2 TRIAL SYNOPSIS

Name of Sponsor/Company: ISA Therapeutics B.V. **Name of Finished Product:** ISA101/ISA101b **Name of Active Ingredient:** HPV Type 16 E6/E7 synthetic long peptides vaccine	**Individual Study Table Referring to Part of the Dossier Volume:** **CTD MODULE 5.3.5**	**(For National Authority Use Only)**

TITLE OF TRIAL

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.

INVESTIGATORS AND TRIAL CENTRES

This trial was conducted in 13 centers in 3 countries.
The Principal Investigator (PI) was Prof. Winald Gerritsen, Radboudumc Nijmegen; The Netherlands.
This trial was conducted by 12 investigators and their co-investigators:

- Dr. Ottevanger; Radboudumc Nijmegen; The Netherlands
- Dr. Kroep, University Medical Centre Leiden (LUMC); The Netherlands
  Prof. van der Hoeven (Investigator until 31th July 2015) at LUMC; The Netherlands
- Prof. Reyners; University Medical Centre Groningen (UMCG); The Netherlands
- Prof. Kenter; Netherlands Cancer Institute Amsterdam (AvL-NKI); The Netherlands
  Academic Medical Centre Amsterdam (AMC); The Netherlands
- Dr. Lalisang; University Medical Centre Maastricht (MUMC); The Netherlands
- Prof. Denys; University Hospital Gent (UZG); Belgium
- Prof. Tjalma; University Hospital Antwerp (UZA); Belgium
- Prof. Vergote; University Hospital Leuven (UZL); Belgium
- Dr. Velu; Chirec Cancer Institute Brussels (CCI); Belgium
- Dr. Goffin University Hospital Liège (CHU - site CHR Citadelle); Belgium
- Prof. Dr. Med. Tanja Fehm, University Hospital Düsseldorf, Germany
- Prof. Dr. Peter Hillemanns, Medizinische Hochschule Hannover, Germany

DATA MONITORING COMMITTEE MEMBERS

- Chair: B.A. Blumenstein, PhD, Statistician; Trial Architecture Consulting, Washington, DC, USA
- Prof. M.H.J. van Oers, Prof. of Hematology (Academisch Medisch Centrum Amsterdam), The Netherlands
- Prof. R.J.M. ten Berge, Prof. of Internal Medicine/Clinical Immunology
  (Academisch Medisch Centrum Amsterdam), The Netherlands

PUBLICATIONS

Abstract: Gerritsen *et. al.*, Feb 2017 (ASCO-SITC)
Correlation between strength of T-cell response against HPV16 and survival after vaccination with HPV16 long peptides in combination with chemotherapy for late-stage cervical cancer.
Abstract: Gerritsen *et. al.*, May 2017 (ASCO)

Association of T cell responses after vaccination with HPV16 long peptides for late stage cervical cancer with prolonged survival
Publication: Massarelli *et. al.*, JAMA Oncol 2018
Combining Immune Checkpoint Blockade and Tumor-Specific Vaccine for Patients With Incurable Human Papillomavirus 16–Related Cancer

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TRIAL PERIOD		**DEVELOPMENT PHASE**
First informed consent:	15Aug2013	Final analysis of Phase I/II
Last study visit before database lock:	09May2018	
Database Lock:	14Aug2018	

OBJECTIVES

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 (IFNα) 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 IFNα 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.

The secondary objective of the trial was:

- To evaluate the clinical efficacy of immunotherapy with ISA101/ISA101b in combination with standard therapy i.e. carboplatin and paclitaxel with or without bevacizumab.

Additional exploratory objectives of the trial as described in Statistical Analysis Plan (SAP) were:

- To evaluate associations between immune response and clinical outcomes.
- To evaluate the effect of dose and baseline attributes on the associations between immune response and clinical outcome.
- To compare the immune status and response data between ISA101 and ISA101b.

METHODS

This was a multicenter, open label, non-randomized Phase I-II trial with expansion and bridging cohorts. 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. The trial was overseen be a Data Monitoring Committee (DMC) that reviewed the safety data and trial conduct at specified time points during the trial.

In the first stage of the trial (Table 1a: cohorts 1-8), eight cohorts of six patients each were enrolled. Four dose levels of ISA101 (20, 40, 100 and 300 µg/peptide) were evaluated with and without 1 µg/kg pegylated IFNα in combination with fixed doses of Standard of Care (SoC) chemotherapy: carboplatin at an Area Under the Curve (AUC) of 6 mg/ml/min and paclitaxel at a dose of 175 mg/m^2.

In the second stage (Table 1a: cohorts 3B and 5B), the expansion stage to determine and confirm the recommended Phase 2 Dose (RP2D), six additional patients were enrolled each at 40 and 100 µg/peptide dose level of ISA101, without pegylated IFNα.

In the bridging cohorts, the third stage (Table 1b: cohorts 9 and 10), the modified vaccine ISA101b was tested using the RP2D of 100 µg/peptide. Six patients were enrolled at the dose level of 100 µg/peptide (cohort 9) in which the dose was given in conjunction with carboplatin and paclitaxel; six more patients were treated in cohort 10, with ISA101b at 100 µg/peptide in addition to carboplatin, paclitaxel, AND bevacizumab.

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The maximum number of ISA101/ISA101b doses per one patient was three to be given over nine weeks. Every patient had to be treated with six cycles (of 3 weeks each) of chemotherapy (carboplatin and paclitaxel +/- bevacizumab), which resulted in a treatment duration of 18 weeks in total. ISA101/ISA101b was administered on Day 15 (±3 days) of Cycles 2, 3 and 4.

Table 1a: **Overview of the ISA101 cohorts and treatment schedule (*per SoC, chemotherapy dose reductions are permitted after Cycle 1; **ISA regimen(s) considered to have an acceptable safety profile in cohorts 1-8)**

Cohort*	# Patients Planned	ISA101	Pegylated IFNα
01	6	20 µg/peptide	-
02	6	20 µg/peptide	1 µg/kg
03	6	40 µg/peptide	-
03B	6	40 µg/peptide**	-
04	6	40 µg/peptide	1 µg/kg
05	6	100 µg/peptide	-
05B	6	100 µg/peptide**	-
06	6	100 µg/peptide	1 µg/kg
07	6	300 µg/peptide	-
08	6	300 µg/peptide	1 µg/kg

Table 1b: **Overview of the ISA101b cohorts and treatment schedules (*per SoC, chemotherapy dose reductions are permitted after Cycle 1; **at the recommendation of the DMC bevacizumab added to treatment cycles)**

Bridging Cohorts	# Patients Planned	ISA101b	Bevacizumab*
09	6	100 µg/peptide	-
10**	6	100 µg/peptide	15 mg/kg

Patients were considered evaluable regarding their HPV16-specific immune responses to the vaccine if they received at least one vaccination with ISA101/ISA101b and had a pre-vaccination blood sample as well as at least one post-vaccination blood sample (all with sufficient Peripheral Blood Mononuclear Cells (PBMCs).

NUMBER OF PATIENTS

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. An overview of the patients is provided in Table 2. All SAF patients from the ISA101 cohorts were summarized as the 'SAF-ISA101 set'; SAF patients from the ISA101 cohorts having survived at least 90 days after administration of the first ISA101 dose were part of the 'SAF90' set which was used for the analysis of the relation between immune outcome and clinical efficacy.

In summary, the total number of patients registered in the trial was 93 with 90 being part of the SAF population because 3 patients never received any trial treatment. The total number of patients receiving at least one ISA101 vaccination was 72 and another 12 patients received at least one dose of ISA101b vaccine.

Table 2: ISA101/101b patient overview- dosing history

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Population	**ISA101**							**ISA101b 100 µg/ peptide**		**All Patients**
	20 µg/ Peptide	40 µg/ Peptide	100 µg/ peptide	300 µg/ Peptide	All ISA101	- prior chemo	+ prior chemo	- Bev-mAb	+ Bev-mAb	
Registered	21	25	21	12	79	42	35	7	7	93
SAF	21	23	21	12	77	42	35	7	6	90
SAF-ISA101	21	23	21	12	77	42	35	0	0	77
SAF90	17	17	20	12	66	38	28	0	0	66
ISA101/ISA101b ≥1 dose	19	20	21	12	72	40	32	6	6	84
All study treatment received	12	15	14	10	51	28	23	2	5	58

INCLUSION CRITERIA

Based on protocol Version 9.0 to be eligible to participate in this trial, candidates must have met the following eligibility criteria:

- Women ≥ 18 years of age.
- Cervical cancer confirmed by histology.
- Advanced (Stage IIIb/IVa with para-aortic lymph nodes involvement beyond the renal vein) or metastatic (Stage IVb) or recurrent cervical cancer confirmed by clinical and/or radiological proof with no curative treatment options.
- Tumor must have been HPV16-positive (determined on archival tumor tissue (≤10 years old); if that was not available a pre-treatment biopsy was required).
- Patients should have been eligible for chemotherapy with carboplatin and paclitaxel, and had consented with chemotherapy with carboplatin and paclitaxel before the start of the informed consent procedure for the study.
- Performance Status (PS) World Health Organization (WHO) scale/Eastern Cooperative Oncology Group (ECOG) ≤ 1.
- For cohort 10, i.e. patients with advanced cervical cancer eligible to receive bevacizumab at each site per SoC. Prior treatment with chemotherapy for recurrent disease was not permitted. However, one prior line of chemotherapy with platinum during primary radio-chemotherapy or platinum-based chemotherapy as neoadjuvant chemotherapy prior to surgery was permitted.
- Written Informed Consent (IC) according to local guidelines.
- Written approval by the treating physician/investigator of his/her clinical judgement that the patient had reasonable life expectancy and was sufficiently fit and motivated to complete the trial treatment and comply to all trial procedures specified by the protocol.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

The final products ISA101/101b consist of two peptide mixes.
ISA101 contains one mix of six peptides (HPV-DP-6P) and one of seven peptides (HPV-DP-7P).
ISA101b is a modified product formulation with two minor modifications: one peptide has been eliminated resulting in two peptide mixes of five (HPV-DP-5P) and seven (HPV-DP-7P) peptides each, and an improved reconstitution solution was used.
On Day 15 (±3 days) of Cycle 2, 3 and 4 patients received the ISA101 or ISA101b vaccination, translating to a total of three administrations, each approximately three weeks apart.
Each ISA101 vaccination included two subcutaneous (SC) injections (one injection containing HPV-DP-7P-peptides and the other HPV-DP-6P-peptides) into two different limbs at the following doses:

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- Patients in cohorts 1 and 2 with ISA101 at a dose of 20 µg/peptide
- Patients in cohort 3, 3B and 4 with ISA101 at a dose of 40 µg/peptide
- Patients in cohort 5, 5B and 6 with ISA101 at a dose of 100 µg/peptide
- Patients in cohort 7 and 8 with ISA101 at a dose of 300 µg/peptide

ISA101b was similarly administered as two injections, one containing the HPV-DP-7P mix and one the HPV-DP-5P mix.

- Patients in cohorts 9 and 10 with ISA101b at dose of 100 µg/peptide

ISA101 lot numbers were 1039816 (HPV-DP-7P) and 1033027 (HPV-DP-6P).
ISA101b lot numbers were 1061895 (HPV-DP-7P) and 1061891 (HPV-DP-5P).

TRIAL DURATION

The trial included three weeks of screening, 18 weeks of treatment (six cycles of chemotherapy), a 30-day follow-up after the end of the last cycle of chemotherapy administration (up to 10 weeks after the last dose of ISA101/101b) for safety, and an additional 34 weeks follow-up after treatment, for assessment of clinical endpoints. The total trial duration was up to 55 weeks per patient. Per amendment (protocol Version 9.0, 27Oct2016), patients were to be followed for Progression Free Survival (PFS) and Overall Survival (OS) for an additional period of up to 3 years or until death, whichever was first. Patients who had already completed all visits and who were still alive were asked to sign another Informed Consent Form (ICF) for the collection of further follow-up information. A schematic overview of the study treatment phase is presented in Table 3.

Table 3: **Treatment schedule (* in cohort 10 only)**

Weeks / **Therapy**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Carboplatin + paclitaxel +/- bevacizumab*	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6		
ISA101 ± pegylated INFα or ISA101b						Vac. 1			Vac. 2			Vac.3						

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CRITERIA FOR EVALUATION

Primary endpoints of the trial were:

Safety

- Safety evaluations included the following safety parameters: Adverse Events (AEs) and Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESI) and changes in laboratory parameters
- The safety profile of ISA101b in the bridging cohorts was qualitatively compared to the safety profile observed at the same dose level of ISA101.

HPV-specific immune responses

- HPV-specific immune responses to the ISA101 vaccine with or without pegylated IFNα in combination with carboplatin and paclitaxel were determined by the quality, breadth and magnitude of the HPV16 E6/E7-specific T-cell responses as measured by a validated assay Interferon gamma (IFNγ) Enzyme-linked Immunosorbent Spot (ELISpot) following injection of the different doses of the ISA101 vaccine.
- The HPV-specific immune responses to ISA101b in the bridging cohorts were qualitatively compared to the responses observed at the same dose level of ISA101.

Secondary endpoints of the trial Were:

- Anti-tumor Efficacy according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
  - Objective Response Rate (ORR) was calculated as the proportion of patients with a best overall response of confirmed Complete Response (CR) or Partial Response (PR).
  - Duration of response was defined as the time from objective response to documented progression or death from any cause
  - PFS was defined as the time from start of carboplatin and paclitaxel treatment to the documented progression or death from any cause.
  - OS was defined as the time from start of carboplatin and paclitaxel treatment to death
- Tumor shrinkage as measured by the sum of longest dimensions of target lesions

STATISTICAL METHODS

The trial was analyzed as per the SAP Version 1.0 Stage 3, dated 31 July 2018 and outputs were produced by the Statistics Department of DICE using the SAS® system Version 9.2.

The Stage 1 and 2 analyses concerned data of the first 10 study cohorts for ISA101 (the dose escalation cohorts 1 to 8 and the expansion cohorts 3B and 5B). Assignment to a cohort was based on patient enrolment date and therefore comparisons between cohorts are confounded.

The Stage 3 analysis was performed after locking the database on 14 August 2018 and concerned the same variables as the Stage 2 analysis. For all stages, the screening and baseline data, the safety data, and the immunological data of the 10 study cohorts of ISA101 and the two bridging cohorts using ISA101b were analyzed. This analysis was performed once the collection of the safety and immunology data during and within 30 days after the last dose of ISA101/ISA101b was considered complete. In addition, collection of the data on clinical response rates for ISA101 and the ISA101b bridging cohorts were complete and collection of other longer-term outcomes, e.g. duration of response, PFS and OS were considered sufficient to address the objectives of the study.

Descriptive statistics for quantitative variables and frequency distribution for ordinal and nominal variables were used for the analysis of the study data.

Full details are given in the SAP Version 1.0 Stage 3 provided in Appendix 16.1.12.

RESULTS

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Safety:

The safety data generated to date with ISA101/101b in this clinical trial are summarized herewith:

- Most of the AEs in the CervISA trial were expected toxicities related to chemotherapy or to complications associated with progression of cervical cancer.
- 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.
- Dose-related Systemic Allergic Reactions (SARs) were reported in 11 of 72 patients, including seven of 12 patients at the 300 µg/peptide dose of ISA101 but none of the12 patients who received ISA101b. These reactions led to drug withdrawal in two of 72 patients who received ISA101 (one each from the 100 or 300 µg/peptide cohort). These events may, in part, be related to the amount of Montanide administered, which is proportional to the dose of the peptide vaccine.
- No new or unexpected safety concerns have been identified for ISA101 or ISA101b compared to the safety profile of the predecessor vaccine, HPV-16-Systemic Long Peptides (SLP).
- The safety profile and immunologic activity of ISA101b appear to be similar to ISA101.
- Dose levels of up to 100 µg/peptide were considered safe and well tolerated while the 300 µg/peptide dose level was associated with a greater frequency of ISRs and SARs. As described below, 100 µg/peptide was selected as the dose to be used in further clinical studies based on these data.

Biomarker Response - Immune Response to ISA101/ISA101b:

- Pre-vaccine: at baseline and after the first cycle of chemotherapy (both time points before the first dose of ISA101/ISA101b) the HPV16-specific immune response was minimal.
- Post-vaccine: after the 2nd and 3rd vaccinations with ISA101 or ISA101b (i.e. at Visits 8 and 10), the HPV16-specific immune response was substantially increased at all doses of the vaccine, particularly at the three highest dose levels of 40, 100 and 300 µg/peptide. The HPV16-specific T-cell immune response appeared similar at the 100 and 300 µg/peptide dose levels indicating a broad dose response curve for the vaccine.
- The HPV16-specific T-cell immune responses without or with pegylated IFNα, as measured by the ELISpot assay, were similar.
- In the patients in whom it was measured (n = 15), the HPV-specific response induced by ISA101/101b vaccination was sustained for at least three months after the last dose of ISA101/ISA101b (corresponding to Visit 13, the last time point assessed).
- The HPV16-specific immune responses to ISA101 and ISA101b were comparable at the Recommended Phase 2 Dose (RP2D) level of 100 µg/peptide.

Clinical Outcomes:

- There were no apparent differences in response rates or PFS between the relatively small cohorts or treatment groups.
- 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.
- There was no association of a stronger non-specific (memory to re-call antigens) immune response with either the HPV16-specific immune responses or OS.
- The association between a higher level of HPV16-specific immune response and a longer median OS was observed in patients without prior chemotherapy (17.3 months vs 15.1 months) as well as in those who had received prior chemotherapy (14.5 months vs 7.8 months). These differences were not statistically significant.

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- There were no apparent differences regarding safety or efficacy of ISA101b when compared to ISA101; it was therefore concluded that ISA101b is not only structurally but also functionally similar to ISA101.

CONCLUSIONS:

A broad dose response curve, as measured by a validated ELISpot assay, was observed for ISA101/ISA101b induced HPV16-specific T-cell responses but there was no apparent increase in HPV16 T-cell responses associated with the addition of pegylated IFNα. Based on the assessment of the safety profile (e.g. the frequency of local ISRs and SARs) and the HPV-specific T-cell response data the 100 µg/peptide dose level was selected as the RP2D for further trials in patients with advanced cancer. These HPV16-specific immune responses to ISA101 and ISA101b were robust and durable. The safety profile and level of HPV-specific immune responses to ISA101b and ISA101 appeared to be comparable. Stronger HPV16-specific immune responses (but not memory, re-call responses) were associated with prolonged OS. This association was observed regardless of whether the patients had received prior chemotherapy for advanced disease. The potential benefit of ISA101/ISA101b in improving OS when added to standard chemotherapy warrants further controlled clinical trials with ISA101b in this and other HPV16-positive cancer indications.

DATE OF FINAL REPORT:

09Aug2019