title	Secondary: Use of analgesia/anaesthesia during labour

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334[24]	333[25]		
Units: Binary (Yes/No)				
Yes	299	278		
No	35	55		

Notes:

[24] - 3 women are missing outcome data

[25] - 4 women are missing outcome data

Statistical analyses

Statistical analysis title	Use of analgesia / anaesthesia during labour

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone

Number of subjects included in analysis	667
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [26]
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.13

Notes:

[26] - DINOPROSTONE is the reference category and risk differences < 0 favour DILAPAN-S®. Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Secondary: Secondary: Any complications during or after labour

End point title	Secondary: Any complications during or after labour

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[27]		
Units: Binary (Yes/No)				
Yes	249	244		
No	88	91		

Notes:

[27] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Any complications during or after labour

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.931 [28]
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.1

Notes:

[28] - DINOPROSTONE is the reference category and risk differences < 0 favour DILAPAN-S®. Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Secondary: Secondary: Failure to achieve vaginal delivery within 24 hours from randomisation

End point title	Secondary: Failure to achieve vaginal delivery within 24 hours from randomisation

End point description:

Where 'Yes' indicates a caesarean section or a vaginal delivery after the time frame specified

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[29]		
Units: Binary (Yes/No)				
Yes	306	272		
No	31	63		

Notes:

[29] - 2 women are missing primary outcome data

Statistical analyses

Statistical analysis title	Failure to achieve vaginal delivery within 24hours

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.0002
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.18

Notes:

[30] - DINOPROSTONE is the reference category and risk differences < 0 favour DILAPAN-S®. Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Secondary: Secondary: Failure to achieve vaginal delivery within 36 hours from randomisation

End point title	Secondary: Failure to achieve vaginal delivery within 36 hours from randomisation

End point description:

Where 'Yes' indicates a caesarean section or a vaginal delivery after the time frame specified

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[31]		
Units: Binary (Yes/No)				
Yes	273	232		
No	64	103		

Notes:

[31] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Failure to achieve vaginal delivery within 36hours

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a mixed poisson model with a log link adjusting for age, BMI and parity as fixed effects, and randomising centre as a random effect.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.39

Secondary: Secondary: Failure to achieve vaginal delivery within 48 hours from randomisation

End point title	Secondary: Failure to achieve vaginal delivery within 48 hours from randomisation

End point description:

Where 'Yes' indicates a caesarean section or a vaginal delivery after the time frame specified

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[32]		
Units: Binary (Yes/No)				
Yes	232	200		
No	105	135		

Notes:

[32] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Failure to achieve vaginal delivery within 48hours

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a mixed poisson model with a log link adjusting for age, BMI and parity as fixed effects, and randomising centre as a random effect.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.39

Secondary: Secondary: Spontaneous vaginal delivery

End point title	Secondary: Spontaneous vaginal delivery

End point description:

End point type	Secondary

End point timeframe:

Baseline/ birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[33]		
Units: Binary (Yes/No)				
Yes	129	133		
No	208	202		

Notes:

[33] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Spontaneous vaginal delivery

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DINOPROSTONE .

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dinoprostone v Dilapan-S
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.505
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.12

Secondary: Secondary: Instrumental delivery due to delay in 2nd stage of labour and/or fetal heart rate abnormalities and/or abnormal FBS

End point title	Secondary: Instrumental delivery due to delay in 2nd stage of labour and/or fetal heart rate abnormalities and/or abnormal FBS

End point description:

End point type	Secondary

End point timeframe:

Baseline/ birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	334[34]		
Units: Binary (Yes/No)				
Yes	71	74		
No	266	260		

Notes:

[34] - 3 women are missing outcome data

Statistical analyses

Statistical analysis title	Instrumental delivery

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.858
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.29

Secondary: Secondary: Caesarean section delivery due to delay in 1st and/or 2nd stage of labour, and/or fetal heart rate abnormalities and/or abnormal FBS

End point title	Secondary: Caesarean section delivery due to delay in 1st and/or 2nd stage of labour, and/or fetal heart rate abnormalities and/or abnormal FBS

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335		
Units: Binary (Yes/No)				
Yes	96	74		
No	241	261		

Statistical analyses

Statistical analysis title	Caesarean section delivery

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.7

Secondary: Secondary: Complications from delivery until discharge

End point title	Secondary: Complications from delivery until discharge

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[35]		
Units: Binary (Yes/No)				
Yes	74	69		
No	263	266		

Notes:
[35] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Complications from delivery until discharge

Statistical analysis description:
DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.648
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.43

Secondary: Secondary: Antibiotic use for pelvic infection

End point title	Secondary: Antibiotic use for pelvic infection

End point description:

End point type	Secondary

End point timeframe:
Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[36]		
Units: Binary (Yes/No)				
Yes	3	2		
No	334	333		

Notes:
[36] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Antibiotic use for pelvic infection

Statistical analysis description:

DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI and parity as fixed effects.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	9.37

Secondary: Secondary: Duration of antibiotic use for pelvic infection

End point title	Secondary: Duration of antibiotic use for pelvic infection

End point description:

No statistical analysis calculated as number of women with this outcome is so small.

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[37]	2[38]		
Units: day				
arithmetic mean (standard deviation)	6.3 (± 4.6)	4.0 (± 2.8)		

Notes:

[37] - Only 3 women have used antibiotics for pelvic infection

[38] - Only 2 women have used antibiotics for pelvic infection

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Length of stay from randomisation

End point title	Secondary: Length of stay from randomisation

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[39]		
Units: day				
arithmetic mean (standard deviation)	4.7 (± 2.4)	4.7 (± 3.0)		

Notes:

[39] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Length of stay from randomisation

Statistical analysis description:

The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum) and is used for summarising skewed data. Comparative analysis uses a ratio of the geometric means.

Geometric mean ratios <1 favour DILAPAN-S®.

The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimisation variables and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.15

Secondary: Secondary: Baby born alive

End point title	Secondary: Baby born alive

End point description:

No statistical analysis conducted as all babies were born alive.

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[40]		
Units: Binary (Yes/No)				
Yes	337	335		
No	0	0		

Notes:

[40] - 2 women are missing outcome data

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: APGAR score at 1 minute

End point title	Secondary: APGAR score at 1 minute

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336[41]	334[42]		
Units: APGAR score				
arithmetic mean (standard deviation)	8.4 (± 1.5)	8.3 (± 1.5)		

Notes:

[41] - 1 women has no outcome data recorded

[42] - 3 women have no outcome data recorded

Statistical analyses

Statistical analysis title	APGAR score at 1 minute

Statistical analysis description:

Median differences < 0 favour DINOPROSTONE.

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	670
Analysis specification	Pre-specified
Analysis type	superiority
Method	Bootstrapping methods
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Secondary: APGAR score at 5 minutes

End point title	Secondary: APGAR score at 5 minutes

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334[43]	333[44]		
Units: APGAR score				
arithmetic mean (standard deviation)	9.2 (± 0.7)	9.4 (± 1.5)		

Notes:

[43] - 3 women are missing outcome data

[44] - 4 woman have missing outcome data

Statistical analyses

Statistical analysis title	APGAR score at 5 minutes

Statistical analysis description:

Median differences < 0 favour DINOPROSTONE

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	667
Analysis specification	Pre-specified
Analysis type	superiority
Method	Bootstrapping methods
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Secondary: APGAR score at 10 minutes

End point title	Secondary: APGAR score at 10 minutes

End point description:

End point type	Secondary

End point timeframe:
Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[45]	57[46]		
Units: APGAR score				
arithmetic mean (standard deviation)	9.7 (± 0.7)	9.4 (± 1.5)		

Notes:
[45] - 288 women have not recorded outcome data
[46] - 280 women do not have outcome data recorded

Statistical analyses

Statistical analysis title	APGAR score at 10 minutes

Statistical analysis description:
Median differences < 0 favour DINOPROSTONE

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Bootstrapping methods
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.17

Secondary: Secondary: Meconium staining noted

End point title	Secondary: Meconium staining noted

End point description:

End point type	Secondary

End point timeframe:
Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336[47]	335[48]		
Units: Binary (Yes/ No)				
Yes	46	44		
No	290	291		

Notes:

[47] - 1 woman is missing outcome data

[48] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Meconium staining noted

Statistical analysis description:

Where DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratios are estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.897
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.5

Secondary: Secondary: Metabolic acidosis

End point title	Secondary: Metabolic acidosis

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147[49]	156[50]		
Units: Binary (Yes/No)				
Yes	14	10		
No	133	146		

Notes:

[49] - 190 women are missing outcome data

[50] - 181 women are missing outcome data

Statistical analyses

Statistical analysis title	Metabolic acidosis

Statistical analysis description:

Where DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratios are estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.613
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.39

Secondary: Secondary: Requirement of review by doctor from neonatal team

End point title	Secondary: Requirement of review by doctor from neonatal team

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[51]		
Units: Binary (Yes/No)				
Yes	123	124		
No	214	211		

Notes:
[51] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Requirement of review by doctor from neonatal team

Statistical analysis description:
Where DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratios are estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.18

Secondary: Secondary: Duration of antibiotic use for neonatal

End point title	Secondary: Duration of antibiotic use for neonatal

End point description:

End point type	Secondary

End point timeframe:
Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[52]	60[53]		
Units: day				
arithmetic mean (standard deviation)	3.6 (± 2.1)	4.3 (± 1.6)		

Notes:
[52] - 1 woman is missing primary outcome data
276 women had no antibiotic use for neonatal infection
[53] - 2 woman is missing primary outcome data
275 women had no antibiotic use for neonatal infection

Statistical analyses

Statistical analysis title	Duration of antibiotic use for neonatal infection

Statistical analysis description:

The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum) and is used for summarising skewed data. Comparative analysis uses a ratio of the geometric means.

Geometric mean ratios <1 favour DILAPAN-S®.

The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimisation variables and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.95

Secondary: Secondary: Admitted to neonatal unit

End point title	Secondary: Admitted to neonatal unit

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[54]		
Units: Binary (Yes/No)				
Yes	45	45		
No	292	290		

Notes:

[54] - 2 women missing outcome data

Statistical analyses

Statistical analysis title	Admitted to neonatal unit

Statistical analysis description:

Where DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratios are estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.44

Secondary: Length of stay in neonatal unit

End point title	Length of stay in neonatal unit

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[55]	45[56]		
Units: day				
arithmetic mean (standard deviation)	5.2 (± 9.1)	3.5 (± 3.5)		

Notes:

[55] - 292 women's babies were not admitted to the neonatal unit

[56] - 290 women's babies were not admitted to the neonatal unit

Statistical analyses

Statistical analysis title	Length of stay in neonatal unit

Statistical analysis description:

The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum) and is used for summarising skewed data. Comparative analysis uses a ratio of the geometric means.

Geometric mean ratios <1 favour DILAPAN-S®.

The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimisation variables and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.05

Secondary: Secondary: Antibiotic use for neonatal infection

End point title	Secondary: Antibiotic use for neonatal infection

End point description:

End point type	Secondary

End point timeframe:

Baseline / birth

End point values	Dilapan-S	Dinoprostone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	335[57]		
Units: Binary (Yes/No)				
Yes	60	60		
No	277	275		

Notes:

[57] - 2 women are missing outcome data

Statistical analyses

Statistical analysis title	Antibiotic use for neonatal infection

Statistical analysis description:

Where DINOPROSTONE is the reference category and risk ratio values <1 favour DILAPAN-S.

Risk ratios are estimated using a mixed binomial model with a log link adjusting for age, BMI and parity and randomising centre as a random effect

Comparison groups	Dilapan-S v Dinoprostone
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.889
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.35

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events will be collected from trial intervention to discharge with the exception of any ongoing adverse events post-discharge, which will be collected up to resolution of the event.

Adverse event reporting additional description:

AEs are commonly encountered in participants receiving Dinoprostone vaginal insert and Dilapan-S. With the safety profiles for both interventions used in this trial being well characterised.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5

Reporting groups

Reporting group title	Dilapan-S

Reporting group description:

DILAPAN-S® is a class IIa medical device. The device is CE marked and available on the market for use wherever cervical softening and dilation are desired.

Reporting group title	Dinoprostone

Reporting group description:

Slow release 10 mg vaginal drug delivery system (Prostaglandin E2)

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: All adverse events are reported as serious

Serious adverse events	Dilapan-S	Dinoprostone	
Total subjects affected by serious adverse events			
subjects affected / exposed	97 / 337 (28.78%)	109 / 337 (32.34%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Missing adverse event details			
subjects affected / exposed	4 / 337 (1.19%)	5 / 337 (1.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Raised CRP levels			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arihythmias neonatal			

subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid and mitral regurgitation			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia neonatal			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (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			
Bowel injury caused at c-section			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chorioamnionitis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum haemorrhage			
subjects affected / exposed	32 / 337 (9.50%)	25 / 337 (7.42%)	
occurrences causally related to treatment / all	0 / 32	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic haematoma			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placental abruption			
subjects affected / exposed	1 / 337 (0.30%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			

subjects affected / exposed	1 / 337 (0.30%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raised temperature			
subjects affected / exposed	1 / 337 (0.30%)	4 / 337 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia and raised temperature			
subjects affected / exposed	3 / 337 (0.89%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilicous vomit neonatal			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cleft lip			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal tachycardia and raised temperature			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia neonatal			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 337 (0.00%)	2 / 337 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium aspiration syndrome			

subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolonged hospital stay neonatal			
subjects affected / exposed	0 / 337 (0.00%)	3 / 337 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raised temperature neonatal			
subjects affected / exposed	0 / 337 (0.00%)	3 / 337 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Baby lost more than 10% birthweight			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe asphyxia, sepsis, hypertension and hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Suspected Neuropraxia			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizures neonatal			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss			
subjects affected / exposed	2 / 337 (0.59%)	2 / 337 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis / suspected sepsis			
subjects affected / exposed	20 / 337 (5.93%)	21 / 337 (6.23%)	
occurrences causally related to treatment / all	0 / 20	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanotic episodes neonatal			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal jaundice			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis / suspected sepsis neonatal			
subjects affected / exposed	11 / 337 (3.26%)	17 / 337 (5.04%)	
occurrences causally related to treatment / all	0 / 11	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Prolonged hospital stay			
subjects affected / exposed	2 / 337 (0.59%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transferred to NNU			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (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			

Pulmonary embolism			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital pneumonia			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pnemothorax neonatal			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disease neonatal			
subjects affected / exposed	1 / 337 (0.30%)	3 / 337 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress neonatal			
subjects affected / exposed	4 / 337 (1.19%)	9 / 337 (2.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest infection neonatal			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal hypertension			
subjects affected / exposed	0 / 337 (0.00%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 337 (0.30%)	1 / 337 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine inversion			

subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (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			
Klebsiella Pneumoniae neonatal			
subjects affected / exposed	1 / 337 (0.30%)	0 / 337 (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: 0 %

Non-serious adverse events	Dilapan-S	Dinoprostone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 337 (0.00%)	0 / 337 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2017	Protocol 1) Change to inclusion and exclusion criteria 2) Change to outcomes 3) Changes to minimisation e.g. data to remove inpatient vs outpatient 4) Changes to adverse events and serious adverse events definitions 5) Update to Propess SmPC to January 2017 version 6) Removal of option for BCTU data entry 7) End of trial definition – extension of timeline 8) Changes to statistical considerations Patient Information Sheet 9) Addition of 'or equivalent' to the PALS details for those sites without a Patient Advice and Liaison Service 10) Explanation of when Propess is usually used 11) More information on the chance of receiving Oxytocin 12) Explicit mention of outpatient possibilities removed 13) Clarification on organisation of the study Maternal Satisfaction Questionnaire 14) Removal of allocation tick boxes 15) Addition of sentence requesting patient to complete the form for the first intervention received if they had both
20 April 2018	Protocol 1. Addition of email address for SAEs (administrative information) 2. Removal of bishop score in eligibility 3. Removal of USS dates in eligibility 4. Update of eligibility/ineligibility to schema 5. Addition of table of responsibilities
02 August 2018	The following modifications have been made to the protocol: Amendment to DILAPAN-S dosing schedule Removal of the need for CTG monitoring Removal of the use of iodine for cervical cleansing Amendment to Discontinuation of intervention Amendment to Withdrawal and re-confirmation of consent Addition of definitions of reportable SAEs and protocol-exempt SAEs not requiring reporting on a SAE form Removal of Sections 7.4-7.6 re CRF completion Inclusion of Investigators Brochure for Dilapan-S Minor typographical amendments and points of clarification

04 December 2019	The following modifications have been made to the Protocol: Minor formatting and typographical changes Change in Funder's organisational details Change in Sponsor Representative details Change in Trial Co-ordinator details Addition of PI signature page Removal of fax number and its use Change in Team Management Leader and contact email Change of primary objective and outcome to remove time limitation of 36 hours Change of name for PROPESS TO DINOPROSTONE Change of info collected on screening log from mothers hospital number and dob to mothers initials and age. Addition of secondary outcome "Failure to achieve vaginal delivery within 36 hours of randomisation. Clarification of Adverse Event reporting procedure and SAE definitions None related protocol changes : o Extension to 31st December 2020 o Inclusion of Reference Safety Information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 February 2021	Opened to recruitment 19th December 2017 Halted due to the Covid Pandemic 18th March 2021 Reopened to recruitment 17th September Recruitment ended 27th January 2021 Study Closure 6th February 2021	-

Notes:

Limitations and caveats

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

Unable to meet the original recruitment target and ended the study earlier than expected due to funding issues and the impact of the pandemic.

Notes: