



Clinical trial results:

A randomised placebo-controlled trial of mifepristone and misoprostol versus misoprostol alone in the medical management of missed miscarriage

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2016-005097-35 |
| Trial protocol | GB |
| Global end of trial date | 13 January 2020 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 18 September 2020 |
| First version publication date | 18 September 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RG_16-076 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN17405024 |
| ClinicalTrials.gov id (NCT number) | NCT03065660 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Room 119, Aston Webb Building, Edgbaston, Birmingham, United Kingdom, B15 2TT |
| Public contact | Adam Devall, University of Birmingham, 44 07971823452, a.j.devall@bham.ac.uk |
| Scientific contact | Leanne Beeson, University of Birmingham, 44 01214149011, mifemiso@trials.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 | 13 January 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 September 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 January 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that in women diagnosed with missed miscarriage up to 13+6 weeks gestation, mifepristone (200mg orally) followed by misoprostol 800mcg taken vaginally, orally or sublingually two days later (MifeMiso) increases the passage of the gestational sac within seven days after randomisation, when compared to a placebo tablet with identical appearance to the mifepristone tablet followed by misoprostol 800mcg taken vaginally, orally or sublingually two days later.

Protection of trial subjects:

Patients undergoing medical management of miscarriage were already likely to be emotionally distressed

but were supported throughout their miscarriage management by their local early pregnancy units. This was the same for the trial participants. However, the subgroup of participants that agreed and consented to a semi-structured qualitative interview to discuss the treatment that they received could have experienced further emotional distress as a result of the interview. Participants who became more distressed during the interview were informed that they could stop the interview at any time and were signposted to their research nurse and/or regional and national miscarriage support resources. The discussion guide was also developed from the evidence base and was discussed in-depth with our PPI group to ensure that questions were appropriate phrased.

Background therapy:

In addition to the mifepristone (200mg orally) or matched placebo on day 0 and misoprostol (800mcg vaginally, orally or sublingually) on day 2 women may have received additional doses of misoprostol (as appropriate and according to local practice) if the gestational sac did not pass by day seven. Women may also have received surgical management if they opted for this. Women may have also been given an anti-emetic when taking the trial medication in order to prevent vomiting and pain relieving drugs (according to local practice).

Evidence for comparator:

Before the NICE guideline CG154 was published in 2012, common practice was to use a combination of mifepristone and misoprostol (MifeMiso combination). The 2012 NICE guideline, however, recommended that misoprostol alone should be given to women having medical management. This recommendation was based on very limited evidence from one study of 115 women, which found no difference between MifeMiso combination and misoprostol alone. Recognising the limited available evidence, the NICE guideline and HTA called for a trial to compare the clinical and cost effectiveness of mifepristone plus misoprostol versus misoprostol alone for the medical management of missed miscarriage.

A dose of 200mg was used for mifepristone as it is the most commonly used dose for the medical management of miscarriage when used with misoprostol and it is the most commonly studied dose in published trials investigating its efficacy in the medical management of miscarriage. Misoprostol 800mcg was administered according to local practice (orally, vaginally or sublingually).

| | |
|---|-------------------|
| Actual start date of recruitment | 20 September 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: 711 |
| Worldwide total number of subjects | 711 |
| EEA total number of subjects | 711 |

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) | 2 |
| Adults (18-64 years) | 709 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The participants in the MifeMiso trial were recruited from 28 hospitals located across the United Kingdom between October 2017 and July 2019.

Pre-assignment

Screening details:

Women were eligible if they were aged 16 years and over, diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 13+6 weeks of pregnancy, chose to have medical management of miscarriage and were willing and able to give informed consent. 2746 women were assessed for eligibility, 2595 were eligible and 711 were randomised.

Period 1

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

Blinding implementation details:

Participants were randomly assigned in a 1:1 ratio to a single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later, or an oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later. The placebo was manufactured by ModePharma Ltd. to be identical to the mifepristone tablet.

Arms

| | |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Mifepristone plus misoprostol |

Arm description:

A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Mifepristone |
| Investigational medicinal product code | SUB08956MIG |
| Other name | Mifegyne |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Single dose of oral mifepristone 200mg

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Misoprostol |
| Investigational medicinal product code | PL 00057/0956 |
| Other name | |
| Pharmaceutical forms | Tablet + vaginal tablet |
| Routes of administration | Oral use, Sublingual use, Vaginal use |

Dosage and administration details:

Single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later

| | |
|------------------|--------------------------|
| Arm title | Placebo plus misoprostol |
|------------------|--------------------------|

Arm description:

An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Single placebo tablet | |
| Investigational medicinal product name | Misoprostol |
| Investigational medicinal product code | PL 00057/0956 |
| Other name | |
| Pharmaceutical forms | Tablet + vaginal tablet |
| Routes of administration | Oral use, Sublingual use, Vaginal use |
| Dosage and administration details: | |
| Single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later | |

| Number of subjects in period 1 | Mifepristone plus misoprostol | Placebo plus misoprostol |
|---|-------------------------------|--------------------------|
| Started | 357 | 354 |
| Completed | 348 | 348 |
| Not completed | 9 | 6 |
| Lost to follow-up | 6 | 3 |
| Discontinued study treatment & not want follow up | 3 | 3 |

Baseline characteristics

Reporting groups

| | |
|---|-------------------------------|
| Reporting group title | Mifepristone plus misoprostol |
| Reporting group description: A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later. | |
| Reporting group title | Placebo plus misoprostol |
| Reporting group description: An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later | |

| Reporting group values | Mifepristone plus misoprostol | Placebo plus misoprostol | Total |
|--|-------------------------------|--------------------------|-------|
| Number of subjects | 357 | 354 | 711 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 1 | 1 | 2 |
| Adults (18-64 years) | 356 | 353 | 709 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 32.8 | 32.7 | - |
| standard deviation | ± 5.6 | ± 5.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 357 | 354 | 711 |
| Male | 0 | 0 | 0 |
| Body Mass Index Units: Subjects | | | |
| <35 | 332 | 328 | 660 |
| ≥35 | 25 | 26 | 51 |
| Previous parity Units: Subjects | | | |
| Nulliparous | 167 | 168 | 335 |
| Parous | 190 | 186 | 376 |
| Gestational age in days Units: Subjects | | | |
| <70 | 176 | 175 | 351 |
| ≥70 | 181 | 179 | 360 |
| Amount of bleeding (Pictorial Blood Assessment Chart score) Units: Subjects | | | |

| | | | |
|---|-----|-----|-----|
| ≤2 | 351 | 348 | 699 |
| ≥3 | 6 | 6 | 12 |
| Ethnic group Units: Subjects | | | |
| White | 296 | 280 | 576 |
| Black | 10 | 17 | 27 |
| South Asian | 38 | 42 | 80 |
| Other | 13 | 15 | 28 |
| Number of gestational sacs Units: Subjects | | | |
| One | 351 | 348 | 699 |
| Two | 6 | 6 | 12 |
| Previous live birth Units: Subjects | | | |
| Zero | 176 | 174 | 350 |
| One | 111 | 118 | 229 |
| Two | 45 | 39 | 84 |
| ≥ Three | 25 | 23 | 48 |
| Previous stillbirth Units: Subjects | | | |
| Zero | 351 | 350 | 701 |
| One | 6 | 3 | 9 |
| Two | 0 | 1 | 1 |
| Previous miscarriage Units: Subjects | | | |
| Zero | 233 | 225 | 458 |
| One | 62 | 77 | 139 |
| Two | 29 | 24 | 53 |
| ≥ Three | 33 | 28 | 61 |
| Previous ectopic pregnancy Units: Subjects | | | |
| Zero | 344 | 345 | 689 |
| One | 13 | 9 | 22 |
| Previous molar pregnancy Units: Subjects | | | |
| Zero | 357 | 353 | 710 |
| One | 0 | 1 | 1 |
| Previous termination Units: Subjects | | | |
| Zero | 304 | 296 | 600 |
| One | 44 | 45 | 89 |
| Two | 7 | 10 | 17 |
| ≥ Three | 2 | 3 | 5 |
| Previous pregnancy of unknown location Units: Subjects | | | |
| Zero | 354 | 354 | 708 |
| One | 3 | 0 | 3 |
| Pregnancy-related pain score at randomization Units: Pain score arithmetic mean | 1.0 | 1.2 | |

| | | | |
|--|-------|--------|---|
| standard deviation | ± 1.8 | ± 2.0 | - |
| Progesterone levels | | | |
| Units: nmol/L | | | |
| arithmetic mean | 17.0 | 22.8 | |
| standard deviation | ± 4.2 | ± 12.8 | - |
| Days from date of ultrasound scan diagnosing missed miscarriage to randomisation | | | |
| Units: days | | | |
| arithmetic mean | 1.5 | 1.9 | |
| standard deviation | ± 3.3 | ± 4.6 | - |

End points

End points reporting groups

| | |
|---|-------------------------------|
| Reporting group title | Mifepristone plus misoprostol |
| Reporting group description: A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later. | |
| Reporting group title | Placebo plus misoprostol |
| Reporting group description: An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later | |

Primary: Failure to pass the gestational sac spontaneously within 7 days after randomisation

| | |
|---|---|
| End point title | Failure to pass the gestational sac spontaneously within 7 days after randomisation |
| End point description: | |
| End point type | Primary |
| End point timeframe: Within 7 days after randomisation | |

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 348 | 348 | | |
| Units: Subjects | 59 | 82 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Primary outcome analysis |
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 696 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 |
| Method | Regression, Logistic |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.99 |

Secondary: Surgical intervention to resolve the miscarriage up to discharge

| | |
|-----------------|--|
| End point title | Surgical intervention to resolve the miscarriage up to discharge |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From time of randomisation up to discharge

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 355 | 353 | | |
| Units: Subjects | 62 | 87 | | |

Statistical analyses

| Statistical analysis title | Key secondary outcome analysis |
|---|--|
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | Regression, Logistic |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 0.95 |

Secondary: Surgical intervention to resolve the miscarriage up to and including day 7 post randomisation

| | |
|-----------------|---|
| End point title | Surgical intervention to resolve the miscarriage up to and including day 7 post randomisation |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to and including day 7 post randomization

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 355 | 353 | | |
| Units: Subjects | 23 | 19 | | |

Statistical analyses

| Statistical analysis title | Secondary outcome analysis |
|---|--|
| Comparison groups | Placebo plus misoprostol v Mifepristone plus misoprostol |
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 2.21 |

Secondary: Surgical intervention to resolve the miscarriage from after day 7 and up to discharge

| | |
|--|---|
| End point title | Surgical intervention to resolve the miscarriage from after day 7 and up to discharge |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| After day 7 from randomisation and up to discharge | |

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 355 | 353 | | |
| Units: Subjects | 39 | 68 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 708 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 0.81 |

Secondary: Need for further doses of misoprostol within 7 days after randomisation

| | |
|-----------------------------------|---|
| End point title | Need for further doses of misoprostol within 7 days after randomisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Within 7 days after randomization | |

| | | | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 356 | 354 | | |
| Units: Subjects | 34 | 48 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 710 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 1.08 |

Secondary: Need for further doses of misoprostol up to discharge

| | |
|-----------------|---|
| End point title | Need for further doses of misoprostol up to discharge |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomisation up to discharge

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 357 | 354 | | |
| Units: Subjects | 50 | 65 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 711 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.09 |

Secondary: Infection requiring outpatient antibiotic treatment

| | |
|-----------------|---|
| End point title | Infection requiring outpatient antibiotic treatment |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomisation up to discharge

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 351 | 351 | | |
| Units: Subjects | 8 | 11 | | |

Statistical analyses

| Statistical analysis title | Secondary outcome analysis |
|---|--|
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 702 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 1.82 |

Secondary: Infection requiring inpatient antibiotic treatment

| | |
|------------------------------------|--|
| End point title | Infection requiring inpatient antibiotic treatment |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation up to discharge | |

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 351 | 351 | | |
| Units: Subjects | 5 | 4 | | |

Statistical analyses

| Statistical analysis title | Secondary outcome analysis |
|----------------------------|--|
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |

| | |
|---|-----------------|
| Number of subjects included in analysis | 702 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 4.74 |

Secondary: Negative pregnancy test result 21 days (\pm 2 days) after randomisation

| | |
|---|--|
| End point title | Negative pregnancy test result 21 days (\pm 2 days) after randomisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 21 days (\pm 2 days) after randomisation | |

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|-----------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 308 | 302 | | |
| Units: Subjects | 237 | 230 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 610 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.14 |

Secondary: Duration of bleeding reported by woman

| | |
|-----------------|--|
| End point title | Duration of bleeding reported by woman |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomisation up until discharge

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|--------------------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 330 | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 16 (\pm 12.6) | 16.3 (\pm 15.2) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Mifepristone plus misoprostol v Placebo plus misoprostol |
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 1.8 |

Secondary: Time from randomisation to discharge

| | |
|-----------------|--------------------------------------|
| End point title | Time from randomisation to discharge |
|-----------------|--------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomisation up until discharge

| End point values | Mifepristone plus misoprostol | Placebo plus misoprostol | | |
|--------------------------------------|-------------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 340 | 337 | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 27 (\pm 14.2) | 27.3 (\pm 14.4) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

From randomisation up until discharge

Adverse event reporting additional description:

Specific adverse events with a severity grade of 3, 4, or 5, from the first administration of trial treatment until the resolution of the miscarriage, whether observed directly or reported by the participant, were collected and recorded.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 14.2 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Mifepristone plus misoprostol |
|-----------------------|-------------------------------|

Reporting group description:

A single dose of oral mifepristone 200mg, followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later.

| | |
|-----------------------|--------------------------|
| Reporting group title | Placebo plus misoprostol |
|-----------------------|--------------------------|

Reporting group description:

An oral placebo tablet followed by a single dose of vaginal, oral or sublingual misoprostol 800mcg 2 days later

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: There were no non-serious adverse events that occurred at a frequency of >5%, therefore there are no events to be reported.

| Serious adverse events | Mifepristone plus misoprostol | Placebo plus misoprostol | |
|---|--|--------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 357 (1.40%) | 2 / 354 (0.56%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Surgical and medical procedures | | | |
| Haemorrhage in pregnancy | Additional description: Significant haemorrhage of 2400mls, required surgical intervention. Participant received blood transfusion of 2 units | | |
| subjects affected / exposed | 1 / 357 (0.28%) | 0 / 354 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Haemorrhage in pregnancy | Additional description: 1 x participant received 2 units of blood after large blood loss. Discharged home with Hb of 100, ERPC, bleeding settled. 1 x participant had emergency surgery and required 5 units of blood. Heavy vaginal bleeding leading to hypovolaemic shock | | |
| subjects affected / exposed | 0 / 357 (0.00%) | 2 / 354 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|---|-----------------|-----------------|
| Ruptured ectopic pregnancy | Additional description: Participant underwent laparoscopic salpingectomy. Undiagnosed ectopic pregnancy at initial USS | | |
| | subjects affected / exposed | 1 / 357 (0.28%) | 0 / 354 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Anaemia of pregnancy | Additional description: Participant experienced fainting episodes and dizziness. Clinical appearance of anaemia following bleeding from miscarriage. Received 2 units of blood and prescribed ferrous sulphate | | |
| | subjects affected / exposed | 1 / 357 (0.28%) | 0 / 354 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Embolism arterial | Additional description: Embolism of uterine artery due to complications from fibroid uterus and surgical management of miscarriage. Arteriovenous malformation of fibroid. Uterine artery embolisation and hysterectomy performed. | | |
| | subjects affected / exposed | 1 / 357 (0.28%) | 0 / 354 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Chronic renal disease | Additional description: Participant had 2 units of blood transfused due to pre-existing chronic renal disease causing anaemia complicated by 250mls blood loss. Participant had a surgical management of miscarriage due to poor renal function and risk of further bleeding. | | |
| | subjects affected / exposed | 1 / 357 (0.28%) | 0 / 354 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Mifepristone plus misoprostol | Placebo plus misoprostol | |
|---|-------------------------------|--------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 357 (0.00%) | 0 / 354 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 January 2017 | <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> 1. Addition of 'amount of bleeding (PBAC score; ≤ 2, ≥ 3)' as a stratification variable 2. Addition of a statement confirming women that have already participated in MifeMiso once cannot participate a second time |
| 01 March 2017 | <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> 1. Addition of ISRCTN and Clinical Trials.gov number 2. Clarification regarding emergency unblinding 3. Addition of rationale for using stated doses of mifepristone and misoprostol 4. Amendment to statements regarding assessment of severity and causality of SAEs 5. Clarification regarding vaginal bleeding as an event not reportable as an SAE 6. 'Resolution of miscarriage' amended to 'discharge' in table 5 7. Clarification that day 21 ± 2 is the point of discharge for women with a negative pregnancy test result 8. Clarification regarding additional EQ-5D-5L questionnaire to be completed by women with an initial positive pregnancy test result 9. Clarification regarding compliance monitoring 10. Clarification regarding primary and secondary endpoint analyses |
| 09 February 2018 | <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> 1. Change of contact details for trial personnel 2. Clarification of primary and secondary outcomes 3. Addition of sublingual route for misoprostol administration 4. Clarification on trial flowchart that repeat scan at day 6-7 not required if scan performed earlier than this time point and sac has passed 5. Clarification that the screening log is accessible through the online randomisation system 6. Clarification of storage temperature for IMP 7. Clarification of ways in which CSQ-8 questionnaire (satisfaction survey) is administered i.e paper and electronic 8. Addition of 'previous participation in the MifeMiso trial' and 'woman not able to attend for day 6-7 ultrasound scan' to list of exclusion criteria 9. Clarification of the end of trial definition 10. Clarification that qualitative interviews may be conducted via video call software e.g. Skype |
| 27 June 2019 | <p>The following changes were made to the protocol:</p> <ol style="list-style-type: none"> 1. Update to trial team contact details 2. Update to secondary outcomes and objectives 3. Reclassification of some secondary outcomes as safety outcomes 4. Clarification regarding unblinding 5. Update to health economic evaluation section 6. Addition of section regarding Blinded Endpoint Review Committee 7. Update to statistical analysis section |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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| We studied the effect in missed miscarriage; therefore, these results are not generalisable to patients diagnosed with incomplete miscarriage. The rationale for this is the anti-progestogenic effect of mifepristone is less likely to have an effect. |
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32853559>