



## Clinical trial results:

## Chlorhexidine gluconate as treatment and prophylaxis of vulvovaginal Candidiasis

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2020-000758-81   |
| Trial protocol           | SE               |
| Global end of trial date | 27 November 2024 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 07 November 2025 |
| First version publication date | 07 November 2025 |

### Trial information

#### Trial identification

|                       |                    |
|-----------------------|--------------------|
| Sponsor protocol code | Chlorhex-KKDS-2021 |
|-----------------------|--------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT05059145 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Karolinska Institutet   |
| Sponsor organisation address | Nobels väg 6, Solna, Sweden, 17177  |
| Public contact               | Nina Bohm-Starke, Karolinska Institutet, Danderyd Hospital.<br>Div of Obstetrics and Gynecology, +46 812355000,<br>nina.bohm-starke@ki.se |
| Scientific contact           | Nina Bohm-Starke, Karolinska Institutet, Danderyd Hospital.<br>Div of Obstetrics and Gynecology, +46 812355000,<br>nina.bohm-starke@ki.se |

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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 17 June 2025     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 27 November 2024 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 27 November 2024 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

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**General information about the trial**

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Main objective of the trial:

To analyze if daily vaginal application of 8 ml of Hibitane® for one week and thereafter once a week for another 11 consecutive weeks is at least as effective as fluconazole 150 mg capsules every third day for the first three doses and thereafter 150 mg once a week for another 11 consecutive weeks regarding treatment- and prophylactic efficacy for recurrent vulvovaginal Candida albicans infection.

Protection of trial subjects:

The first ethical approval on the clinical trial was granted by the Swedish Ethical Review Authority on September 8, 2020 (Dnr 2020-04035) and the second application including more advanced molecular analyses was granted on February 6, 2022 (Dnr 2021-06538-02). All participants provided written informed consent prior to enrollment.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 25 April 2022 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Sweden: 23 |
| Worldwide total number of subjects   | 23         |
| EEA total number of subjects         | 23         |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 23 |
| From 65 to 84 years                       | 0  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Recruitment (began April 27, 2022) was conducted via advertisements at regional gynecological clinics and on social media, inviting women with RVVC to contact the research midwife at the Women's Department at Danderyd Hospital for further information. Women meeting the age and symptom criteria were invited to a screening visit.

### Pre-assignment

Screening details:

Inclusion criteria: women aged 18-50y with a history of RVVC ( $\geq 3$  episodes of Candida infection in the past year); current symptoms consistent with acute vulvovaginal candidiasis; culture-confirmed C. albicans susceptible to FLZ.

### Period 1

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

### Arms

|                              |                                     |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes                                 |
| <b>Arm title</b>             | Chlorhexidine gluconate (Hibitane®) |

Arm description:

The CHG group received Hibitane® 1% vaginal cream, 7.5 mL nightly for 7 days as acute treatment, followed by prophylactic treatment with 7.5 mL once weekly for 11 consecutive weeks.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | Hibitane                |
| Investigational medicinal product code | SUB01215MIG             |
| Other name                             | CHLORHEXIDINE GLUCONATE |
| Pharmaceutical forms                   | Vaginal cream           |
| Routes of administration               | Vaginal use             |

Dosage and administration details:

Daily vaginal application of 8 ml of Hibitane® for one week and thereafter once a week for another 11 consecutive weeks.

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

Arm description:

The FLZ group received oral capsules Fluconazole® 150 mg every third day for the first three doses (acute phase), followed by 150 mg once weekly for 11 consecutive weeks (prophylactic phase).

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Fluconazole       |
| Investigational medicinal product code | SUB07674MIG       |
| Other name                             |                   |
| Pharmaceutical forms                   | Capsule           |
| Routes of administration               | Oral use          |

Dosage and administration details:

Fluconazole 150 mg capsules every third day for the first three doses and thereafter 150 mg once a week for another 11 consecutive weeks.

| Number of subjects in period 1 | Chlorhexidine gluconate (Hibitane®) | Fluconazole® |
|--------------------------------|-------------------------------------|--------------|
|                                |                                     |              |
| Started                        | 12                                  | 11           |
| Completed                      | 5                                   | 11           |
| Not completed                  | 7                                   | 0            |
| Adverse event, non-fatal       | 7                                   | -            |

## Baseline characteristics

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Chlorhexidine gluconate (Hibitane®) |
|-----------------------|-------------------------------------|

Reporting group description:

The CHG group received Hibitane® 1% vaginal cream, 7.5 mL nightly for 7 days as acute treatment, followed by prophylactic treatment with 7.5 mL once weekly for 11 consecutive weeks.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Fluconazole® |
|-----------------------|--------------|

Reporting group description:

The FLZ group received oral capsules Fluconazole® 150 mg every third day for the first three doses (acute phase), followed by 150 mg once weekly for 11 consecutive weeks (prophylactic phase).

| Reporting group values                             | Chlorhexidine gluconate (Hibitane®) | Fluconazole® | Total |
|--|-------------------------------------|--------------|-------|
| Number of subjects                                 | 12                                  | 11           | 23    |
| Age categorical<br>Units: Subjects                 |                                     |              |       |
| In utero   |                                     |              | 0     |
| Preterm newborn infants (gestational age < 37 wks) |                                     |              | 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)                               |                                     |              | 0     |
| From 65-84 years                                   |                                     |              | 0     |
| 85 years and over                                  |                                     |              | 0     |
| Age continuous<br>Units: years                     |                                     |              |       |
| median   | 33                                  | 32           |       |
| full range (min-max)                               | 24 to 46                            | 23 to 45     | -     |
| Gender categorical<br>Units: Subjects              |                                     |              |       |
| Female   | 12                                  | 11           | 23    |
| Male   | 0                                   | 0            | 0     |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Chlorhexidine gluconate (Hibitane®)              |
| Reporting group description:<br>The CHG group received Hibitane® 1% vaginal cream, 7.5 mL nightly for 7 days as acute treatment, followed by prophylactic treatment with 7.5 mL once weekly for 11 consecutive weeks.  |  |
| Reporting group title  | Fluconazole®                                     |
| Reporting group description:<br>The FLZ group received oral capsules Fluconazole® 150 mg every third day for the first three doses (acute phase), followed by 150 mg once weekly for 11 consecutive weeks (prophylactic phase).  |  |
| Subject analysis set title   | Chlorhexidine gluconate (Hibitane®) after 1 week |
| Subject analysis set type  | Full analysis                                    |
| Subject analysis set description:<br>7 participants in the CHG group chose to withdraw from the study due to local pain and discomfort, and did not attend the planned visits at 3 months (end of prophylactic treatment) and 6 months (follow-up visit). Therefore, this primary result will only present end points for the first follow-up 1 week after acute treatment where we have results from all 11 in the CHG-group. |  |

### Primary: The proportion of women in each group that has cleared the infection after 1week of treatment

|   |  |
|---|--|
| End point title   | The proportion of women in each group that has cleared the infection after 1week of treatment <sup>[1]</sup> |
| End point description:<br>The early termination of the study with less than 50% of the planned number of participants (30+30 in each study arm) has impact on the interpretation of the results. However, the primary outcome of negative candida cultures after one week of treatment for an acute episode of vulvovaginal candidiasis showed an equal response in both study groups. This preliminary result indicates that chlorhexidine could be an effective alternative treatment for recurrent vulvovaginal candidiasis, but the drug in this study (Hibitane®) cannot be used, which will be the preliminary conclusion of the study. |  |
| End point type  | Primary  |
| End point timeframe:<br>The proportion of women in each group that has cleared the infection after 1week of treatment, defined as negative cultures for Candida albicans.   |  |

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned follow-up visits at 1 week, 3 months and 6 months. But 7 participants in CHG-group withdrew after 1 week of treatment due to adverse events, therefore we cannot report from the 3 and 6 months visits. We chose to only report from the first 1 week visit where all the CHG-group attended. However, it is important to present the withdrawal due to adverse events, hence we showed the planned baseline period arm "Chlorhexidine gluconate (Hibitane®)" but cannot do a full report.

| End point values            | Fluconazole®    | Chlorhexidine gluconate (Hibitane®) after 1 week |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group | Subject analysis set                             |  |  |
| Number of subjects analysed | 11              | 12   |  |  |
| Units: Number of patients   | 12              | 9  |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | The proportion that has cleared infection                       |
| Comparison groups                       | Fluconazole® v Chlorhexidine gluconate (Hibitane®) after 1 week |
| Number of subjects included in analysis | 23  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority   |
| P-value                                 | = 0.82  |
| Method                                  | Fisher exact  |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events occurred within the acute treatment period (first week of treatment), or during the prophylactic treatment period between week 2 to 3 months after study start.

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

### Dictionary used

|                 |     |
|-----------------|-----|
| Dictionary name | n/a |
|-----------------|-----|

|                    |     |
|--------------------|-----|
| Dictionary version | n/a |
|--------------------|-----|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Fluconazole® |
|-----------------------|--------------|

|                                |  |
|--------------------------------|--|
| Reporting group description: - |  |
|--------------------------------|--|

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Chlorhexidine gluconate (Hibitane®) |
|-----------------------|-------------------------------------|

|                                |  |
|--------------------------------|--|
| Reporting group description: - |  |
|--------------------------------|--|

| Serious adverse events                            | Fluconazole®   | Chlorhexidine gluconate (Hibitane®) |  |
|---|----------------|-------------------------------------|--|
| Total subjects affected by serious adverse events |                |                                     |  |
| subjects affected / exposed                       | 0 / 11 (0.00%) | 0 / 12 (0.00%)                      |  |
| number of deaths (all causes)                     | 0              | 0                                   |  |
| number of deaths resulting from adverse events    | 0              | 0                                   |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Fluconazole®    | Chlorhexidine gluconate (Hibitane®) |  |
|---|-----------------|-------------------------------------|--|
| Total subjects affected by non-serious adverse events |                 |                                     |  |
| subjects affected / exposed                           | 3 / 11 (27.27%) | 8 / 12 (66.67%)                     |  |
| Nervous system disorders                              |                 |                                     |  |
| Headache  |                 |                                     |  |
| subjects affected / exposed                           | 1 / 11 (9.09%)  | 0 / 12 (0.00%)                      |  |
| occurrences (all)                                     | 1               | 0                                   |  |
| Gastrointestinal disorders                            |                 |                                     |  |
| Nausea  |                 |                                     |  |
| subjects affected / exposed                           | 2 / 11 (18.18%) | 0 / 12 (0.00%)                      |  |
| occurrences (all)                                     | 2               | 0                                   |  |
| Diarrhoea   |                 |                                     |  |

|  |  |                      |  |
|--|--|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1  | 0 / 12 (0.00%)<br>0  |  |
| Reproductive system and breast disorders         |  |                      |  |
| Pain   | Additional description: Local symptoms of pain, discomfort and irritation of the vulva and vagina after the vaginal application of the study drug. |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0  | 8 / 12 (66.67%)<br>8 |  |
| Discomfort                                       | Additional description: Local symptoms of pain, discomfort and irritation of the vulva and vagina after the vaginal application of the study drug. |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0  | 8 / 12 (66.67%)<br>8 |  |
| Irritability                                     | Additional description: Local symptoms of pain, discomfort and irritation of the vulva and vagina after the vaginal application of the study drug. |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0  | 8 / 12 (66.67%)<br>8 |  |

## 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

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

|  |
|--|
| The early termination of the study with less than 50% of the planned number of participants (30+30 in each study arm) has impact on the interpretation of the results. |
|--|

Notes: