



Clinical trial results:

A multicenter, open label Phase I/II study to determine the safety and immune modulating effects of the therapeutic Human Papilloma Virus Type 16 (HPV16) E6/E7 Synthetic Long Peptides Vaccine (ISA101/ISA101b) immunotherapy in combination with standard of care therapy (carboplatin and paclitaxel with or without bevacizumab) in women with HPV16-positive advanced or recurrent cervical cancer who have no curative treatment options.

Summary

EudraCT number	2013-001804-12
Trial protocol	DE NL BE
Global end of trial date	01 September 2018

Results information

Result version number	v1 (current)
This version publication date	24 October 2019
First version publication date	24 October 2019
Summary attachment (see zip file)	ISA_Clinical Study Report_Synopsis_V1.0_09Aug2019 (SMS-0179_ISA_Clinical Study Report_Synopsis_V1.0_09Aug2019.pdf)

Trial information

Trial identification

Sponsor protocol code	ISA-HPV-01-12
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02128126
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ISA Therapeutics B.V.
Sponsor organisation address	J.H. Oortweg 19, Leiden, Netherlands, 2333 CH
Public contact	Sonja Visscher, ISA Therapeutics B.V., info@isa-pharma.com
Scientific contact	Kees Melief, ISA Therapeutics B.V., melief@isa-pharma.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	26 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2018
Global end of trial reached?	Yes
Global end of trial date	01 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this trial were:

To assess the safety and tolerability of different doses of the ISA101 vaccine with or without pegylated Interferon Alpha (IFN α) as combination therapy with carboplatin and paclitaxel.

To assess the HPV-specific immune responses to different doses of the ISA101 vaccine with or without pegylated IFN α as combination therapy with carboplatin and paclitaxel.

To qualitatively assess the safety profile of ISA101b vaccine compared to ISA101 at the same dose level(s).

To assess the safety of ISA101b vaccine with carboplatin, paclitaxel with or without bevacizumab.

To qualitatively assess the HPV-specific immune responses of ISA101b vaccine relative to the same dose level(s) of ISA101.

To qualitatively assess the HPV-specific immune responses of ISA101b vaccine with carboplatin, paclitaxel with or without bevacizumab.

Protection of trial subjects:

Patients receiving ISA101(b) were closely monitored for at least 4 hours after vaccination to provide means for immediate treatment of allergic reactions should that be necessary (precautions include availability of staff well-trained in resuscitation, intravenous access for administration of fluids, antihistamines and corticosteroids, and epinephrine for intramuscular injection).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	Netherlands: 44
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	81
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 13 centers in 3 countries: Belgium, The Netherlands and Germany.

First ICF was signed: 15Aug2013.

Last study visit before database lock: 09May2018

Pre-assignment

Screening details:

Patients with advanced (Stage IIIb-IVa with involvement of lymph nodes beyond the renal vein) or metastatic (stage IVb) or recurrent HPV16-positive cervical cancer for whom no curative treatment options existed were enrolled.

Total number of patients registered was 93 with 90 being part of safety set.

Period 1

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

Arms

Arm title	ISA101/ISA101b with SoC therapy
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Arm description:

Synthetic Long Peptides Vaccine (ISA101/ ISA101b) immunotherapy in combination with standard of care therapy (carboplatin and paclitaxel with or without bevacizumab).

* Stage 1: 8 cohorts of 6 patients each, 4 dose levels of ISA101 (20, 40, 100 and 300 µg/peptide) with and without 1 µg/kg pegylated IFNα in combination with fixed doses of Standard of Care (SoC) chemotherapy: carboplatin at an AUC of 6 mg/ml/min and paclitaxel at a dose of 175 mg/m².

* Stage 2: 6 additional patients were enrolled each at 40 and 100 µg/peptide dose level of ISA101, without pegylated IFNα.

* Stage 3: ISA101b was tested using the RP2D of 100 µg/peptide. 6 patients were enrolled at the dose level of 100 µg/peptide (cohort 9) in which the dose was given in conjunction with carboplatin at an AUC of 6mg/ml/min and paclitaxel; 6 more patients were treated with ISA101b at 100 µg/peptide in addition to carboplatin, paclitaxel, AND bevacizumab

Arm type	Experimental
Investigational medicinal product name	ISA101/ISA101b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients eligible for the trial were assigned to a cohort in order of entry. Each patient was to receive 3 doses of vaccine (ISA101 or ISA101b) over nine weeks in Cycles 2, 3 and 4 of a total of up to six cycles of chemotherapy (18 weeks, without dose interruption/delays)

The ISA101 vaccine contains nine HPV16 E6 and four HPV16 E7 SLP.

The peptides were dissolved in DMSO and subsequently diluted in WFI and emulsified with Montanide. The final ratio of DMSO / WFI / Montanide is 20/30/50.

The ISA101b vaccine contains nine HPV16 E6 and three HPV16 E7 SLP.

The peptides are reconstituted with Macrogolglycerol Ricinoleate (Reconstitution Solution) and mixed with Montanide

The ISA101/ISA101b vaccine is administered via two SC injections in two different limbs.

Stage 1: four dose levels of ISA101 (20, 40, 100 and 300 µg/peptide)

Stage 2: 40 and 100 µg/peptide dose level of ISA101,

Stage 3: ISA101b of 100 µg/peptide.

Investigational medicinal product name	Pegnitron
Investigational medicinal product code	
Other name	pegylated interferon alpha
Pharmaceutical forms	Powder for solution for injection, Solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegnitron is administered SC according to the SPC
 Stage 1: with and without 1 µg/kg pegylated IFNα
 Stage 2: without pegylated IFNα
 Stage 3: without pegylated IFNα

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Stage 1: fixed doses of Standard of Care (SoC) chemotherapy paclitaxel at a dose of 175 mg/m².
 Stage 2: fixed doses of Standard of Care (SoC) chemotherapy paclitaxel at a dose of 175 mg/m². with and without bevacizumab
 Stage 3: fixed doses of Standard of Care (SoC) chemotherapy paclitaxel at a dose of 175 mg/m².

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	cis-Diammine(1,1-cyclobutanedicarboxylato)platinum
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Stage 1: dose of Standard of Care (SoC) chemotherapy: carboplatin at an Area Under the Curve (AUC) of 6 mg/ml/min
 Stage 2: dose of Standard of Care (SoC) chemotherapy: carboplatin at an Area Under the Curve (AUC) of 6 mg/ml/min
 Stage 3: dose of Standard of Care (SoC) chemotherapy: carboplatin at an Area Under the Curve (AUC) of 6 mg/ml/min

Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	bevacizumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Stage 1 & 2: No bevacizumab
 Stage 3: in cohort 10 only, bevacizumab 15 mg/kg per standard of care

Number of subjects in period 1	ISA101/ISA101b with SoC therapy
Started	90
Completed	58
Not completed	32
Progression disease	15
Consent withdrawn by subject	1
death	3
inability/unwillingness	1

Adverse event	12
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Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: the total number of patients registered in the trial was 93 with 90 being part of the SAF (Safety set) population because 3 patients never received any trial treatment.	

Reporting group values	Overall trial	Total	
Number of subjects	90	90	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	81	81	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous			
Units: years			
median	48.5		
full range (min-max)	28.4 to 74.4	-	
Gender categorical			
Units: Subjects			
Female	90	90	
Male	0	0	

Subject analysis sets

Subject analysis set title	Subjects who received at least 1 dose of ISA101/ISA101b
Subject analysis set type	Sub-group analysis
Subject analysis set description: The total number of patients receiving at least one dose of ISA101 vaccination was 72 and another 12 patients received at least one dose of ISA101b vaccine.	
Subject analysis set title	Subjects for ISA101
Subject analysis set type	Sub-group analysis
Subject analysis set description: SAF-ISA101 Population is 77 (cohort 1 - 8) note: 5 of them never received any dose of ISA101	
Subject analysis set title	Subjects for ISA101b
Subject analysis set type	Sub-group analysis
Subject analysis set description: SAF-ISA101 Population is 13 (cohort 9-10)	

Reporting group values	Subjects who received at least 1 dose of ISA101/ISA101b	Subjects for ISA101	Subjects for ISA101b
Number of subjects	84	77	13
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)	77	69	12
From 65-84 years	7	8	1
85 years and over	0	0	0
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	ISA101/ISA101b with SoC therapy
Reporting group description: Synthetic Long Peptides Vaccine (ISA101/ ISA101b) immunotherapy in combination with standard of care therapy (carboplatin and paclitaxel with or without bevacizumab). * Stage 1: 8 cohorts of 6 patients each, 4 dose levels of ISA101 (20, 40, 100 and 300 µg/peptide) with and without 1 µg/kg pegylated IFNα in combination with fixed doses of Standard of Care (SoC) chemotherapy: carboplatin at an AUC of 6 mg/ml/min and paclitaxel at a dose of 175 mg/m ² . * Stage 2: 6 additional patients were enrolled each at 40 and 100 µg/peptide dose level of ISA101, without pegylated IFNα. * Stage 3: ISA101b was tested using the RP2D of 100 µg/peptide. 6 patients were enrolled at the dose level of 100 µg/peptide (cohort 9) in which the dose was given in conjunction with carboplatin at an AUC of 6mg/ml/min and paclitaxel; 6 more patients were treated with ISA101b at 100 µg/peptide in addition to carboplatin, paclitaxel, AND bevacizumab	
Subject analysis set title	Subjects who received at least 1 dose of ISA101/ISA101b
Subject analysis set type	Sub-group analysis
Subject analysis set description: The total number of patients receiving at least one dose of ISA101 vaccination was 72 and another 12 patients received at least one dose of ISA101b vaccine.	
Subject analysis set title	Subjects for ISA101
Subject analysis set type	Sub-group analysis
Subject analysis set description: SAF-ISA101 Population is 77 (cohort 1 - 8) note: 5 of them never received any dose of ISA101	
Subject analysis set title	Subjects for ISA101b
Subject analysis set type	Sub-group analysis
Subject analysis set description: SAF-ISA101 Population is 13 (cohort 9-10)	

Primary: Subjects With at Least One TEAE (Treatment-Emergent Adverse Ev, TEAE Related to ISA101(b), TEAE Related to IFNα, TEAE Related to Chemotherapy, TEAE Related to Bevacizumab, Serious TEAE, TEAE of NCI-CTC Grade 3, 4, or 5, and TEAE Leading to Drug Withdrawal

End point title	Subjects With at Least One TEAE (Treatment-Emergent Adverse Ev, TEAE Related to ISA101(b), TEAE Related to IFNα, TEAE Related to Chemotherapy, TEAE Related to Bevacizumab, Serious TEAE, TEAE of NCI-CTC Grade 3, 4, or 5, and TEAE Leading to Drug Withdrawal ^[1]
End point description: A TEAE was reported in 89 out of 90 patients. The one patient without any TEAEs experienced rapid progression after the first chemotherapy cycle, this patient did not received any dose ISA101(b). The reported AE was "increased pain", which was not related to any therapy and started before the first chemotherapy administration. Almost all patients (98.9%) reported chemotherapy related AEs. AEs related to ISA101/ISA101b were reported for 80.0% of all patients, with a somewhat lower frequency of vaccine-related events recorded for the ISA101b bridging cohorts compared with the ISA101 cohorts at the same peptide concentration of 100 µg/peptide, 69.2% versus 100% respectively.	
End point type	Primary
End point timeframe: The study will include 3 weeks of screening, 18 weeks of treatment, 30-day follow up after treatment for safety, and 34 weeks follow up after treatment for clinical response	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.	

End point values	ISA101/ISA101b with SoC therapy			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: number				
number (not applicable)				
Any TEAE	89			
TEAE related to ISA101/ISA101b	72			
TEAE related to Pegylated IFNa	29			
TEAE related to bevacizumab	2			
TEAE related to Chemotherapy	89			
Serious TEAE	49			
NCI-CTC grade 3, 4, or 5 TEAEs	73			
TEAEs Leading to Drug Withdrawal	13			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-Emergent Systemic Allergic Reactions (TESAR) Related to ISA101(b):Subjects With at Least One TESAR, Serious TESAR, TESAR of NCI-CTC Grade 3, 4, or 5, and TESAR Leading to Drug Withdrawal

End point title	Treatment-Emergent Systemic Allergic Reactions (TESAR) Related to ISA101(b):Subjects With at Least One TESAR, Serious TESAR, TESAR of NCI-CTC Grade 3, 4, or 5, and TESAR Leading to Drug Withdrawal ^[2]
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End point description:

Overview of Reported TESAR ((treatment emergent serious allergic reaction) Related to ISA101/ISA101b

End point type	Primary
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End point timeframe:

The study will include 3 weeks of screening, 18 weeks of treatment, 30-day follow up after treatment for safety, and 34 weeks follow up after treatment for clinical response

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Subjects who received at least 1 dose of ISA101/ISA101b			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: unit(s)				
number (not applicable)				
patients who received ISA101/ISA101b	84			
Any TESAR	11			
Serious TESAR	5			
NCI-CTCAE Grade 3 or 4 TESAR	3			
Leading to drug withdrawal	2			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-Emergent Injection Site Reactions (TEISR) related to ISA101(b): subjects With at Least One TEISR , Serious TEISR, TEISR of NCI-CTC Grade 3, 4, or 5, and TEISR Leading to Drug Withdrawal of Patients Treated with ISA101/ISA101b

End point title	Treatment-Emergent Injection Site Reactions (TEISR) related to ISA101(b): subjects With at Least One TEISR , Serious TEISR, TEISR of NCI-CTC Grade 3, 4, or 5, and TEISR Leading to Drug Withdrawal of Patients Treated with ISA101/ISA101b ^[3]
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End point description:

Treatment emergent dose-related Injection Site Reactions (ISRs) to ISA101 were the most frequent AEs reported to be related to ISA101 with ISRs occurring in most patients who received ISA101. Most of the local ISRs were reported to be Grade 1 to 2 in severity.

End point type	Primary
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End point timeframe:

The study will include 3 weeks of screening, 18 weeks of treatment, 30-day follow up after treatment for safety, and 34 weeks follow up after treatment for clinical response.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Subjects who received at least 1 dose of ISA101/ISA101b			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: unit(s)				
number (not applicable)				
number of patients who received ISA101 (b)	84			
Any TEISR	59			
Serious TEISR	0			
NCI-CTC grade 3, 4, or 5 TEISR	1			
TEISR Leading to Drug Withdrawal	1			

Statistical analyses

No statistical analyses for this end point

Primary: HPV specific immune response to the ISA101 vaccine

End point title	HPV specific immune response to the ISA101 vaccine ^[4]
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End point description:

See CSR synopsis in attachment page 7 for description of Biomarker Response - Immune Response to ISA101/ISA101b

Spearman correlation

r = correlation coefficient

MRM = Memory Response Mix; ESM = maximum of MRM at visits 8 and 10; ESMC = maximum of MRM at Visit 8 and 10 - MRM at Visit 4; ESMCP = $100 * (ESM - MRM \text{ at visit } 4) / MRM \text{ at visit } 4$

ESSMEDIAN = for each of the 6 epitopes the maximum over visit 8 and 10. ESSMEDIAN is the median of the 6 maxima.

End point type	Primary
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End point timeframe:

The study will include 3 weeks of screening, 18 weeks of treatment, 30-day follow up after treatment for safety, and 34 weeks follow up after treatment for clinical response

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Subjects for ISA101			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: unit(s)				
number (not applicable)				
ESSMEDIAN - ESM r	0.058			
ESSMEDIAN - ESMC r	0.012			
ESSMEDIAN - ESMCP r	-0.083			
ESMCP - ESM r	0.331			
ESMCP - ESMC r	0.885			
ESMC - ESM r	0.636			

Statistical analyses

No statistical analyses for this end point

Primary: IMMUNE OUTCOME DATA

End point title	IMMUNE OUTCOME DATA ^[5]
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End point description:

ESM = maximum of MRM at visits 8 and 10

MRM = Memory Response Mix

ESSMEDIAN = for each of the 6 epitopes the maximum over visit 8 and 10. ESSMEDIAN is the median of the 6 maxima

End point type	Primary
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End point timeframe:

The study will include 3 weeks of screening, 18 weeks of treatment, 30-day follow up after treatment for safety, and 34 weeks follow up after treatment for clinical response

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Subjects for ISA101			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: units				
number (not applicable)				
ESM median in cohort with 20 microgram ISA101	193.50			
ESM median in cohort with 40 microgram ISA101	259.00			
ESM median in cohort with 100 microgram ISA101	286.0			
ESM median in cohort with 300 microgram ISA101	248.00			
ESM median in cohort with IFNa	250.00			
ESM median in cohort without IFNa	246.00			
ESM median of patients without prior chemo	248.00			
ESM median of patients with prior chemo	228.00			
ESM median of all cohorts	248.00			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response
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End point description:

Patients who had a stronger HPV16-specific immune response to ISA101 (greater than or equal to the median) had a statistically significant prolongation of median OS of 16.8 months compared to those who had a lower HPV-specific immune response (median OS of 11.2 months). These data indicate a strong association between the strength of the HPV-specific immune response induced by ISA101 treatment and OS.

Patients who had a stronger HPV16-specific immune response to ISA101 (greater than or equal to the median) had a statistically significant prolongation of median OS of 16.8 months compared to those who had a lower HPV-specific immune response (median OS of 11.2 months). These data indicate a strong association between the strength of the HPV-specific immune response induced by ISA101 treatment and OS.

End point type	Secondary
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End point timeframe:

CT/MRI scan at baseline, Day 1 of cycle 4, EoT visit and at week 30, 42, 52

End point values	Subjects for ISA101			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: units				
number (not applicable)				
Complete response	4			
Partial response	27			
Stable disease	31			
Progressive disease	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were monitored for AEs from Inform Consent Form signature and during each patient visit until 30 days after end of treatment visit.

Adverse event reporting additional description:

All reported (S)AEs are the (S)AEs with the onset of first treatment.

In this data base only events related to ISA101(b) are reported.

Most of the (S)AEs in the CervISA trial were expected toxicities related to chemotherapy or to complications associated with progression of cervical cancer.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	received at least one dose of ISA101 group
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Reporting group description:

A total of 93 patients registered for the trial, 79 for the evaluation of ISA101 and 14 for the ISA101b evaluation.

The Safety Set (SAF) for the trial was defined as all patients who received at least one dose of chemotherapy or other trial treatment:

For ISA101, the SAF population was 77 patients of whom 72 received at least one dose of ISA101 vaccine and 51 patients completed all trial related treatments.

For ISA101b, the SAF population was 13 patients, 12 of whom received at least one dose of ISA101b vaccine and seven completed all study related treatments.

Most of the (S)AEs in the CervISA trial were expected toxicities related to chemotherapy or to complications associated with progression of cervical cancer.

Only ISA101 related (S)AE are reported in this database

Reporting group title	received at least one dose of ISA101b group
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Reporting group description:

A total of 93 patients registered for the trial, 79 for the evaluation of ISA101 and 14 for the ISA101b evaluation.

The Safety Set (SAF) for the trial was defined as all patients who received at least one dose of chemotherapy or other trial treatment:

For ISA101, the SAF population was 77 patients of whom 72 received at least one dose of ISA101 vaccine and 51 patients completed all trial related treatments.

For ISA101b, the SAF population was 13 patients, 12 of whom received at least one dose of ISA101b vaccine and seven completed all study related treatments.

Most of the (S)AEs in the CervISA trial were expected toxicities related to chemotherapy or to complications associated with progression of cervical cancer.

Only ISA101(b) related (S)AE are reported in this database.

Serious adverse events	received at least one dose of ISA101 group	received at least one dose of ISA101b group	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 72 (22.22%)	1 / 12 (8.33%)	
number of deaths (all causes)	6	0	
number of deaths resulting from adverse events	0	0	

Injury, poisoning and procedural complications			
Injection related reaction			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaccination complication			
subjects affected / exposed	2 / 72 (2.78%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 72 (2.78%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 72 (6.94%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			

subjects affected / exposed	2 / 72 (2.78%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 12 (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: 5 %

Non-serious adverse events	received at least one dose of ISA101 group	received at least one dose of ISA101b group	
Total subjects affected by non-serious adverse events subjects affected / exposed	63 / 72 (87.50%)	9 / 12 (75.00%)	
Injury, poisoning and procedural complications Vaccination complication subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 3	0 / 12 (0.00%) 0	
Nervous system disorders Memory impairment subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0 1 / 72 (1.39%) 1	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	7 / 72 (9.72%) 7 1 / 72 (1.39%) 1 1 / 72 (1.39%) 2 4 / 72 (5.56%) 5 2 / 72 (2.78%) 2	1 / 12 (8.33%) 3 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Influenza like illness	12 / 72 (16.67%) 13	0 / 12 (0.00%) 0	

subjects affected / exposed occurrences (all)	11 / 72 (15.28%) 20	2 / 12 (16.67%) 4	
injection site reac subjects affected / exposed occurrences (all)	27 / 72 (37.50%) 34	6 / 12 (50.00%) 9	
Injection site swelling subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 12 (8.33%) 1	
Pyrexia subjects affected / exposed occurrences (all)	12 / 72 (16.67%) 22	3 / 12 (25.00%) 3	
Vaccination site erythema subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 2	1 / 12 (8.33%) 1	
Vaccination site induration subjects affected / exposed occurrences (all)	6 / 72 (8.33%) 7	0 / 12 (0.00%) 0	
Vaccination site reaction subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 5	2 / 12 (16.67%) 3	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	1 / 12 (8.33%) 1	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 12 (8.33%) 1	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	1 / 12 (8.33%) 1	
Infections and infestations Bronchiolitis subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 12 (8.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2013	Protocol V2.0 Initial approved protocol Belgium (BE)
09 January 2014	Protocol V2.1, Initial approved protocol the Netherlands (NL)
11 July 2014	protocol V3.0 , Approved for BE and NL
14 July 2015	Protocol V4.0, Approved for BE and NL
22 October 2015	Protocol V5.0, Approved for BE and NL
21 January 2016	Protocol V6.0, Approved for BE and NL
24 June 2016	Protocol V7.0, Approved for BE and NL
05 August 2016	Protocol V8.0, Initial approved protocol Germany (DE)
27 October 2016	Protocol V9.0, Approved for BE, NL and DE

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported