



## Clinical trial results:

**A double-blind, placebo-controlled multicenter trial on the effect of clindamycin and a live biotherapeutic on the reproductive outcomes of IVF patients with abnormal vaginal microbiota**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-002385-31 |
| Trial protocol           | DK             |
| Global end of trial date | 16 August 2023 |

### Results information

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| Result version number             | v1 (current)                        |
| This version publication date     | 30 August 2024                      |
| First version publication date    | 30 August 2024                      |
| Summary attachment (see zip file) | RCT Manuscript (RCT_Manuscript.pdf) |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 2015/582 |
|-----------------------|----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                                |
|------------------------------|------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | The Fertility Clinic Skive, Skive regional Hopsital                                            |
| Sponsor organisation address | Reservevej 25, Skive, Denmark, 7800                                                            |
| Public contact               | Peter Humaidan, The Fertility Clinic Skive, Skive regional Hopsital, peter.humaidan@midt.rm.dk |
| Scientific contact           | Peter Humaidan, The Fertility Clinic Skive, Skive regional Hopsital, peter.humaidan@midt.rm.dk |

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                       | 16 August 2023 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 16 August 2023 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 16 August 2023 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The aim of the present trial is to investigate the effect of antibiotic and probiotic treatment on the reproductive outcome of IVF patients with abnormal vaginal microbiota (AVM). The aim is to investigate whether treatment of AVM improve the success-rate of IVF patients.

Protection of trial subjects:

The study was approved by the scientific Ethics Committee of the Central Denmark Region - Project ID: M-2017-157-17

Written informed consent was obtained from all participants prior to inclusion.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 01 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 | Denmark: 338 |
| Worldwide total number of subjects   | 338          |
| EEA total number of subjects         | 338          |

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)                 | 0   |
| Adults (18-64 years)                      | 338 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The first patient was enrolled in December 2017 and the last patient was enrolled in september 2022. Patients were recruited from four danish fertility clinics.

### Pre-assignment

Screening details:

A total of 1535 patients were screened and 338 patient were randomized. However, 72 patients were not included in the modified intention to treat (mITT) analysis. This resulted in 94 CLLA, 88 CLPL, and 84 PLPL patients included in the primary mITT analysis.

### Period 1

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

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Active Treatment 1 |

Arm description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V (2 x 109 CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration, but patients are allowed to use all 21 applicators

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Clindamycin   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

300 mg 2 times per day for 7 days

|                                        |                             |
|----------------------------------------|-----------------------------|
| Investigational medicinal product name | LACTIN-V                    |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Powder for vaginal solution |
| Routes of administration               | Vaginal use                 |

Dosage and administration details:

LACTIN-V (2 x 109 CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Active Treatment 2 |
|------------------|--------------------|

Arm description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V placebo (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. The LACTIN-V placebo regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum

of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of Lactin-V placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

|                                                                         |                              |
|-------------------------------------------------------------------------|------------------------------|
| Arm type                                                                | Experimental                 |
| Investigational medicinal product name                                  | Clindamycin                  |
| Investigational medicinal product code                                  |                              |
| Other name                                                              |                              |
| Pharmaceutical forms                                                    | Capsule, hard                |
| Routes of administration                                                | Oral use                     |
| Dosage and administration details:<br>300 mg 2 times per day for 7 days |                              |
| <b>Arm title</b>                                                        | Inactive treatment (placebo) |

Arm description:

Matching clindamycin placebo 2 times per day for 7 days followed by LACTIN-V placebo (Osel Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V placebo regimen is once daily from clindamycin stop and the following 7 days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of live biotherapeutic placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

|                                                                         |                             |
|-------------------------------------------------------------------------|-----------------------------|
| Arm type                                                                | Placebo                     |
| Investigational medicinal product name                                  | Clindamycin (placebo)       |
| Investigational medicinal product code                                  |                             |
| Other name                                                              |                             |
| Pharmaceutical forms                                                    | Capsule, hard               |
| Routes of administration                                                | Oral use                    |
| Dosage and administration details:<br>300 mg 2 times per day for 7 days |                             |
| Investigational medicinal product name                                  | LACTIN-V (placebo)          |
| Investigational medicinal product code                                  |                             |
| Other name                                                              |                             |
| Pharmaceutical forms                                                    | Powder for vaginal solution |
| Routes of administration                                                | Vaginal use                 |

Dosage and administration details:

LACTIN-V (2 x 10<sup>9</sup> CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Active Treatment 1 | Active Treatment 2 | Inactive treatment (placebo) |
|-----------------------------------------------------|--------------------|--------------------|------------------------------|
| Started                                             | 94                 | 88                 | 84                           |
| Completed                                           | 94                 | 88                 | 84                           |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 338 patients were randomized however, 72 patients were not included in the modified intention to treat (mITT) analysis. This resulted in a total of 266 patients.

## Baseline characteristics

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Active Treatment 1 |
|-----------------------|--------------------|

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V (2 x 10<sup>9</sup> CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration, but patients are allowed to use all 21 applicators

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Active Treatment 2 |
|-----------------------|--------------------|

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V placebo (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. The LACTIN-V placebo regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of Lactin-V placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Inactive treatment (placebo) |
|-----------------------|------------------------------|

Reporting group description:

Matching clindamycin placebo 2 times per day for 7 days followed by LACTIN-V placebo (Osel Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V placebo regimen is once daily from clindamycin stop and the following 7 days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of live biotherapeutic placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

| Reporting group values | Active Treatment 1 | Active Treatment 2 | Inactive treatment (placebo) |
|------------------------|--------------------|--------------------|------------------------------|
| Number of subjects     | 94                 | 88                 | 84                           |
| Age categorical        |                    |                    |                              |
| Units: Subjects        |                    |                    |                              |
| Adults (18-64 years)   | 94                 | 88                 | 84                           |
| Age continuous         |                    |                    |                              |
| Units: years           |                    |                    |                              |
| median                 | 31.5               | 31.8               | 31.4                         |
| standard deviation     | ± 4.7              | ± 4.5              | ± 4.7                        |
| Gender categorical     |                    |                    |                              |
| Units: Subjects        |                    |                    |                              |
| Female                 | 94                 | 88                 | 84                           |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 266   |  |  |
| Age categorical        |       |  |  |
| Units: Subjects        |       |  |  |
| Adults (18-64 years)   | 266   |  |  |
| Age continuous         |       |  |  |
| Units: years           |       |  |  |
| median                 | -     |  |  |
| standard deviation     | -     |  |  |

|                    |     |  |  |
|--------------------|-----|--|--|
| Gender categorical |     |  |  |
| Units: Subjects    |     |  |  |
| Female             | 266 |  |  |

### Subject analysis sets

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Full analysis               |
| Subject analysis set type  | Modified intention-to-treat |

Subject analysis set description:

Primary analysis was modified intention to treat (mITT) defined as all patients with embryo transfer less than 63 days from the active treatment start until day 1 in the embryo transfer cycle.

| Reporting group values | Full analysis |  |  |
|------------------------|---------------|--|--|
| Number of subjects     | 266           |  |  |
| Age categorical        |               |  |  |
| Units: Subjects        |               |  |  |
| Adults (18-64 years)   | 266           |  |  |
| Age continuous         |               |  |  |
| Units: years           |               |  |  |
| median                 |               |  |  |
| standard deviation     | ±             |  |  |
| Gender categorical     |               |  |  |
| Units: Subjects        |               |  |  |
| Female                 | 266           |  |  |

## End points

### End points reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Active Treatment 1 |
|-----------------------|--------------------|

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V (2 x 10<sup>9</sup> CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration, but patients are allowed to use all 21 applicators

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Active Treatment 2 |
|-----------------------|--------------------|

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V placebo (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. The LACTIN-V placebo regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of Lactin-V placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Inactive treatment (placebo) |
|-----------------------|------------------------------|

Reporting group description:

Matching clindamycin placebo 2 times per day for 7 days followed by LACTIN-V placebo (Osel Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V placebo regimen is once daily from clindamycin stop and the following 7 days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of live biotherapeutic placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Full analysis |
|----------------------------|---------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

Primary analysis was modified intention to treat (mITT) defined as all patients with embryo transfer less than 63 days from the active treatment start until day 1 in the embryo transfer cycle.

### Primary: Clinical pregnancy rate

|                 |                         |
|-----------------|-------------------------|
| End point title | Clinical pregnancy rate |
|-----------------|-------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Gestational week 7-9

| End point values            | Active Treatment 1 | Active Treatment 2 | Inactive treatment (placebo) | Full analysis        |
|-----------------------------|--------------------|--------------------|------------------------------|----------------------|
| Subject group type          | Reporting group    | Reporting group    | Reporting group              | Subject analysis set |
| Number of subjects analysed | 94                 | 88                 | 84                           | 266                  |
| Units: Fetal heart beat     | 39                 | 41                 | 38                           | 118                  |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                                                             | Fisher's exact test                                                    |
| Statistical analysis description:<br>For each treatment group CLLA, CLPL and PLPL the estimated proportions, risk ratios (RR) and their confidence intervals were calculated using uni- and multivariate logistic regression analyses by generalized linear models with log-link function. The significance level for the final analysis was set at 4.9% (95.1% confidence intervals) due to the preplanned interim analysis where an alpha of 0.1% was used. |                                                                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                             | Active Treatment 1 v Active Treatment 2 v Inactive treatment (placebo) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                       | 266                                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                        | Pre-specified                                                          |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                 | equivalence                                                            |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                       | = 0.49                                                                 |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Fisher exact                                                           |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                            | Risk ratio (RR)                                                        |

## Secondary: Live birth rate

|                               |                 |
|-------------------------------|-----------------|
| End point title               | Live birth rate |
| End point description:        |                 |
| End point type                | Secondary       |
| End point timeframe:<br>Birth |                 |

| End point values            | Active Treatment 1 | Active Treatment 2 | Inactive treatment (placebo) | Full analysis        |
|-----------------------------|--------------------|--------------------|------------------------------|----------------------|
| Subject group type          | Reporting group    | Reporting group    | Reporting group              | Subject analysis set |
| Number of subjects analysed | 94                 | 88                 | 84                           | 266                  |
| Units: Birth                | 37                 | 40                 | 34                           | 111                  |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                                                             | Fisher's exact test                                                    |
| Statistical analysis description:<br>For each treatment group CLLA, CLPL and PLPL the estimated proportions, risk ratios (RR) and their confidence intervals were calculated using uni- and multivariate logistic regression analyses by generalized linear models with log-link function. The significance level for the final analysis was set at 4.9% (95.1% confidence intervals) due to the preplanned interim analysis where an alpha of 0.1% was used. |                                                                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                             | Active Treatment 2 v Inactive treatment (placebo) v Active Treatment 1 |

|                                         |                 |
|-----------------------------------------|-----------------|
| Number of subjects included in analysis | 266             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | equivalence     |
| P-value                                 | = 0.49          |
| Method                                  | Fisher exact    |
| Parameter estimate                      | Risk ratio (RR) |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14 weeks

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

### Reporting groups

|                       |      |
|-----------------------|------|
| Reporting group title | CLLA |
|-----------------------|------|

Reporting group description: -

|                       |      |
|-----------------------|------|
| Reporting group title | CLPL |
|-----------------------|------|

Reporting group description: -

|                       |      |
|-----------------------|------|
| Reporting group title | PLPL |
|-----------------------|------|

Reporting group description: -

| Serious adverse events                             | CLLA           | CLPL           | PLPL           |
|----------------------------------------------------|----------------|----------------|----------------|
| Total subjects affected by serious adverse events  |                |                |                |
| subjects affected / exposed                        | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| number of deaths (all causes)                      | 0              | 0              | 0              |
| number of deaths resulting from adverse events     |                |                |                |
| Surgical and medical procedures                    |                |                |                |
| Appendicitis                                       |                |                |                |
| subjects affected / exposed                        | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all    | 0 / 3          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all         | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                                  |                |                |                |
| Obs apoplexia, not confirmed                       |                |                |                |
| subjects affected / exposed                        | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all    | 0 / 3          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all         | 0 / 0          | 0 / 0          | 0 / 0          |
| Pregnancy, puerperium and perinatal conditions     |                |                |                |
| Arthrogryposis multiplex congenita=> late abortion |                |                |                |
| subjects affected / exposed                        | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all    | 0 / 3          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all         | 0 / 0          | 0 / 0          | 0 / 0          |
| Foetus mors                                        |                |                |                |

|                                                       |                |                |                |
|-------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                           | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all       | 0 / 3          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Extrauterine pregnancy                                |                |                |                |
| subjects affected / exposed                           | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all       | 0 / 3          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Trisomi 21=> abortion                                 |                |                |                |
| subjects affected / exposed                           | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all       | 0 / 3          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |
| Radius hypoplasia, normal amniocentesis => live birth |                |                |                |
| subjects affected / exposed                           | 3 / 94 (3.19%) | 1 / 88 (1.14%) | 3 / 84 (3.57%) |
| occurrences causally related to treatment / all       | 0 / 3          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all            | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | CLLA             | CLPL             | PLPL             |
|-------------------------------------------------------|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events |                  |                  |                  |
| subjects affected / exposed                           | 23 / 94 (24.47%) | 24 / 88 (27.27%) | 22 / 84 (26.19%) |
| General disorders and administration site conditions  |                  |                  |                  |
| Nausea                                                |                  |                  |                  |
| subjects affected / exposed                           | 8 / 94 (8.51%)   | 16 / 88 (18.18%) | 17 / 84 (20.24%) |
| occurrences (all)                                     | 8                | 16               | 17               |
| Fatigue                                               |                  |                  |                  |
| subjects affected / exposed                           | 12 / 94 (12.77%) | 11 / 88 (12.50%) | 15 / 84 (17.86%) |
| occurrences (all)                                     | 12               | 11               | 15               |
| Bloating                                              |                  |                  |                  |
| subjects affected / exposed                           | 23 / 94 (24.47%) | 24 / 88 (27.27%) | 19 / 84 (22.62%) |
| occurrences (all)                                     | 23               | 24               | 19               |
| Headache                                              |                  |                  |                  |
| subjects affected / exposed                           | 4 / 94 (4.26%)   | 6 / 88 (6.82%)   | 7 / 84 (8.33%)   |
| occurrences (all)                                     | 4                | 6                | 7                |

|                                                                                                                   |                        |                        |                        |
|-------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 94 (0.00%)<br>0    | 1 / 88 (1.14%)<br>1    | 0 / 84 (0.00%)<br>0    |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                       | 12 / 94 (12.77%)<br>12 | 11 / 88 (12.50%)<br>11 | 15 / 84 (17.86%)<br>15 |
| Reproductive system and breast disorders<br>Vaginal discharge<br>subjects affected / exposed<br>occurrences (all) | 13 / 94 (13.83%)<br>13 | 14 / 88 (15.91%)<br>14 | 22 / 84 (26.19%)<br>22 |
| Vaginal itching<br>subjects affected / exposed<br>occurrences (all)                                               | 8 / 94 (8.51%)<br>8    | 2 / 88 (2.27%)<br>2    | 2 / 84 (2.38%)<br>2    |
| Vaginal pain<br>subjects affected / exposed<br>occurrences (all)                                                  | 2 / 94 (2.13%)<br>2    | 2 / 88 (2.27%)<br>2    | 2 / 84 (2.38%)<br>2    |
| Vaginal smell<br>subjects affected / exposed<br>occurrences (all)                                                 | 1 / 94 (1.06%)<br>1    | 1 / 88 (1.14%)<br>1    | 1 / 84 (1.19%)<br>1    |
| Vaginal bleeding<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 94 (0.00%)<br>0    | 3 / 88 (3.41%)<br>3    | 0 / 84 (0.00%)<br>0    |
| Vaginal rash<br>subjects affected / exposed<br>occurrences (all)                                                  | 2 / 94 (2.13%)<br>2    | 1 / 88 (1.14%)<br>1    | 0 / 84 (0.00%)<br>0    |
| Vaginal candida<br>subjects affected / exposed<br>occurrences (all)                                               | 4 / 94 (4.26%)<br>4    | 2 / 88 (2.27%)<br>2    | 0 / 84 (0.00%)<br>0    |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 94 (2.13%)<br>2    | 1 / 88 (1.14%)<br>1    | 1 / 84 (1.19%)<br>1    |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported