



## Clinical trial results:

**A phase 4, randomized, open label multi-centre clinical study to evaluate efficacy of Isoprinosine® in female subjects with low-grade cervical dysplasia caused by HrHPV.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2017-004235-36    |
| Trial protocol           | CZ                |
| Global end of trial date | 02 September 2020 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 09 June 2022 |
| First version publication date | 09 June 2022 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | EWO-ISO-2017/2 |
|-----------------------|----------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Ewopharma AG   |
| Sponsor organisation address | Vordergasse 43, Schaffhausen, Switzerland, CH-8200   |
| Public contact               | Global medical affairs department, Ewopharma International s.r.o., 00421 259429825, e.salapova@ewopharma.com |
| Scientific contact           | Global medical affairs department, Ewopharma International s.r.o., 00421 259429825, e.salapova@ewopharma.com |

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                       | 31 January 2022   |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 02 September 2020 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 02 September 2020 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate whether the treatment with IAD contributes to the regression of low grade lesions ASC-US or LSIL (CIN I) cervical lesions associated with HrHPV infection.

Protection of trial subjects:

Safety and rights of subjects were protected, and the study was conducted in accordance with the protocol. Any other study agreements, International Council for Harmonization (ICH) Good Clinical Practice (GCP), IECs, and all applicable regulatory requirements were met.

Background therapy:

N/A, Wait-and-watch approach as a standard of care until progression or spontaneous regression of intraepithelial lesion.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 17 December 2018 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Czechia: 171 |
| Worldwide total number of subjects   | 171          |
| EEA total number of subjects         | 171          |

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)                      | 171 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Czech Republic was the only country to participate. The study was initiated on 17 Dec 2018 (First Patient In) and completed on 02 Sep 2020 (Last Patient Out). Subjects were randomly assigned between 26 November 2018 to 11 March 2020 into two groups.

### Pre-assignment

Screening details:

Pre-screening took up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before Screening (V1). Randomization was performed in 1:1 ratio (study group (IAD) : control group (wait-and-watch as SOC)); stratification by smoking >10 cigarettes/day. 597 subjects were screened, 171 subjects were enrolled.

### 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>             | Study Group |

Arm description:

IAD treatment started after randomization on Day 1. On each treatment cycle, subjects received IAD 3x1g (3x2 tablets 500mg daily) for 2 weeks followed by 2 weeks without treatment and this had to be repeated until the End of Study (V4, i.e., 6 cycles of treatment) or progression. In case of withdrawal for any reason a follow up phone call had to be performed for safety.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Isoprinosine® |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Tablet        |
| Routes of administration               | Oral use      |

Dosage and administration details:

Name of Finished Product: Isoprinosine®, Name of Active Ingredient: Inosine acedoben dimepranol. IAD formulation is a white to off-white tablet containing the active ingredient Inosine acedoben dimepranol (500 mg) and excipients (mannitol, wheat starch, povidone, and magnesium stearate).

The dosage established for one treatment cycle was 3x1g (3x2 tablets 500 mg daily) for 2 weeks (14 days) followed by 2 weeks (14 days) without treatment and this had to be repeated until the end of study or progression. Study treatment had to be taken approximately at the same time every day. No regimen modifications were established for this study. However, the only modification could have been the discontinuation of treatment according to the investigator's criteria.

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

Arm description:

Control group - Wait-and-watch: There is no treatment for HrHPV infection so far, and standard of care is wait-and-watch approach till progression or spontaneous regression of intraepithelial lesions.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| <b>Number of subjects in period 1</b> | Study Group | Control Group |
|---------------------------------------|-------------|---------------|
| Started                               | 84          | 87            |
| Completed                             | 79          | 84            |
| Not completed                         | 5           | 3             |
| Consent withdrawn by subject          | 2           | -             |
| Adverse event, non-fatal              | 1           | -             |
| Other                                 | -           | 1             |
| Progression                           | 2           | 2             |

## Baseline characteristics

### Reporting groups

|  |               |
|--|---------------|
| Reporting group title  | Study Group   |
| Reporting group description:   |               |
| IAD treatment started after randomization on Day 1. On each treatment cycle, subjects received IAD 3x1g (3x2 tablets 500mg daily) for 2 weeks followed by 2 weeks without treatment and this had to be repeated until the End of Study (V4, i.e., 6 cycles of treatment) or progression. In case of withdrawal for any reason a follow up phone call had to be performed for safety. |               |
| Reporting group title  | Control Group |
| Reporting group description:   |               |
| Control group - Wait-and-watch: There is no treatment for HrHPV infection so far, and standard of care is wait-and-watch approach till progression or spontaneous regression of intraepithelial lesions.   |               |

| Reporting group values                             | Study Group | Control Group | Total |
|--|-------------|---------------|-------|
| Number of subjects                                 | 84          | 87            | 171   |
| Age categorical<br>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)                          | 0           | 0             | 0     |
| Adults (18-64 years)                               | 84          | 87            | 171   |
| From 65-84 years                                   | 0           | 0             | 0     |
| 85 years and over                                  | 0           | 0             | 0     |
| Age continuous<br>Units: years                     |             |               |       |
| arithmetic mean                                    | 30.9        | 32.1          |       |
| standard deviation                                 | ± 6.9       | ± 7.5         | -     |
| Gender categorical<br>Units: Subjects              |             |               |       |
| Female   | 84          | 87            | 171   |
| Male   | 0           | 0             | 0     |
| Smoking status<br>Units: Subjects                  |             |               |       |
| Never  | 46          | 51            | 97    |
| Current  | 33          | 32            | 65    |
| Former   | 5           | 4             | 9     |
| Race<br>Units: Subjects                            |             |               |       |
| Caucasian  | 84          | 87            | 171   |
| Other  | 0           | 0             | 0     |

## End points

### End points reporting groups

|  |               |
|--|---------------|
| Reporting group title  | Study Group   |
| Reporting group description:<br>IAD treatment started after randomization on Day 1. On each treatment cycle, subjects received IAD 3x1g (3x2 tablets 500mg daily) for 2 weeks followed by 2 weeks without treatment and this had to be repeated until the End of Study (V4, i.e., 6 cycles of treatment) or progression. In case of withdrawal for any reason a follow up phone call had to be performed for safety. |               |
| Reporting group title  | Control Group |
| Reporting group description:<br>Control group - Wait-and-watch: There is no treatment for HrHPV infection so far, and standard of care is wait-and-watch approach till progression or spontaneous regression of intraepithelial lesions.   |               |

### Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Primary analysis

|   |   |
|---|---|
| End point title   | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Primary analysis |
| End point description:<br>Primary variable (regression) as a derived composite variable defined as negativity of both cytological and histological tests. It was a combination of PAP smear test, histological test and COBAS® HPV test. Summary statistics were calculated by treatment group and by study visit for each component of the primary endpoint.<br>The analysis of the primary variable reflected the restriction on the randomisation implied by the stratification by study centre. The two-sided 95% CI for the treatment difference was calculated using stratified Newcombe CI for proportion differences with the Cochran-Mantel-Haenszel weights. The adjusted effect was obtained by weighted average of stratum specific rate differences.<br>Primary analysis was done in Full Analysis Set (FAS), which was as complete as possible and the closest to the intention-to-treat ideal according to ICH E9. Subject was excluded from FAS if she failed in inclusion criterion No. 2 or 3 or there was no data post randomisation available |   |
| End point type  | Primary   |
| End point timeframe:<br>From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).  |   |

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 81              | 87              |  |  |
| Units: Totals               | 12              | 27              |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Primary Variable Analysis (FAS population) |
| Statistical analysis description:<br>The analysis of the primary variable reflected the restriction on the randomisation implied by the stratification by study centre. The two-sided 95% CI for the treatment difference was calculated using stratified Newcombe CI for proportion differences with the Cochran-Mantel-Haenszel weights. The adjusted effect was obtained by weighted average of stratum specific rate differences. |  |

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Control Group v Study Group |
| Number of subjects included in analysis | 168                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| Parameter estimate                      | Treatment difference (%)    |
| Point estimate                          | -14.8                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -27                         |
| upper limit                             | -2.1                        |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Primary Variable: Logistic Model (FAS population) |
|-----------------------------------|---|

Statistical analysis description:

The treatment-by-centre interaction was analysed by using of logistic model with logit link function used with the goal to gain supporting arguments

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Study Group v Control Group |
| Number of subjects included in analysis | 168                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.8997 <sup>[1]</sup>     |
| Method                                  | Chi-squared                 |

Notes:

[1] - p-value for treatment = 0.0118, p-value for centre was 0.0679

### **Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Secondary analysis**

|                 |   |
|-----------------|---|
| End point title | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Secondary analysis |
|-----------------|---|

End point description:

Primary variable (regression) as a derived composite variable defined as negativity of both cytological and histological tests. It was a combination of PAP smear test, histological test and COBAS® HPV test. Summary statistics were calculated by treatment group and by study visit for each component of the primary endpoint.

The analysis of the primary variable reflected the restriction on the randomisation implied by the stratification by study centre. The two-sided 95% CI for the treatment difference was calculated using stratified Newcombe CI for proportion differences with the Cochran-Mantel-Haenszel weights. The adjusted effect was obtained by weighted average of stratum specific rate differences.

Secondary analysis of the primary variable was done in Per-Protocol analyses set (PPS) defined as all subjects from the FAS population without any major protocol deviation as defined in section 12 of the study protocol, except for a lack of the ICF completion.

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

End point timeframe:

From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 75              | 81              |  |  |
| Units: Totals               | 12              | 24              |  |  |

## Statistical analyses

| Statistical analysis title              | Primary Variable Analysis (PPS population) |
|---|--|
| Comparison groups                       | Study Group v Control Group                |
| Number of subjects included in analysis | 156  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| Parameter estimate                      | Treatment difference (%)                   |
| Point estimate                          | -12  |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -24.7                                      |
| upper limit                             | 1.2  |

## Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Age ≥35 years

|                 |   |
|-----------------|---|
| End point title | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Age ≥35 years |
|-----------------|---|

End point description:

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

End point timeframe:

From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 39              |  |  |
| Units: Totals               | 7               | 10              |  |  |

## Statistical analyses

| Statistical analysis title | Primary Variable: Subgroup analysis, Age ≥35 years |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Although subgroup analyses were not planned initially, the analysis of the primary outcome was



repeated for some groups in order to obtain a better knowledge of drug efficacy versus the non-intervention approach.

This was an analysis of regression in FAS population, Age  $\geq 35$  years.

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Study Group v Control Group |
| Number of subjects included in analysis | 69                          |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.825                     |
| Method                                  | Chi-squared                 |

---

**Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Age  $\geq 35$  years, with exclusions**

|  |  |
|--|--|
| End point title  | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Age $\geq 35$ years, with exclusions |
| End point description:   |  |
| Age $\geq 35$ years, excluded cases with HPV-type change   |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4). |  |

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 29              | 37              |  |  |
| Units: Totals               | 7               | 10              |  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Age $\geq 35$ years, excluded cases with HPV-type change |
| Statistical analysis description:  |  |
| Although subgroup analyses were not planned initially, the analysis of the primary outcome was repeated for some groups in order to obtain a better knowledge of drug efficacy versus the non-intervention approach. |  |
| This was an analysis of regression in FAS population, Age $\geq 35$ years, excluded cases with HPV-type change.  |  |
| Comparison groups  | Study Group v Control Group                              |
| Number of subjects included in analysis  | 66   |
| Analysis specification   | Post-hoc   |
| Analysis type  | superiority  |
| P-value  | = 0.79   |
| Method   | Chi-squared  |

**Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Age ≤40 years, with exclusion due to worsening of PAP Smear test**

|  |  |
|--|--|
| End point title  | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Age ≤40 years, with exclusion due to worsening of PAP Smear test |
| End point description:<br>Age ≤40 years, excluded cases with PAP Smear test getting worse during Visit 1,2,3   |  |
| End point type   | Primary  |
| End point timeframe:<br>From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4). |  |

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 48              | 50              |  |  |
| Units: Totals               | 11              | 23              |  |  |

**Statistical analyses**

|   |  |
|---|--|
| Statistical analysis title  | Age ≤40 years, with exclusion due PAP Smear test |
| Statistical analysis description:<br>Although subgroup analyses were not planned initially, the analysis of the primary outcome was repeated for some groups in order to obtain a better knowledge of drug efficacy versus the non-intervention approach.<br>This was an analysis of regression in FAS population, Age ≤40 years, excluded cases with PAP Smear test getting worse during Visit 1,2,3 |  |
| Comparison groups   | Study Group v Control Group                      |
| Number of subjects included in analysis   | 98   |
| Analysis specification  | Post-hoc   |
| Analysis type   | superiority                                      |
| P-value   | = 0.029  |
| Method  | Chi-squared                                      |

**Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Negativity of COBAS® test on Visit 4**

|   |  |
|---|--|
| End point title   | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Negativity of COBAS® test on Visit 4 |
| End point description:<br>Negativity of COBAS® test on Visit 4, 9 subjects in which COBAS® test detected change of the HPV type excluded from FAS |  |
| End point type  | Primary  |

End point timeframe:

From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 74              | 83              |  |  |
| Units: Totals               |                 |                 |  |  |
| Negative                    | 20              | 35              |  |  |
| Positive                    | 54              | 48              |  |  |

## Statistical analyses

| Statistical analysis title | Negativity of COBAS® test on Visit 4 |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Although subgroup analyses were not planned initially, the analysis of the primary outcome was repeated for some groups in order to obtain a better knowledge of drug efficacy versus the non-intervention approach.

This was an analysis of regression in FAS population, Negativity of COBAS® test on Visit 4, 9 subjects in which COBAS® test detected change of the HPV type excluded from FAS

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Study Group v Control Group |
| Number of subjects included in analysis | 157                         |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.065                     |
| Method                                  | Chi-squared                 |

## Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Negativity of PAP-Smear test on Visit 4

|                 |   |
|-----------------|---|
| End point title | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Negativity of PAP-Smear test on Visit 4 |
|-----------------|---|

End point description:

Negativity of PAP-Smear test on Visit 4, 49 subjects in PAP-Smear test detected change of the HPV type excluded from FAS

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

End point timeframe:

From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 51              | 66              |  |  |
| Units: Totals               |                 |                 |  |  |
| Negative                    | 15              | 31              |  |  |
| Positive                    | 36              | 35              |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Negativity of PAP-Smear test on Visit 4 |
| Comparison groups                       | Study Group v Control Group             |
| Number of subjects included in analysis | 117                                     |
| Analysis specification                  | Post-hoc                                |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.0059                                |
| Method                                  | Chi-squared                             |

## Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Ongoing diagnosis related to immune system function

|                 |   |
|-----------------|---|
| End point title | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Ongoing diagnosis related to immune system function |
|-----------------|---|

End point description:

Ongoing diagnosis related to immune system function: Asthma, Asthma bronchiale, Crohns disease, Diabetes mellitus, Diabetes mellitus II, Fatigue, Fatigue states, Fatigue syndrome, Hyperthyreosis, Hypothyreosis, Hypothyroidism, Hypothyreosa, Chronic gastritis, Chronic rhinitis, Systemic mycosis; 24 cases excluded from FAS

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

End point timeframe:

From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 69              | 75              |  |  |
| Units: Totals               | 12              | 23              |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Ongoing diagnosis related to immune system functio |
|----------------------------|--|

Statistical analysis description:

Although subgroup analyses were not planned initially, the analysis of the primary outcome was

repeated for some groups in order to obtain a better knowledge of drug efficacy versus the non-intervention approach.

This was an analysis of regression in FAS population, Ongoing diagnosis related to immune system function, 24 cases excluded from FAS

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Study Group v Control Group |
| Number of subjects included in analysis | 144                         |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.064                     |
| Method                                  | Chi-squared                 |

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**Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Ongoing allergies and diagnosis related to immune system function**

|                        |   |
|------------------------|---|
| End point title        | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Ongoing allergies and diagnosis related to immune system function |
| End point description: | Ongoing allergies and diagnosis related to immune system function, 35 cases excluded from FAS   |
| End point type         | Primary   |
| End point timeframe:   | From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).                                |

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 64              | 71              |  |  |
| Units: Totals               | 11              | 22              |  |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| Statistical analysis title        | Allergies and diagnosis related to immune system  |
| Statistical analysis description: | Although subgroup analyses were not planned initially, the analysis of the primary outcome was repeated for some groups in order to obtain a better knowledge of drug efficacy versus the non-intervention approach.<br>This was an analysis of regression in FAS population, Ongoing allergies and diagnosis related to immune system function, 35 cases excluded from FAS |
| Comparison groups                 | Study Group v Control Group   |

|   |             |
|---|-------------|
| Number of subjects included in analysis | 135         |
| Analysis specification                  | Post-hoc    |
| Analysis type                           | superiority |
| P-value                                 | = 0.062     |
| Method                                  | Chi-squared |

---

**Primary: Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Exclusion due to use of oral contraceptive and ongoing diagnosis related to immune system function**

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|                 |  |
|-----------------|--|
| End point title | Proportion of subjects with regression of low grade lesions LSIL (CIN I) in 6 months after randomization - Subgroup analyses, Exclusion due to use of oral contraceptive and ongoing diagnosis related to immune system function |
|-----------------|--|

End point description:

Use of Oral contraceptives and with ongoing diagnosis related to immune system function excluded from FAS

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

End point timeframe:

From pre-screening (Up to 12 months from cytological confirmed ASC-US or LSIL, or histologically confirmed CIN 1, or both before V1) to End of Study Visit (V4).

---

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 43              | 51              |  |  |
| Units: Totals               | 10              | 19              |  |  |

**Statistical analyses**

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Exclusion due to oral contraceptive use |
|-----------------------------------|---|

Statistical analysis description:

Although subgroup analyses were not planned initially, the analysis of the primary outcome was repeated for some groups in order to obtain a better knowledge of drug efficacy versus the non-intervention approach.

This was an analysis of regression in FAS population, Use of Oral contraceptives and with ongoing diagnosis related to immune system function excluded from FAS

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Study Group v Control Group |
| Number of subjects included in analysis | 94                          |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.143                     |
| Method                                  | Chi-squared                 |

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**Secondary: Proportion of subjects with HrHPV negative cervical samples assessed**

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**by COBAS test between IAD treatment group and control group - Visit 4**

|  |  |
|--|--|
| End point title  | Proportion of subjects with HrHPV negative cervical samples assessed by COBAS test between IAD treatment group and control group - Visit 4 |
| End point description:<br>The analysis was done for both Visit 3 and Visit 4 separately.<br>Analyses population: Full Analysis Set (FAS), which was as complete as possible and the closest to the intention-to-treat ideal according to ICH E9. Subject was excluded from FAS if she failed in inclusion criterion No. 2 or 3 or there was no data post randomisation available |  |
| End point type   | Secondary  |
| End point timeframe:<br>From Screening to Visit 4 (End of Study).  |  |

| End point values            | Study Group     | Control Group   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 80              | 86              |  |  |
| Units: Totals               | 20              | 35              |  |  |

**Statistical analyses**

|   |                                 |
|---|---------------------------------|
| Statistical analysis title              | Negative COBAS® Test at Visit 4 |
| Comparison groups                       | Study Group v Control Group     |
| Number of subjects included in analysis | 166                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| Parameter estimate                      | Treatment difference (%)        |
| Point estimate                          | -14.3                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -27.8                           |
| upper limit                             | 0                               |

**Secondary: The overall safety and tolerability of IAD as assessed by evaluating of adverse events and serious adverse events (SAE) reported during the course of the study**

|  |   |
|--|---|
| End point title  | The overall safety and tolerability of IAD as assessed by evaluating of adverse events and serious adverse events (SAE) reported during the course of the study |
| End point description:<br>AEs coded by MedDRA were listed and summarised by treatment group. Counts of patients experiencing AE were presented by MedDRA System Organ Class (SOC), MedDRA Preferred Term (PT), causality and severity. Summary of AEs is presented here. |   |
| End point type   | Secondary   |
| End point timeframe:<br>AE data collection begun after a subject signed the ICF and continued until study completion (V4,  |   |

completers) or until completion of safety follow up (performed for withdrawals only as phone call after 14 days after withdrawal).

---

| <b>End point values</b>         | Study Group     | Control Group   |  |  |
|---------------------------------|-----------------|-----------------|--|--|
| Subject group type              | Reporting group | Reporting group |  |  |
| Number of subjects analysed     | 84              | 87              |  |  |
| Units: Totals                   |                 |                 |  |  |
| Any AE                          | 17              | 14              |  |  |
| Related                         | 4               | 0               |  |  |
| Severe Intensity                | 0               | 1               |  |  |
| Serious AE                      | 1               | 1               |  |  |
| Death= an AE with fatal outcome | 0               | 0               |  |  |

### **Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE data collection begun after a subject signed the ICF and continued until study completion (V4, completers) or until completion of safety follow up (performed for withdrawals only as phone call after 14 days after withdrawal).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 23.0   |

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Study Group |
|-----------------------|-------------|

Reporting group description:

IAD treatment started after randomization on Day 1. On each treatment cycle, subjects received IAD 3x1g (3x2 tablets 500mg daily) for 2 weeks followed by 2 weeks without treatment and this had to be repeated until the End of Study (V4, i.e., 6 cycles of treatment) or progression. In case of withdrawal for any reason a follow up phone call had to be performed for safety.

|                       |               |
|-----------------------|---------------|
| Reporting group title | Control Group |
|-----------------------|---------------|

Reporting group description:

Control group - Wait-and-watch: There is no treatment for HrHPV infection so far, and standard of care is wait-and-watch approach till progression or spontaneous regression of intraepithelial lesions.

| Serious adverse events                            | Study Group    | Control Group  |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 1 / 84 (1.19%) | 1 / 87 (1.15%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |
| Injury, poisoning and procedural complications    |                |                |  |
| Meniscus injury                                   |                |                |  |
| subjects affected / exposed                       | 0 / 84 (0.00%) | 1 / 87 (1.15%) |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                        |                |                |  |
| Abdominal pain upper                              |                |                |  |
| subjects affected / exposed                       | 1 / 84 (1.19%) | 0 / 87 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                     | Study Group      | Control Group  |  |
|---|------------------|----------------|--|
| Total subjects affected by non-serious adverse events |                  |                |  |
| subjects affected / exposed                           | 10 / 84 (11.90%) | 4 / 87 (4.60%) |  |
| Nervous system disorders                              |                  |                |  |
| Headache  |                  |                |  |
| subjects affected / exposed                           | 3 / 84 (3.57%)   | 0 / 87 (0.00%) |  |
| occurrences (all)                                     | 4                | 0              |  |
| Infections and infestations                           |                  |                |  |
| Nasopharyngitis                                       |                  |                |  |
| subjects affected / exposed                           | 4 / 84 (4.76%)   | 1 / 87 (1.15%) |  |
| occurrences (all)                                     | 4                | 1              |  |
| Tonsillitis   |                  |                |  |
| subjects affected / exposed                           | 3 / 84 (3.57%)   | 0 / 87 (0.00%) |  |
| occurrences (all)                                     | 3                | 0              |  |
| Vulvovaginal mycotic infection                        |                  |                |  |
| subjects affected / exposed                           | 0 / 84 (0.00%)   | 3 / 87 (3.45%) |  |
| occurrences (all)                                     | 0                | 3              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 26 September 2018 | <p>Protocol Version 3, dated 20 Aug 2018, Amendment 1</p> <p>Considering the immunomodulatory effects of the tested product Isoprinosine, exclusion of patients with HIV infection was recommended by CZ RA during review of the initial clinical trial application. Examination for HIV antibodies level during screening in order to exclude patients with positive results was requested by CZ RA.</p> <p>Following changes were made to the original Protocol:</p> <ol style="list-style-type: none"><li>1. Exclusion criterion 1: ASC-H was added</li><li>2. Exclusion criterion 12: HIV Positive Subjects</li><li>3. Exclusion criterion 13: Subjects with liver disorder (severe liver function impairment, AST and ALT value greater than 3 times the upper limit of normal</li><li>4. HIV test was added to the Table 1: Schedule of assessment at the V1-Screening visit</li><li>5. HIV test was added to the visit schedule and Assessment to the screening period describing Screening visit V1</li><li>6. Other administrative and minor formatting changes were made.</li></ol>   |
| 29 March 2019     | <p>Protocol Version 4, dated 25 Feb 2019, Amendment 2</p> <p>Summary of significant changes:</p> <ol style="list-style-type: none"><li>1. Inclusion criterion 1: Upper age limit was changed from 40 years to 47 years</li><li>2. Inclusion criterion 2: Cytologically confirmed ASC-US/LSIL within the last 24 weeks before randomisation was changed to: Cytologically confirmed ASC-US/LSIL or histologically confirmed CIN1 or both within the last 12 month before the screening (V1) visit. In case the cytological examination was not done or was negative in pre-screening period, histologically confirmed CIN 1 will prevail.</li><li>3. Exclusion criterion 2: Subjects participating in any clinical trial within 3 months before enrolment was changed to: Subjects using any investigational drug within 3 months before enrolment.</li><li>4. Exclusion criterion 7: abnormal serum creatinine at screening (V1) visit was changed to: increase of serum creatinine at screening (V1) visit assessed as clinically significant by investigator.</li><li>5. Exclusion criterion 11: Subject with a history of gout, hyperuricaemia, urolithiasis was changed to: Subjects with a history of gout, urolithiasis and clinically significant hyperuricemia assessed by investigator at the V1.</li><li>6. Address of EU Legal Representative of Sponsor was changed from Hlavná 13, 831 01 Bratislava, Slovakia to Prokopa Velkého 52, 811 04 Bratislava, Slovakia.</li></ol> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported