



## 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 |
| Scientific contact           | Amanda Cotterill, Birmingham Clinical Trials Unit, University of Birmingham, +44 7795303779, a.cotterill.2@bham.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                       | 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       |
| <b>Arm title</b>             | 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

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | 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                                      |

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**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.

| <b>Number of subjects in period 1</b> | 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:<br>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:<br>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<br>(Caribbean/African/other) | 33        | 19           | 52    |
| Asian/Asian British<br>(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<br>Units: Subjects |     |     |     |
| Yes  | 75  | 57  | 132 |
| No   | 262 | 278 | 540 |
| Missing  | 0   | 2   | 2   |
| Reduced fetal movement<br>Units: Subjects                          |     |     |     |
| Yes  | 73  | 57  | 130 |
| No   | 264 | 278 | 542 |
| Missing  | 0   | 2   | 2   |
| Diabetes mellitus/ gestational diabetes<br>Units: Subjects         |     |     |     |
| Yes  | 52  | 45  | 97  |
| No   | 285 | 290 | 575 |
| Missing  | 0   | 2   | 2   |
| Large for gestational age<br>Units: Subjects                       |     |     |     |
| Yes  | 42  | 44  | 86  |
| No   | 295 | 291 | 586 |
| Missing  | 0   | 2   | 2   |
| Pre-eclampsia<br>Units: Subjects                                   |     |     |     |
| Yes  | 13  | 18  | 31  |
| No   | 324 | 317 | 641 |
| Missing  | 0   | 2   | 2   |
| Gestational hypertension<br>Units: Subjects                        |     |     |     |
| Yes  | 13  | 11  | 24  |
| No   | 324 | 324 | 648 |
| Missing  | 0   | 2   | 2   |
| Small for gestational age<br>Units: Subjects                       |     |     |     |
| Yes  | 16  | 8   | 24  |
| No   | 321 | 327 | 648 |
| Missing  | 0   | 2   | 2   |
| Maternal age<br>Units: Subjects                                    |     |     |     |
| Yes  | 11  | 11  | 22  |
| No   | 326 | 324 | 650 |
| Missing  | 0   | 2   | 2   |
| Low PAPP-A<br>Units: Subjects                                      |     |     |     |
| Yes  | 10  | 7   | 17  |
| No   | 327 | 328 | 655 |
| Missing  | 0   | 2   | 2   |
| Maternal hepatic disease<br>Units: Subjects                        |     |     |     |
| Yes  | 4   | 3   | 7   |

|   |     |     |     |
|---|-----|-----|-----|
| No  | 333 | 332 | 665 |
| Missing   | 0   | 2   | 2   |
| Elected by mother<br>Units: Subjects                                      |     |     |     |
| Yes   | 3   | 4   | 7   |
| No  | 334 | 331 | 665 |
| Missing   | 0   | 2   | 2   |
| Rhesus isoimmunisation /increasing<br>antibody titre<br>Units: Subjects   |     |     |     |
| Yes   | 4   | 1   | 5   |
| No  | 333 | 334 | 667 |
| Missing   | 0   | 2   | 2   |
| Maternal renal disease<br>Units: Subjects                                 |     |     |     |
| Yes   | 2   | 2   | 4   |
| No  | 335 | 333 | 668 |
| Missing   | 0   | 2   | 2   |
| Previous miscarriages<br>Units: Subjects                                  |     |     |     |
| None  | 248 | 254 | 502 |
| ≥ 1   | 89  | 81  | 170 |
| Missing   | 0   | 2   | 2   |
| Previous termination of pregnancies<br>Units: Subjects                    |     |     |     |
| None  | 292 | 300 | 592 |
| ≥ 1   | 45  | 35  | 80  |
| Missing   | 0   | 2   | 2   |
| Previous deliveries >24 weeks<br>Units: Subjects                          |     |     |     |
| No  | 268 | 270 | 538 |
| Yes   | 69  | 65  | 134 |
| Missing   | 0   | 2   | 2   |
| Presence of risk factor for GBS<br>Units: Subjects                        |     |     |     |
| Yes   | 25  | 31  | 56  |
| No  | 312 | 304 | 616 |
| Missing   | 0   | 2   | 2   |
| Bishop score on initiation of cervical<br>ripening ≥ 6<br>Units: Subjects |     |     |     |
| Yes   | 53  | 49  | 102 |
| No  | 284 | 287 | 571 |
| Missing   | 0   | 1   | 1   |
| Randomising centre<br>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 continuous                    |        |        |   |
| 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:<br>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:<br>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:<br>Where 'Yes' indicates a caesarean section or a vaginal delivery after the time frame specified |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline / birth   |  |

| End point values            | Dilapan-S       | Dinoprostone       |  |  |
|-----------------------------|-----------------|--------------------|--|--|
| Subject group type          | Reporting group | Reporting group    |  |  |
| Number of subjects analysed | 337             | 335 <sup>[1]</sup> |  |  |
| 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:<br>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 <sup>[2]</sup> | 282 <sup>[3]</sup> |  |  |
| 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 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  |

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

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|                 |  |
|-----------------|--|
| 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 <sup>[4]</sup> | 282 <sup>[5]</sup> |  |  |
| 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 <sup>[6]</sup> | 332 <sup>[7]</sup> |  |  |
| 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**

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[8]</sup> | 219 <sup>[9]</sup> |  |  |
| 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

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[10]</sup> | 327 <sup>[11]</sup> |  |  |
| 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 <sup>[12]</sup> | 118 <sup>[13]</sup> |  |  |
| 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 <sup>[14]</sup> | 258 <sup>[15]</sup> |  |  |
| 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 <sup>[16]</sup> | 331 <sup>[17]</sup> |  |  |
| 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 <sup>[18]</sup> | 331 <sup>[19]</sup> |  |  |
| 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

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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

|                             |                     |                     |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| <b>End point values</b>     | Dilapan-S           | Dinoprostone        |  |  |
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 335 <sup>[20]</sup> | 331 <sup>[21]</sup> |  |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Required oxytocin for induction of labour |
| Statistical analysis description:<br>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       |   |

|                             |                     |                     |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| <b>End point values</b>     | Dilapan-S           | Dinoprostone        |  |  |
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 336 <sup>[22]</sup> | 331 <sup>[23]</sup> |  |  |
| 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

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Required oxytocin for augmentation of labour |
| Statistical analysis description:<br>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 <sup>[24]</sup> | 333 <sup>[25]</sup> |  |  |
| 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 <sup>[26]</sup> |
| 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 <sup>[27]</sup> |  |  |
| 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 <sup>[28]</sup>                  |
| 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 <sup>[29]</sup> |  |  |
| 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 <sup>[30]</sup>                        |
| 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 <sup>[31]</sup> |  |  |
| 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:<br>Where 'Yes' indicates a caesarean section or a vaginal delivery after the time frame specified |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline / birth   |   |

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

Notes:

[32] - 2 women are missing outcome data

### Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Failure to achieve vaginal delivery within 48hours |
| Statistical analysis description:<br>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:<br>Baseline/ birth |   |

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

Notes:

[33] - 2 women are missing outcome data

## Statistical analyses

| <b>Statistical analysis title</b> | 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 <sup>[34]</sup> |  |  |
| 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 <sup>[35]</sup> |  |  |
| Units: Binary (Yes/No)      |                 |                     |  |  |
| Yes                         | 74              | 69                  |  |  |
| No                          | 263             | 266                 |  |  |

Notes:

[35] - 2 women are missing outcome data

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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

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

Notes:

[36] - 2 women are missing outcome data

## Statistical analyses

|  |                                     |
|--|-------------------------------------|
| <b>Statistical analysis title</b>  | Antibiotic use for pelvic infection |
| Statistical analysis description:<br>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:<br>No statistical analysis calculated as number of women with this outcome is so small. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline / birth   |  |

|                                      |                   |                   |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| <b>End point values</b>              | Dilapan-S         | Dinoprostone      |  |  |
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 3 <sup>[37]</sup> | 2 <sup>[38]</sup> |  |  |
| 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 <sup>[39]</sup> |  |  |
| 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 <sup>[40]</sup> |  |  |
| 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 <sup>[41]</sup> | 334 <sup>[42]</sup> |  |  |
| Units: APGAR score                   |                     |                     |  |  |
| arithmetic mean (standard deviation) | 8.4 ( $\pm$ 1.5)    | 8.3 ( $\pm$ 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 <sup>[43]</sup> | 333 <sup>[44]</sup> |  |  |
| 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

|  |                                  |
|--|----------------------------------|
| <b>Statistical analysis title</b>          | 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 <sup>[45]</sup> | 57 <sup>[46]</sup> |  |  |
| 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 <sup>[47]</sup> | 335 <sup>[48]</sup> |  |  |
| 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 <sup>[49]</sup> | 156 <sup>[50]</sup> |  |  |
| 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 <sup>[51]</sup> |  |  |
| Units: Binary (Yes/No)      |                 |                     |  |  |
| Yes                         | 123             | 124                 |  |  |
| No                          | 214             | 211                 |  |  |

Notes:

[51] - 2 women are missing outcome data

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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

|                                      |                    |                    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| <b>End point values</b>              | Dilapan-S          | Dinoprostone       |  |  |
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 60 <sup>[52]</sup> | 60 <sup>[53]</sup> |  |  |
| 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

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[54]</sup> |  |  |
| Units: Binary (Yes/No)      |                 |                     |  |  |
| Yes                         | 45              | 45                  |  |  |
| No                          | 292             | 290                 |  |  |

Notes:

[54] - 2 women missing outcome data

## Statistical analyses

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[55]</sup> | 45 <sup>[56]</sup> |  |  |
| 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 <sup>[57]</sup> |  |  |
| 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<sup>[1]</sup>

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           |  |
| Bilious 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           |  |
| Pneumothorax 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 %

| <b>Non-serious adverse events</b>                     | 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 | <p>Protocol</p> <ol style="list-style-type: none"> <li>1) Change to inclusion and exclusion criteria</li> <li>2) Change to outcomes</li> <li>3) Changes to minimisation e.g. data to remove inpatient vs outpatient</li> <li>4) Changes to adverse events and serious adverse events definitions</li> <li>5) Update to Propess SmPC to January 2017 version</li> <li>6) Removal of option for BCTU data entry</li> <li>7) End of trial definition – extension of timeline</li> <li>8) Changes to statistical considerations</li> </ol> <p>Patient Information Sheet</p> <ol style="list-style-type: none"> <li>9) Addition of 'or equivalent' to the PALS details for those sites without a Patient Advice and Liaison Service</li> <li>10) Explanation of when Propess is usually used</li> <li>11) More information on the chance of receiving Oxytocin</li> <li>12) Explicit mention of outpatient possibilities removed</li> <li>13) Clarification on organisation of the study</li> </ol> <p>Maternal Satisfaction Questionnaire</p> <ol style="list-style-type: none"> <li>14) Removal of allocation tick boxes</li> <li>15) Addition of sentence requesting patient to complete the form for the first intervention received if they had both</li> </ol> |
| 20 April 2018   | <p>Protocol</p> <ol style="list-style-type: none"> <li>1. Addition of email address for SAEs (administrative information)</li> <li>2. Removal of bishop score in eligibility</li> <li>3. Removal of USS dates in eligibility</li> <li>4. Update of eligibility/ineligibility to schema</li> <li>5. Addition of table of responsibilities</li> </ol>   |
| 02 August 2018  | <p>The following modifications have been made to the protocol:</p> <p>Amendment to DILAPAN-S dosing schedule</p> <p>Removal of the need for CTG monitoring</p> <p>Removal of the use of iodine for cervical cleansing</p> <p>Amendment to Discontinuation of intervention</p> <p>Amendment to Withdrawal and re-confirmation of consent</p> <p>Addition of definitions of reportable SAEs and protocol-exempt SAEs not requiring reporting on a SAE form</p> <p>Removal of Sections 7.4-7.6 re CRF completion</p> <p>Inclusion of Investigators Brochure for Dilapan-S</p> <p>Minor typographical amendments and points of clarification</p>  |

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

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

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: