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, Schauffhausen, 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
Arm title	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.

Arm title	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

Number of subjects in period 1	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 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 Units: years			
arithmetic mean	30.9	32.1	
standard deviation	± 6.9	± 7.5	-
Gender categorical Units: Subjects			
Female	84	87	171
Male	0	0	0
Smoking status Units: Subjects			
Never	46	51	97
Current	33	32	65
Former	5	4	9
Race Units: Subjects			
Caucasian	84	87	171
Other	0	0	0

End points

End points 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.

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:

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.
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:

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:

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

Statistical analysis title	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 [1]
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 ≥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 ≥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 ≥35 years, with exclusions

End point description:

Age ≥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 ≥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 ≥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:

Age ≤40 years, excluded cases with PAP Smear test getting worse during Visit 1,2,3

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	48	50		
Units: Totals	11	23		

Statistical analyses

Statistical analysis title	Age ≤40 years, with exclusion due PAP Smear test

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 ≤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:

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, Hypothyrreosa, 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

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.
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

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

Statistical analysis title	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

Secondary: Proportion of subjects with HrHPV negative cervical samples assessed

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:

The analysis was done for both Visit 3 and Visit 4 separately.
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:

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:

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:

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).

End point values	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

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 %

Non-serious adverse events	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	Protocol Version 3, dated 20 Aug 2018, Amendment 1 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. Following changes were made to the original Protocol: 1. Exclusion criterion 1: ASC-H was added 2. Exclusion criterion 12: HIV Positive Subjects 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 4. HIV test was added to the Table 1: Schedule of assessment at the V1-Screening visit 5. HIV test was added to the visit schedule and Assessment to the screening period describing Screening visit V1 6. Other administrative and minor formatting changes were made.
29 March 2019	Protocol Version 4, dated 25 Feb 2019, Amendment 2 Summary of significant changes: 1. Inclusion criterion 1: Upper age limit was changed from 40 years to 47 years 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. 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. 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. 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. 6. Address of EU Legal Representative of Sponsor was changed from Hlavná 13, 831 01 Bratislava, Slovakia to Prokopa Veľkého 52, 811 04 Bratislava, Slovakia.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported